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(54) **"MEDICAL ARTICLES COATED WITH
ORGANOPOLYSILOXANE CONTAINING A
PROTEIN SOLUTION"**

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Related U.S. Application Data

(60) Division of application No. 12/739,009, filed on Jan.
14, 2011, now Pat. No. 8,633,034, filed as application

(57) **ABSTRACT**

This invention relates to methods for evaluating or inhibiting
the aggregation of a protein in an aqueous suspension includ-
ing organopolysiloxane and medical articles coated with
organopolysiloxane containing a protein solution including
sugar and non-ionic surfactant.

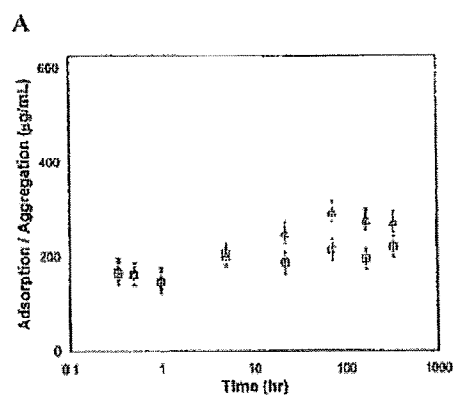


Fig. 1A

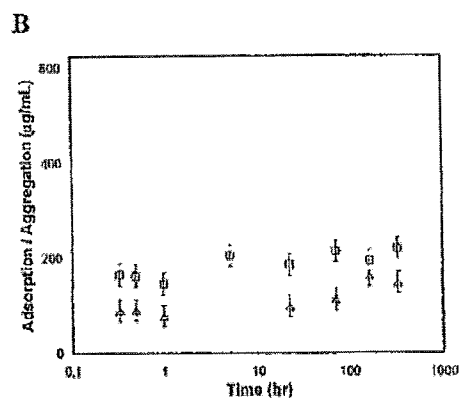


Fig. 1B

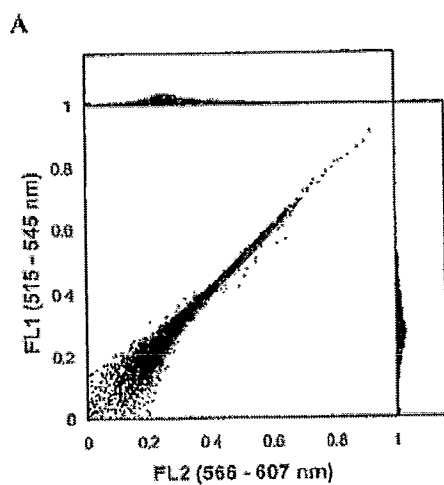


Fig. 2A

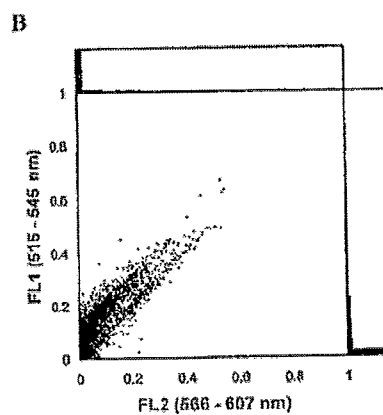


Fig. 2B

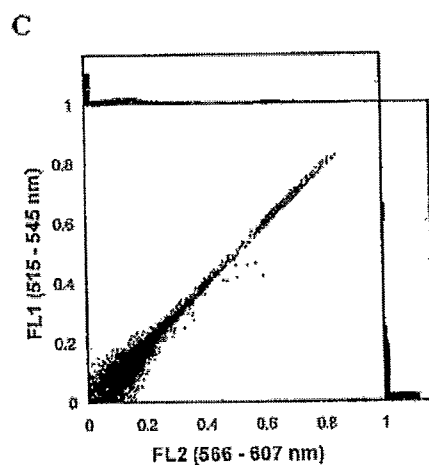


Fig. 2C

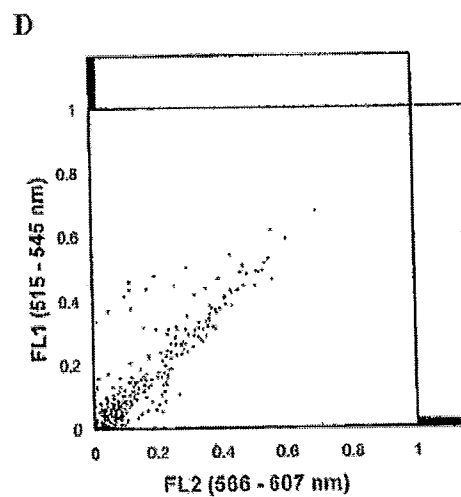


Fig. 2D

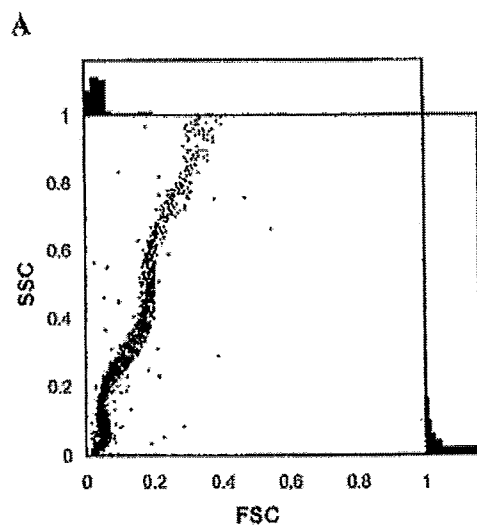


Fig. 3A

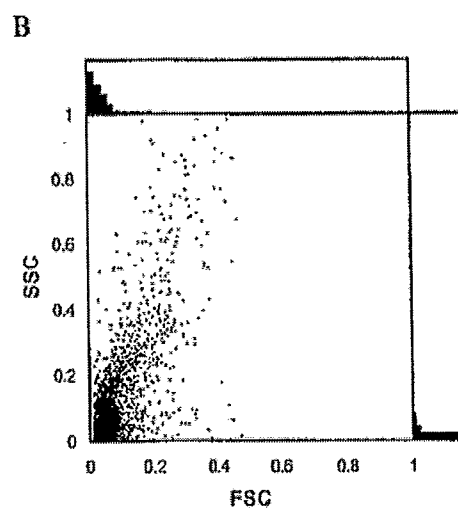


Fig. 3B

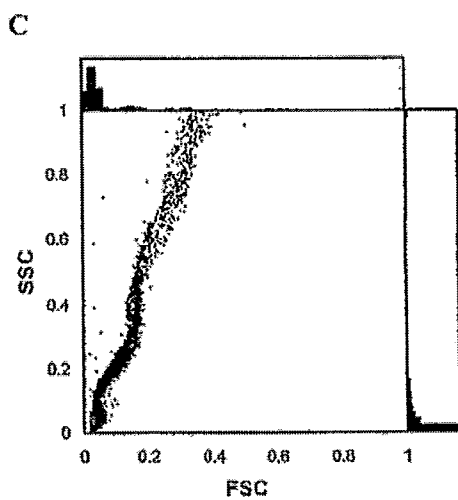


Fig. 3C

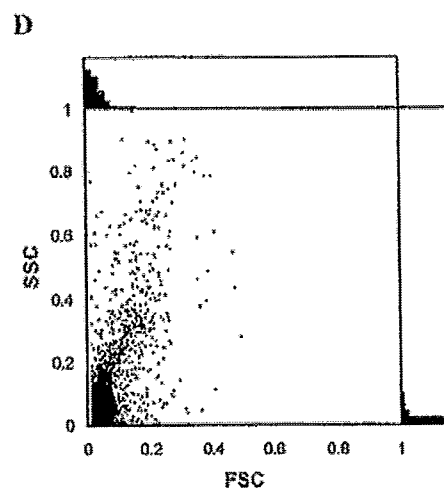


Fig. 3D

A

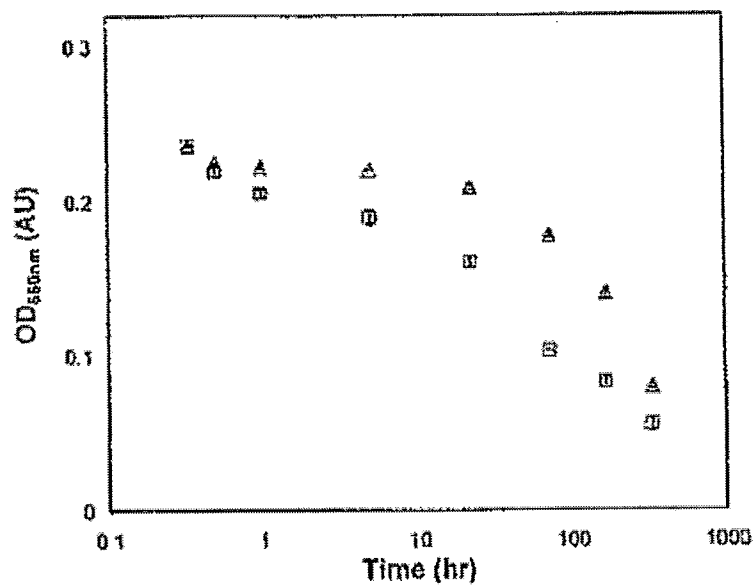


Fig. 4A

B

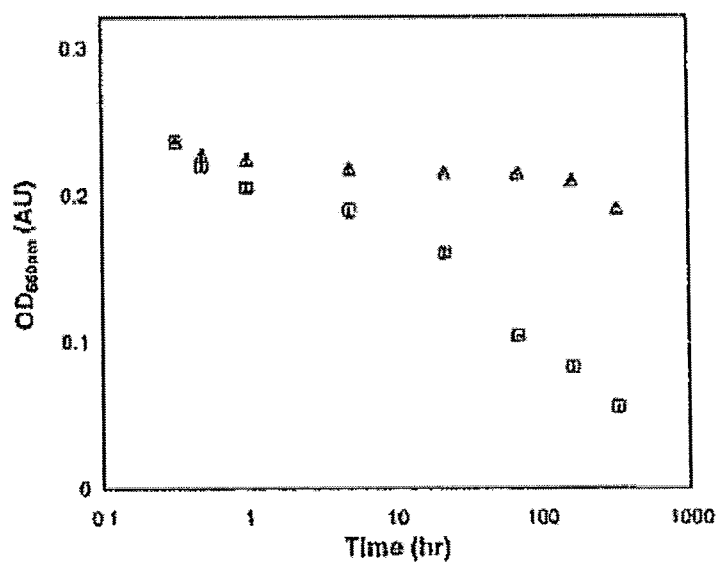


Fig. 4B

A

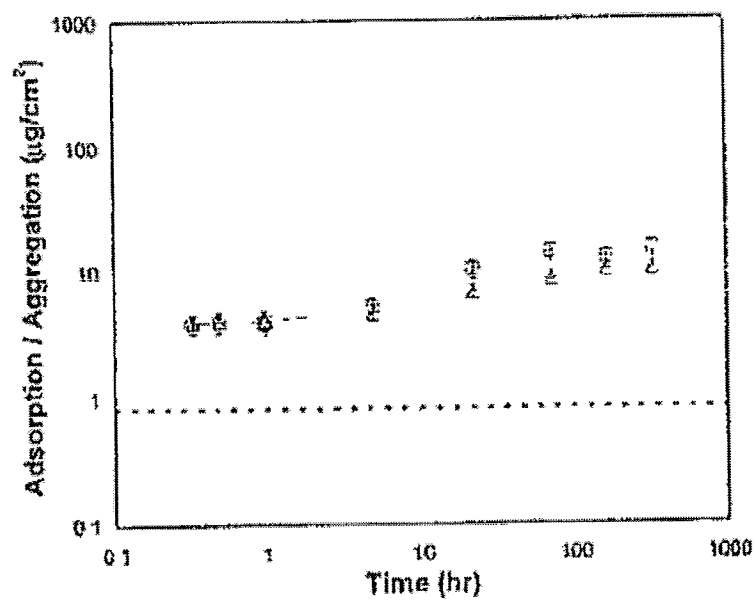


Fig. 5A

B

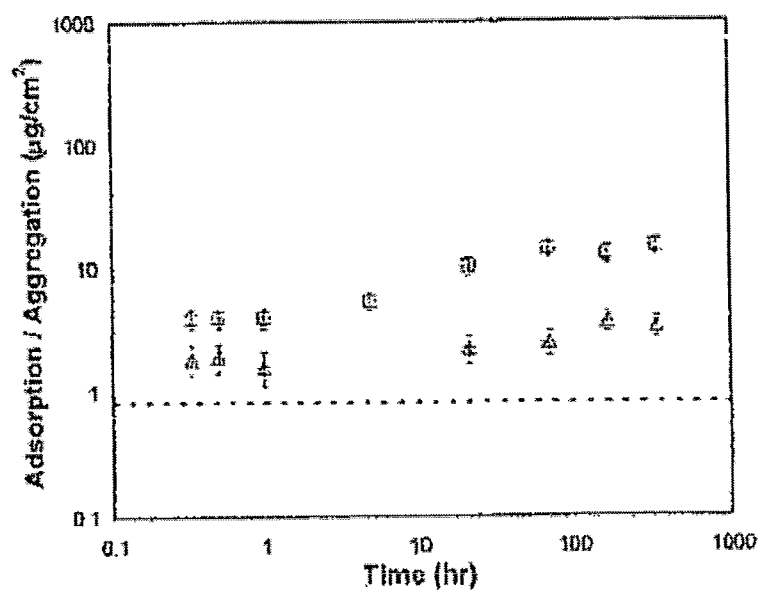


Fig. 5B

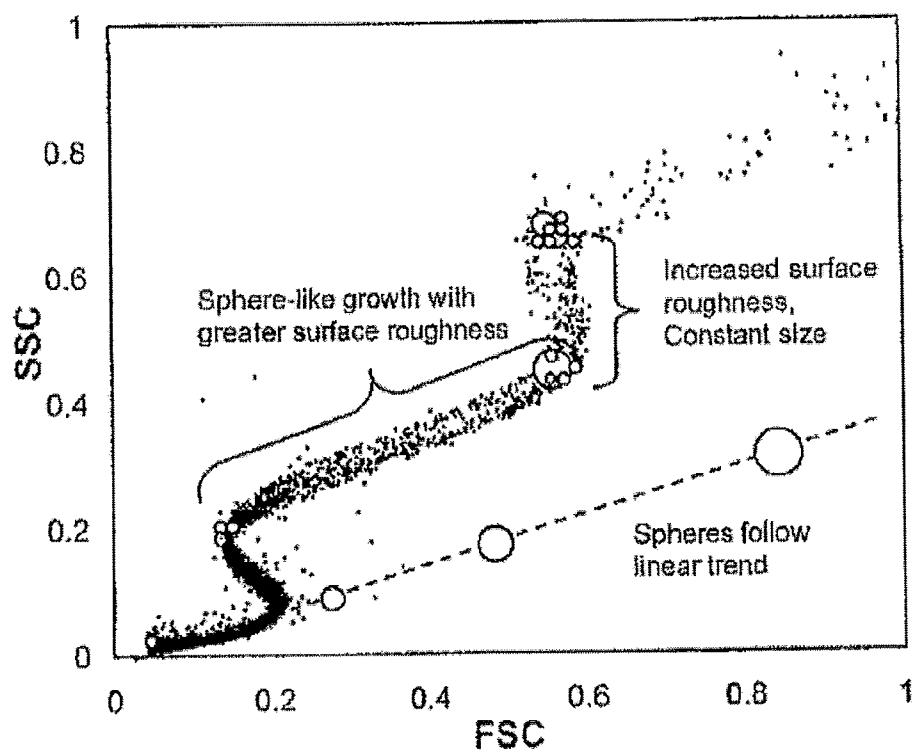
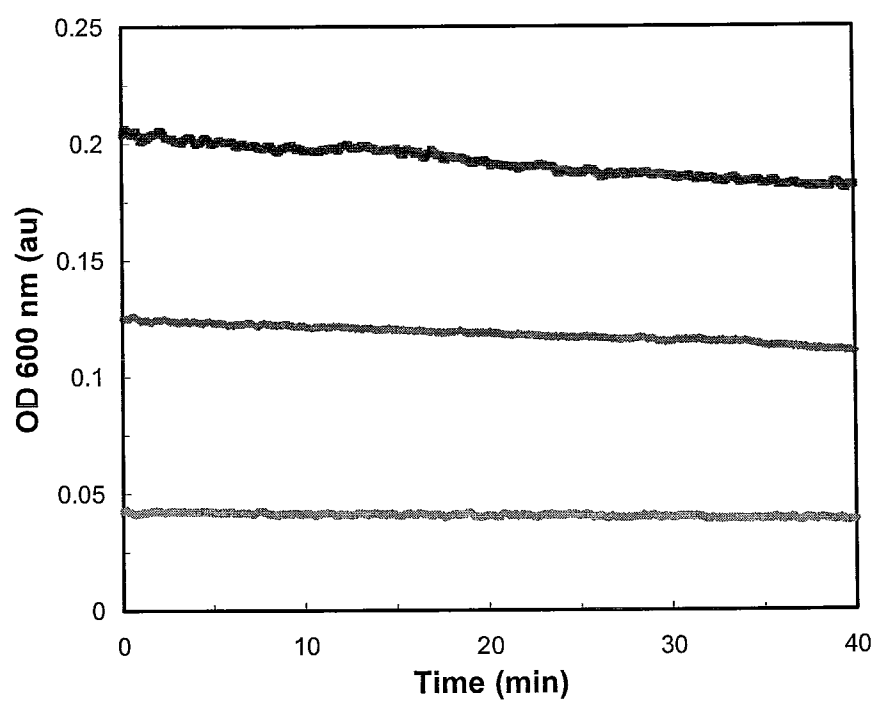


Fig. 6



Effect of Oil Viscosity on Oil Loading in Suspension

Fig. 7

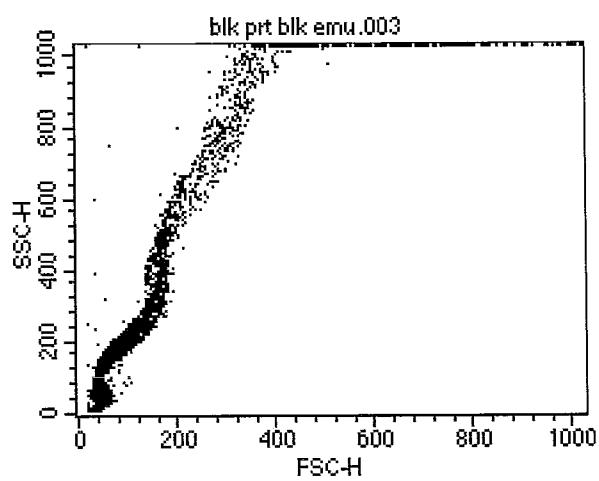


Fig. 8

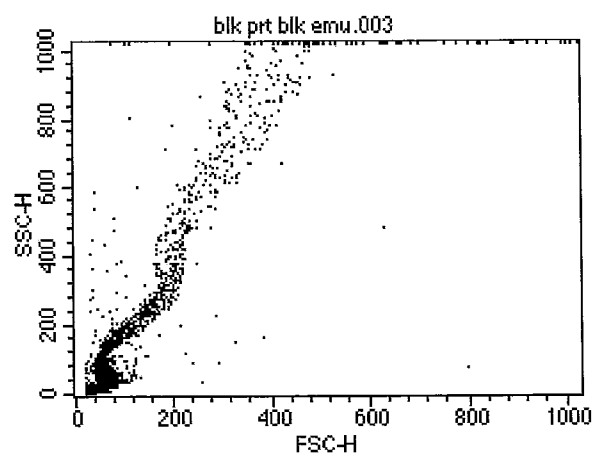


Fig. 9

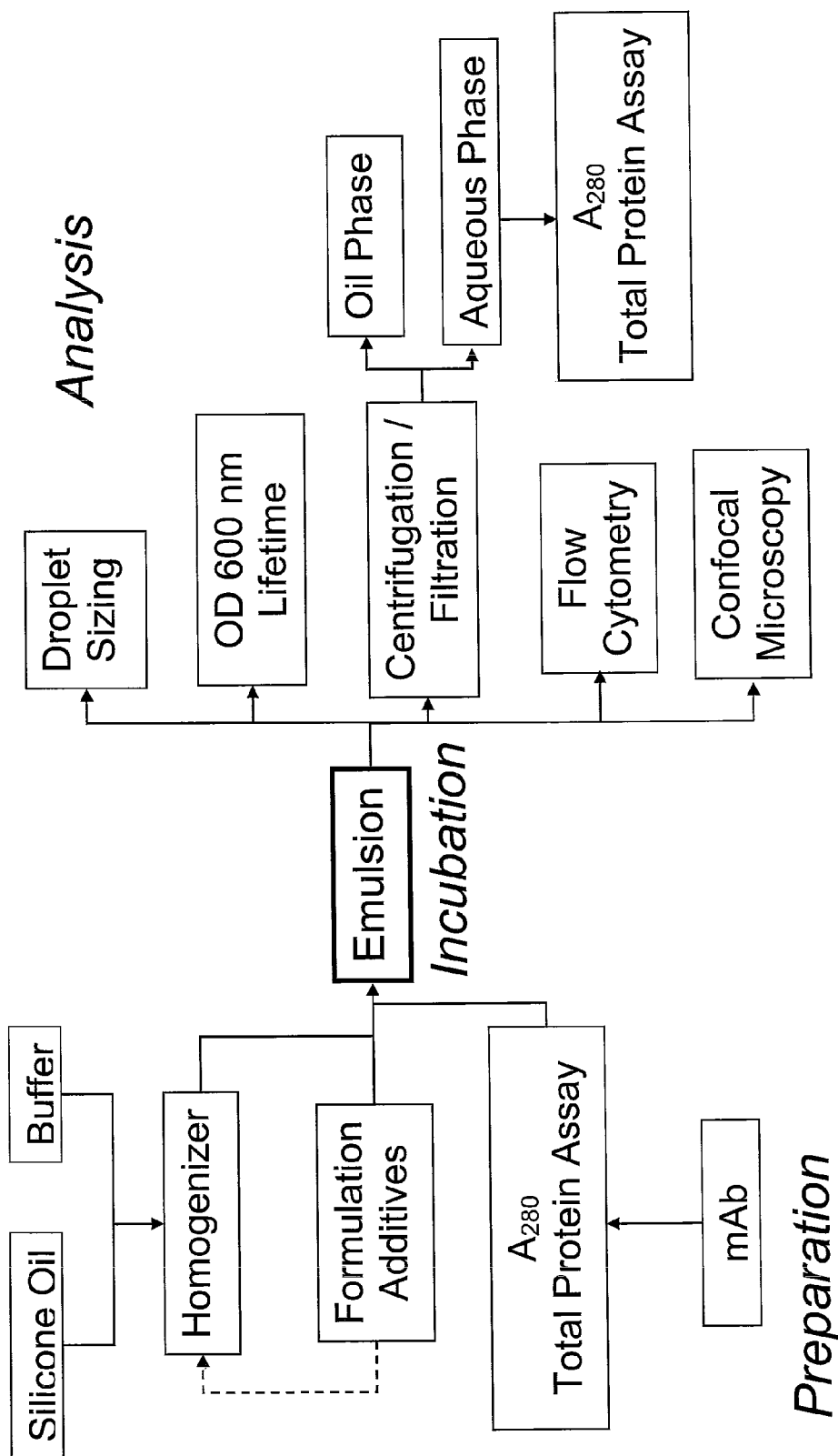


Fig. 10

**"MEDICAL ARTICLES COATED WITH
ORGANOPOLYSILOXANE CONTAINING A
PROTEIN SOLUTION"**

**CROSS-REFERENCE TO RELATED
APPLICATION**

[0001] This application is a divisional application of U.S. patent application Ser. No. 12/739,009 entitled "Methods for Evaluating the Aggregation of a Protein in a Suspension Including Organopolysiloxane and Medical Articles Coated with Organopolysiloxane Containing a Protein Solution" filed Jan. 14, 2011, which is a utility application under §371 of International PCT application PCT/US2008/080721 filed Oct. 22, 2008 which claims the benefit of U.S. Provisional Patent Application Ser. No. 60/999,920 and which is a continuation-in-part application of International PCT application PCT/US2008/068136 filed Jun. 25, 2008, which claims the benefit of U.S. Provisional Patent Application Ser. No. 60/937,179, the entire disclosures of each of which are hereby incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

[0002] 1. Field of the Invention

[0003] This invention relates to methods for evaluating the aggregation of a proteinaceous material in a suspension comprising an organopolysiloxane and medical components having surfaces coated with organopolysiloxane(s) and containing suspensions of proteinaceous materials.

[0004] 2. Description of Related Art

[0005] Therapeutic proteins provide numerous unique and critical treatments for diseases and conditions, such as diabetes, cancer, hemophilia, rheumatoid arthritis, multiple sclerosis and myocardial infarction. There are already dozens of protein products on the market and hundreds more are in preclinical and clinical development. Furthermore, with the recent advent of robust methods for "humanizing" antibodies, there has been a new resurgence in biotechnology product development due to the tremendous increase in the number of antibody products being investigated for treatments of human disease. With modern genomic and proteomic approaches, new safer and more effective protein therapeutics are being discovered daily. However, if a protein product cannot be stabilized adequately, its benefit to human health will never be realized. The shelf life required for economic viability of a typical protein pharmaceutical product is 18-24 months. Achieving this goal is particularly difficult because of the relatively low thermodynamic stability of the protein in its native state. The activity of a protein depends on its native, three-dimensional structure. In addition, proteins are highly susceptible to the formation of non-native aggregates and precipitates, even under conditions that thermodynamically greatly favor the native state over the unfolded state (e.g., neutral pH at 37° C.). The biological activity of a protein in an aggregate is usually greatly reduced. More importantly, non-native protein aggregates can cause adverse reactions in patients, such as immune response or anaphylactic shock. The capacity of aggregates of a given protein to induce adverse responses cannot be predicted; nor can the maximal level of aggregates required for safety be determined without costly and time-consuming clinical trials.

[0006] Thus, a major goal of formulation science is to design a formulation in which aggregation is kept to an extremely low level. Generally, the goal is to have no more

than 1-2% of the entire protein population form aggregates over the shelf life of the product. Even under solution conditions where protein physical stability appears to be optimized so as to minimize protein aggregation in the bulk solution, there can be formation of visible and subvisible protein particles that may constitute only a minute fraction of the total protein population. The presence of even a small number of protein particles can render a product clinically unacceptable. Protein particulates are particularly immunogenic. Although particulates are desirable for vaccine formulations (where protein molecules are bound to aluminum salt particles), in a therapeutic protein product, the immune response to such particles can cause severe adverse responses in patients. Thus, even though the mass of protein that aggregates can be so small as to have essentially no deleterious effect on product potency, safety can be greatly compromised.

[0007] Particle formation can occur routinely during processing steps such as pumping of protein solution during vial/syringe filling. In other cases, particle formation may appear to be random. For example, particles may be seen in a small fraction of vials or prefilled syringes in a given product lot. Other times, a product filled into a given lot of vials or syringes may form protein particles in a large fraction of the containers. Unfortunately, these particles appear downstream of sterile filtration steps and cannot be removed by filtration during subcutaneous, intradermal, or intramuscular injection.

[0008] Silicone oils are commonly used as lubricants in medical articles. While silicone oils are not subject to oxidation, migration and stick could occur for pre-filled syringes, and high breakout and/or breakloose forces are a problem. Silicone oil has been shown under certain conditions, even at low concentrations, to induce protein aggregation. Several newly commercialized aqueous protein products, including erythropoietins (e.g., Recormon™ and Eprex™), interferons (e.g., Avonex™ and Rebif™) and rheumatoid arthritis therapies (e.g., Enbrel™ and Humira™) are manufactured in pre-filled syringes. Inner surfaces of prefilled syringes are coated with silicone oil to enhance syringe functionality, and consequently, formulated protein is exposed to silicone oil surfaces. Silicone oil induced therapeutic protein aggregation is a concern in the pharmaceutical industry, potentially leading to loss of product and increased manufacturing costs.

[0009] There is a need for methods to assess aqueous suspensions or emulsions having proteinaceous materials to determine appropriate aggregation inhibitors to include in the solution to inhibit aggregation. The results of these investigations will provide the understanding needed for advising companies on how to develop protein formulations that are resistant to silicone oil-induced protein aggregation. In addition, an experimental system that allows rapid formulation screening is desirable. Thus, pharmaceutical and biotechnology companies can follow a rational formulation development plan to quickly optimal formulations for each protein that avoid the problem of silicone oil-induced protein aggregation and the potential adverse responses in patients. Model proteins and appropriate solution conditions can be determined that can be used for testing new syringes or medical articles in development.

SUMMARY OF THE INVENTION

[0010] In some non-limiting embodiments, the present invention provides methods for evaluating the aggregation of a proteinaceous material in a suspension comprising an organopolysiloxane, comprising: (a) providing an aqueous sus-

pension of a fluorescently-labeled organopolysiloxane and a fluorescently-labeled proteinaceous material; (b) measuring relative particle fluorescence intensity of the fluorescently-labeled organopolysiloxane and the fluorescently-labeled proteinaceous material using fluorescence-activated particle sorting; and (c) comparing the relative intensity of the fluorescently-labeled organopolysiloxane to the relative intensity of the fluorescently-labeled proteinaceous material.

[0011] In some non-limiting embodiments, the present invention provides methods for inhibiting the aggregation of a proteinaceous material in a suspension comprising an organopolysiloxane, comprising: (a) providing a plurality of aqueous suspensions of a fluorescently-labeled organopolysiloxane and a fluorescently-labeled proteinaceous material, wherein each aqueous suspension further comprises at least one aggregation inhibitor selected from the group consisting of non-ionic surfactants and sugars wherein (i) the at least one aggregation inhibitor is different in each aqueous suspension, or (ii) the amount of aggregation inhibitor is different in each aqueous suspension; (b) measuring relative particle fluorescence intensity of the fluorescently-labeled organopolysiloxane and the fluorescently-labeled proteinaceous material in each aqueous suspension using fluorescence-activated particle sorting; (c) comparing the relative intensity of the fluorescently-labeled organopolysiloxane to the relative intensity of the fluorescently-labeled proteinaceous material for each aqueous suspension; and (d) selecting at least one aggregation inhibitor for use in a suspension comprising a proteinaceous material based upon the comparison of the relative intensity of the fluorescently-labeled organopolysiloxane to the relative intensity of the fluorescently-labeled proteinaceous material for each aqueous suspension.

[0012] In some non-limiting embodiments, the present invention provides medical articles, comprising: (a) a container comprising a chamber for receiving a solution, wherein the inner surface of the chamber has a coating thereon prepared from a composition comprising an organopolysiloxane; and (b) a solution comprising: (i) at least one proteinaceous material; (ii) at least one non-ionic surfactant; and (iii) at least one sugar.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] The present invention will best be understood from the following description of specific embodiments when read in connection with the accompanying drawings:

[0014] FIG. 1A is a plot of adsorption/aggregation of mAb with silicone oil as a function of time for a formulation including sucrose, mAb and silicone oil and a formulation including mAb and silicone oil;

[0015] FIG. 1B is a plot of adsorption/aggregation of mAb with silicone oil as a function of time for a formulation including sucrose, mAb and silicone oil and a formulation including sucrose, non-ionic surfactant, mAb and silicone oil according to the present invention;

[0016] FIG. 2A is a fluorescence intensity scatter plot of FL1 intensity and FL2 intensity for a control formulation without sucrose or surfactant;

[0017] FIG. 2B is a fluorescence intensity scatter plot of FL1 intensity and FL2 intensity for a formulation with sucrose;

[0018] FIG. 2C is a fluorescence intensity scatter plot of FL1 intensity and FL2 intensity for a formulation with non-ionic surfactant;

[0019] FIG. 2D is a fluorescence intensity scatter plot of FL1 intensity and FL2 intensity for a formulation with sucrose and non-ionic surfactant according to the present invention;

[0020] FIG. 3A is a scatter plot of side light scattering (90° light scattering) versus forward light scattering (180° light scattering) of silicone oil droplets for a control formulation without sucrose or surfactant;

[0021] FIG. 3B is a scatter plot of side light scattering (90° light scattering) versus forward light scattering (180° light scattering) of silicone oil droplets for a formulation with sucrose;

[0022] FIG. 3C is a scatter plot of side light scattering (90° light scattering) versus forward light scattering (180° light scattering) of silicone oil droplets for a formulation with non-ionic surfactant;

[0023] FIG. 3D is a scatter plot of side light scattering (90° light scattering) versus forward light scattering (180° light scattering) of silicone oil droplets for a formulation with non-ionic surfactant according to the present invention;

[0024] FIG. 4A is a plot of light obscuration as a function of time for a formulation including sucrose, mAb and silicone oil and a formulation including mAb and silicone oil;

[0025] FIG. 4B is a plot of light obscuration as a function of time for a formulation including sucrose, mAb and silicone oil and a formulation including sucrose, non-ionic surfactant, mAb and silicone oil according to the present invention.

[0026] FIG. 5A is a plot of adsorption/aggregation of mAb with silicone oil as a function of time for a formulation including sucrose, mAb and silicone oil and a formulation including mAb and silicone oil;

[0027] FIG. 5B is a plot of adsorption/aggregation of mAb with silicone oil as a function of time for a formulation including sucrose, mAb and silicone oil and a formulation including sucrose, non-ionic surfactant, mAb and silicone oil

[0028] FIG. 6 is a hypothetical representation of silicone oil droplet and agglomerate distribution based on forward and side light scattering;

[0029] FIG. 7 is a plot of light obscuration as a function of time for silicone oil emulsion formulations for three different silicone oil viscosities;

[0030] FIG. 8 is a scatter plot of side light scattering (90° light scattering) versus forward light scattering (180° light scattering) of silicone oil droplets for a formulation prepared from 1000 cSt silicone oil;

[0031] FIG. 9 is a scatter plot of side light scattering (90° light scattering) versus forward light scattering (180° light scattering) of silicone oil droplets for a formulation prepared from 12,500 cSt silicone oil; and

[0032] FIG. 10 is a flow chart of a method for preparing and analyzing samples of organopolysiloxane solutions according to the present invention.

DETAILED DESCRIPTION

[0033] Other than in the operating examples, or where otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about". Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present invention. At the very least, and not as an attempt to limit the application of the

doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

[0034] Notwithstanding that the numerical ranges and parameters setting forth the broad scope of the invention are approximations, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical values, however, inherently contain certain errors necessarily resulting from the standard deviation found in their respective testing measurements. Furthermore, when numerical ranges of varying scope are set forth herein, it is contemplated that any combination of these values inclusive of the recited values may be used.

[0035] Also, it should be understood that any numerical range recited herein is intended to include all sub-ranges subsumed therein. For example, a range of “1 to 10” is intended to include all sub-ranges between and including the recited minimum value of 1 and the recited maximum value of 10, that is, having a minimum value equal to or greater than 1 and a maximum value of equal to or less than 10.

[0036] While not intending to be bound by any theory, protein particle formation can arise from heterogeneous nucleation of protein aggregates on the surfaces of nanoparticles and microparticles of foreign materials. These particulate contaminants can include metals or silicone shed from vial filling pumps, tungsten microparticles produced during manufacture of glass syringes, and glass nanoparticles shed as a result of high-temperature depyrogenation procedures. The formation of protein particles in silicone oil-treated pre-filled syringes, which can be nucleated by microdroplets of silicone oil, also can be of concern. Although such particles—and the protein aggregates that may result from them—are ubiquitous, virtually no systematic characterization of the problem and the mechanisms governing it have been addressed in the literature. Without such insight, industry will continue to be plagued with protein aggregation events and the resulting loss of product, increased costs, and safety risks to patients.

[0037] Homogeneous protein aggregation can be inhibited by using thermodynamic stabilizers (e.g., sucrose) that shift the native state ensemble away from structurally expanded conformations and toward the structurally most compact species. Stabilizers such as sucrose increase protein thermodynamic stability because they are preferentially excluded from the surface of protein molecules. Concomitant with preferential exclusion is an increase in protein chemical potential. The magnitudes of these two effects is directly proportional to the surface area of the protein exposed to solvent and are independent of the chemical properties of the side chains of exposed residues. Preferentially excluded solutes increase the free energy barrier between the most compact native state and the fully unfolded state or structurally expanded species within the native state ensemble, because the latter have a greater surface area and, hence, greater increase in chemical potential. Thus, sucrose shifts the equilibrium away from structurally expanded, aggregation-competent species.

[0038] In addition to thermodynamic modulation of species distribution within the protein molecular population, the energetics of protein-protein interactions in solution are important determinants of the kinetics of protein aggregation. Partial unfolding of a protein is not sufficient, by itself, to cause aggregation. They must also follow an assembly reaction, wherein two or more protein molecules aggregate. The

kinetics of this process are modulated by protein-protein intermolecular energies, which can in turn be altered by changing solution conditions. Such “colloidal” stability can be related to the second osmotic virial coefficient, B₂₂. This parameter is greatly affected by charge-charge interactions between protein molecules. Hence, changes in solution pH and ionic strength alter protein-protein interactions.

[0039] In some non-limiting embodiments, the methods of the present invention can be useful in connection with preparation of pre-filled syringes in which the surfaces are coated with silicone oil. Silicone oil is desirable to assure smooth, free travel of the stopper through the barrel of the syringe as the product is injected.

[0040] In some non-limiting embodiments, the present invention provides a method for evaluating the aggregation of a proteinaceous material in a suspension comprising an organopolysiloxane, comprising: (a) providing an aqueous suspension (or emulsion) of a fluorescently-labeled organopolysiloxane and a fluorescently-labeled proteinaceous material; (b) measuring relative particle fluorescence intensity of the fluorescently-labeled organopolysiloxane and the fluorescently-labeled proteinaceous material using fluorescence-activated particle sorting; and (c) comparing the relative intensity of the fluorescently-labeled organopolysiloxane to the relative intensity of the fluorescently-labeled proteinaceous material.

[0041] As used herein, “proteinaceous material” means a material comprising at least one protein. As used herein, a “protein” is a large organic compound comprising amino acids arranged in a linear chain and joined together by peptide bonds between the carboxyl and amino groups of adjacent amino acid residues, for example fibrous proteins, globular proteins, and protein complexes. Non-limiting examples of suitable proteinaceous materials for use in the present invention include monoclonal antibodies (mAb or moAb), monospecific antibodies that are identical because they are produced by one type of immune cell that are all clones of a single parent cell. Non-limiting examples of suitable monoclonal antibodies include infliximab, basiliximab, abciximab, daclizumab, gemtuzumab, alemtuzumab, rituximab, palivizumab, trastuzumab and etanercept. Other non-limiting examples of suitable proteinaceous materials include Granulocyte Colony Stimulating Factor (e.g., Neupogen™), erythropoietins (e.g., Recormon™ and Eprex™), interferons (e.g., Avonex™ and Rebi™) and rheumatoid arthritis therapies (e.g., Enbrel™ and Humira™). The proteinaceous material is labeled or has attached thereto a fluorescent moiety capable of fluorescing upon exposure to ultraviolet or infrared light, as discussed in detail below.

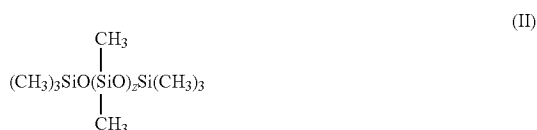
[0042] In some non-limiting embodiments, the proteinaceous material is present in the solution in a concentration of about 20 to about 600 µg/mL, or about 100 to about 300 µg/mL based upon total volume of the aqueous solution.

[0043] The organopolysiloxane can be any organopolysiloxane or silicone oil, for example such as can be used to coat surfaces of medical articles such as syringe barrels. In some non-limiting embodiments, the organopolysiloxane has a viscosity ranging from about 100 to about 1,000,000 centistokes (cSt), prior to any curing step, or about 1,000 cSt to about 100,000 cSt, or about 1,000 cSt to about 15,000 cSt, or about 12,500 cSt.

[0044] In some non-limiting embodiments, the organopolysiloxane comprises an alkyl-substituted organopolysiloxane, for example as is represented by the following structural Formula (I):



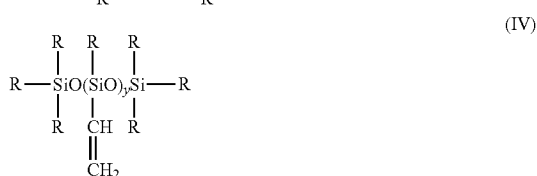
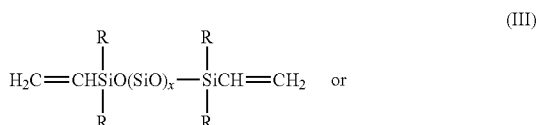
wherein R is alkyl and Z is about 30 to about 4,500. In some non-limiting embodiments, the organopolysiloxane of Formula (I) can be represented by the following structural Formula (II):



wherein Z can be as above, or for example can be about 300 to about 2,000, about 300 to about 1,800, or about 300 to about 1,350. In some non-limiting embodiments, the organopolysiloxane is a polydimethylsiloxane, such as DOW CORNING® 360 polydimethylsiloxane or NUSIL polydimethylsiloxane having a viscosity ranging from about 100 to about 1,000,000 cSt.

[0045] In some non-limiting embodiments, the organopolysiloxane comprises one or more curable or reactive functional groups, such as alkenyl groups. Each alkenyl group can be independently selected from the group consisting of vinyl, allyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl and decenyl. One skilled in the art would understand that the organopolysiloxane can comprise one or more of any of the above types of alkenyl groups and mixtures thereof. In some embodiments, at least one alkenyl group is vinyl. Higher alkenyl or vinyl content provides more efficient crosslinking.

[0046] In some non-limiting embodiments, the organopolysiloxane can be represented by the following structural Formulae (III) or (IV):



wherein R is alkyl, haloalkyl, aryl, haloaryl, cycloalkyl, sila-cyclopentyl, aralkyl, and mixtures thereof; X is about 60 to

about 1,000, preferably about 200 to about 320; and y is about 3 to about 25. Copolymers and mixtures of these polymers also are contemplated.

[0047] Non-limiting examples of useful vinyl functional organopolysiloxanes include: vinyl dimethylsiloxyl terminated polydimethylsiloxanes; trimethylsiloxyl terminated vinylmethyl, dimethylpolysiloxane copolymers; vinyl dimethylsiloxyl terminated vinylmethyl, dimethylpolysiloxane copolymers; divinylmethylsiloxyl terminated polydimethylsiloxanes; vinyl, n-butylmethyl terminated polydimethylsiloxanes; and vinylphenylmethylsiloxyl terminated polydimethylsiloxanes.

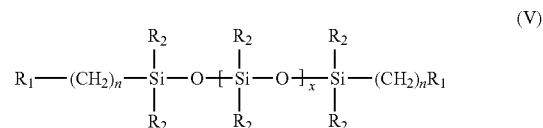
[0048] In some embodiments, a mixture of siloxane polymers selected from those of Formulae II, III and/or IV can be used. For example, the mixture can comprise two different molecular weight vinyl dimethylsiloxyl terminated polydimethylsiloxane polymers, wherein one of the polymers has an average molecular weight of about 1,000 to about 25,000 and preferably about 16,000, and the other polymer has an average molecular weight of about 30,000 to about 71,000 and preferably about 38,000. Generally, the lower molecular weight siloxane can be present in amounts of about 20% to about 80%, such as about 60% by weight of this mixture; and the higher molecular weight siloxane can be present in amounts of about 80% to about 20%, such as about 40% by weight of this mixture.

[0049] Another non-limiting example of a suitable vinyl functional organopolysiloxane is (7.0-8.0% vinylmethylsiloxane)-dimethylsiloxane copolymer, trimethylsiloxyl terminated, such as VDT-731 vinylmethylsiloxane copolymer which is commercially available from Gelest, Inc. of Morrisville, Pa.

[0050] In some non-limiting embodiments, the organopolysiloxane can comprise at least two polar groups. Each polar group can be independently selected from the group consisting of acrylate, methacrylate, amino, imino, hydroxy, epoxy, ester, alkyl, isocyanate, phenolic, polyurethane oligomeric, polyamide oligomeric, polyester oligomeric, polyether oligomeric, polyol, and carboxypropyl groups. One skilled in the art would understand that the organopolysiloxane can comprise one or more of any of the above polar groups and mixtures thereof. In some non-limiting embodiments, the polar groups are acrylate groups, for example, acryloxypropyl groups. In other embodiments, the polar groups are methacrylate groups, such as methacryloxypropyl groups. The organopolysiloxane having polar groups can further comprise one or more alkyl groups and/or aryl groups, such as methyl groups, ethyl groups, or phenyl groups.

[0051] Non-limiting examples of such organopolysiloxanes include [15-20% (acryloxypropyl)methylsiloxane]-dimethylsiloxane copolymer, such as UMS-182 acrylate functional siloxane, which is available from Gelest, Inc. of Morrisville, Pa., and SILCOLEASE® PC970 acrylated silicone polymer, which is available from Rhodia-Silicones.

[0052] In some non-limiting embodiments, such an organopolysiloxane can be represented by the Formula (V):



wherein R_1 is selected from the group consisting of acrylate, methacrylate, amino, imino, hydroxy, epoxy, ester, alkyloxy, isocyanate, phenolic, polyurethane oligomeric, polyamide oligomeric, polyester oligomeric, polyether oligomeric, polyol, carboxypropyl, and fluoro groups; and R_2 is alkyl, n ranges from 2 to 4, and x is an integer sufficient to give the lubricant a viscosity of about 100 to 1,000,000 cSt.

[0053] In some non-limiting embodiments, the organopolysiloxane can further comprise one or more fluoro groups, such as $-F$ or fluoroalkyl groups such as trifluoromethyl groups. Other useful organopolysiloxanes include polyfluoroalkylmethyl siloxanes and fluoroalkyl, dimethyl siloxane copolymers.

[0054] In some non-limiting embodiments, the composition can further comprise one or more cyclic siloxane(s), for example, octamethylcyclotetrasiloxane and/or decamethylcyclopentasiloxane.

[0055] In some non-limiting embodiments, the organopolysiloxane can be represented by the following structural Formula (VI):



wherein R is haloalkyl, aryl (such as phenyl), haloaryl, cycloalkyl, silacyclopentyl, alkyl and mixtures thereof; and Z is about 20 to about 1,800.

[0056] In some non-limiting embodiments, the organopolysiloxane comprises at least two pendant hydrogen groups. Non-limiting examples of suitable organopolysiloxanes comprising at least two pendant hydrogen groups include organopolysiloxanes having pendant hydrogen groups along the polymer backbone or terminal hydrogen groups. In some non-limiting embodiments, the organopolysiloxane can be represented by the following structural Formulae (VII):



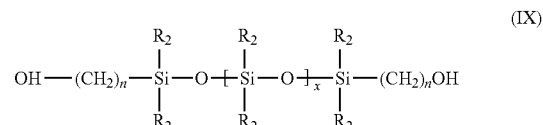
wherein p is about 8 to about 125, for example, about 30. In other non-limiting embodiments, the organopolysiloxane can be represented by the following structural Formula (VIII):



wherein p is about 140 to about 170, for example, about 150 to about 160. A mixture of these polymers can be used comprising two different molecular weight materials. For example, about 2% to about 5% by weight of the mixture of a trimethylsiloxy terminated polymethylhydrosiloxane having an average molecular weight of about 400 to about 7,500, for example about 1900, can be used in admixture with about 98% to about 95% of a dimethylhydro siloxy-terminated polydimethylsiloxane having an average molecular weight of about 400 to about 37,000 and preferably about 12,000. Non-limiting examples of useful organopolysiloxanes comprising at least two pendant hydrogen groups include dimethylhydro

terminated polydimethylsiloxanes; methylhydro, dimethylpolysiloxane copolymers; dimethylhydrosiloxy terminated methyloctyl dimethylpolysiloxane copolymers; and methylhydro, phenylmethyl siloxane copolymers.

[0057] In some non-limiting embodiments, the composition comprises hydroxy functional siloxanes, for example a hydroxy functional siloxane comprising at least two hydroxyl groups, such as for example:



wherein R_2 is alkyl, n ranges from 0 to 4, and x is an integer sufficient to give the lubricant a viscosity of about 100 to 1,000,000 cSt. In some non-limiting embodiments, moisture-curable siloxanes which have moisture-curing character as a result of functionality include siloxanes having functional groups such as: alkoxy; aryloxy; oxime; epoxy; $-OOCR$; N,N -dialkylamino; N,N -dialkylaminoxyl; N -alkylamido; $-O-NH-C(O)-R$; $-O-C(=NCH_3)-NH-CH_3$; and $-O-C(CH_3)=CH_2$, wherein R is H or hydrocarbyl. As used herein, "moisture-curable" means that the siloxane is curable at ambient conditions in the presence of atmospheric moisture.

[0058] Mixtures of any of the organopolysiloxanes discussed above can be used in the present invention.

[0059] In some non-limiting embodiments, the organopolysiloxane comprises about 0.001 to about 1 weight percent of the solution.

[0060] The proteinaceous material and organopolysiloxane are each labeled with a fluorescent moiety that fluoresces at a different wavelength of light. The fluorescent moiety can be selected from moieties that fluoresce in the green range (525-585 nm) (usually labeled FL1), such as FITC, Alexa Fluor 488, GFP, CFDA-SE, DyLight 488, PE Phycoerythrin, PE-Cy Phycoerythrin cyanine, FITC Fluorescein Isothiocyanate, GFP Green Fluorescence Protein, CFDA-SE Carboxyfluorescein Diacetate Succinimidyl Ester, PI Phosphoinositide; in the orange range (usually FL2), such as PE Phycoerythrin; in the red range (usually FL3): PerCP Peridinin Chlorophyll Protein, PE-Alexa Fluor 700, PE-Cy5 (TR1-COLOR), PE-Cy5.5, PI; in the infra-red range (usually FL4): PE-Alexa Fluor 750, PE-Cy7; using red diode laser (635 nm) or blue argon laser.

[0061] For scanned particles, forward light scattering (FSC, 1800 light scattering), side light scattering (SSC, 90° light scattering), green fluorescence intensity (FL1, 525-585 nm) and red fluorescence intensity (FL2, 585-600 nm) can be measured. For example, the proteinaceous material can be chemically labeled with Alexa Fluor® 488 dye (Invitrogen Corporation, Carlsbad, Calif.) according to well-documented protocols (MP 00143, Amine-Reactive Probes, Invitrogen Corporation). To label the silicone oil, Nile red dye can be dissolved in silicone oil at 5 mg/mL Nile red, 9-diethylamino-5-benzophenoxazine-5-one, is an extremely hydrophobic dye whose fluorescence is fully quenched in water. Alexa Fluor® 488 dye has an emission maximum of 519 nm, and Nile red dye has an emission maximum of 628 nm. Suspensions with chemically labeled mAb and dyed silicone oil can be scanned

with a BD FACScan™ Flow Cytometer analyzer or BD LSR II Flow Cytometer (Becton, Dickinson and Company, Franklin Lakes, N.J.).

[0062] Flow cytometry is an analytical process for counting, examining, and sorting microscopic particles suspended in a stream of fluid. It allows simultaneous multiparametric analysis of the physical and/or chemical characteristics of single particles flowing through an optical and/or electronic detection apparatus. In the flow cytometer, a beam of light (usually laser light) of a single wavelength is directed onto a hydrodynamically focused stream of fluid. A plurality of detectors are aimed at the point where the stream passes through the light beam; one in line with the light beam (Forward Scatter or FSC) and several perpendicular to it (Side Scatter (SSC) and one or more fluorescent detectors). Each suspended particle passing through the beam scatters the light in some direction, and fluorescent chemicals attached to the particle may be excited into emitting light at a lower frequency than the light source. This combination of scattered and fluorescent light is detected by the detectors. By analyzing fluctuations in brightness at each detector (one for each fluorescent emission peak) it is possible to derive various types of information about the physical and chemical structure of each individual particle. FSC correlates with the cell volume and SSC depends on the inner complexity of the particle (i.e., shape of the nucleus, the amount and type of particle or the particle roughness). Some flow cytometers form images of each cell's fluorescence, scattered light, and transmitted light.

[0063] Flow cytometers are capable of analyzing several thousand particles every second, and can actively separate and isolate particles having specified properties. A flow cytometer includes a flow cell-liquid stream (solution) which carries and aligns the cells so that they pass single file through the light beam for sensing; one or more light sources, such as a mercury or xenon lamp, high power water-cooled lasers (argon, krypton, dye laser), low power air-cooled lasers (argon (488 nm), red-HeNe (633 nm), green-HeNe, HeCd (UV)), or diode lasers (blue, green, red, violet); multiple detectors and Analog to Digital Conversion (ADC) system which generates FSC and SSC as well as fluorescence signals; a linear or logarithmic amplification system, and a computer for analysis of the signals. The data generated by flow-cytometers can be plotted in two dimensional dot plots or even in three dimensions. The regions on these plots can be sequentially separated, based on fluorescence intensity, by creating a series of subset extractions, termed "gates". The plots are often made on logarithmic scales. Because different fluorescent dyes' emission spectra overlap, signals at the detectors have to be compensated electronically as well as computationally. Often, data accumulated using the flow cytometer can be re-analyzed (using software such as WinMDI).

[0064] Fluorescence-activated cell sorting or particle sorting is a specialized type of flow cytometry. It provides a method for sorting a heterogeneous mixture of particles into two or more containers, one cell at a time, based upon the specific light scattering and fluorescent characteristics of each cell. It records fluorescent signals from individual cells, and physically separates cells of particular interest. The acronym FACS is trademarked and owned by Becton Dickinson.

[0065] The particle suspension is entrained in the center of a narrow, rapidly flowing stream of liquid. The flow is arranged so that there is a large separation between particles relative to their diameter. A vibrating mechanism causes the

stream of particles to break into individual droplets. The system is adjusted so that there is a low probability of more than one particles being in a droplet. Just before the stream breaks into droplets the flow passes through a fluorescence measuring station where the fluorescent character of interest of each particles is measured. An electrical charging ring is placed just at the point where the stream breaks into droplets. A charge is placed on the ring based on the immediately-prior fluorescence intensity measurement and the opposite charge is trapped on the droplet as it breaks from the stream. The charged droplets then fall through an electrostatic deflection system that diverts droplets into containers based upon their charge. In some systems, the charge is applied directly to the stream and the droplet breaking off retains charge of the same sign as the stream. The stream is then returned to neutral after the droplet breaks off.

[0066] By using an apparatus such as a fluorescence activated particle scanning device or FACS® flow cytometer, relative particle fluorescence intensity of the fluorescently-labeled organopolysiloxane and the fluorescently-labeled proteinaceous material can be determined using fluorescence-activated particle sorting. The relative intensity of the fluorescently-labeled organopolysiloxane can be compared to the relative intensity of the fluorescently-labeled proteinaceous material and the amount of proteinaceous material aggregated or agglomerated with the organopolysiloxane can be determined. "Aggregation" of the proteinaceous material with the organopolysiloxane includes proteinaceous material adsorption to organopolysiloxane as well as proteinaceous material aggregation nucleated by organopolysiloxane, and includes any irreversible association between organopolysiloxane and the proteinaceous material.

[0067] Each solution is analyzed by fluorescence activated particle scanning to determine particle composition. Fluorescence activated particle scanning can be used to analyze particle size, morphology, and relative particle fluorescence. Other useful analyses include determination of suspension turbidity, silicone oil droplet number concentration, and silicone oil droplet size distribution. Optical densities can be determined using a PerkinElmer Lambda 35 spectrophotometer (Wellesley, Mass.). After brief and gentle agitation to deflocculate droplet agglomerates, silicone oil suspension optical densities can be measured at 660 nm as functions of time and formulation condition. In aqueous filtrate, proteinaceous material absorbance at 280 nm can be measured to determine mAb concentrations. Alternatively, proteinaceous material concentrations can be measured with a Coomassie dye binding assay (Coomassie Plus™ Better Bradford Assay Kit, Pierce Biotechnology, Rockford, Ill.).

[0068] Silicone oil droplet size distributions can be measured using a Coulter LS230 laser diffraction particle size analyzer (Beckman Coulter, Fullerton, Calif.). Relative size distributions can be measured for suspensions immediately after homogenization and as a function of time up to 2 weeks after suspension preparation. From silicone oil droplet relative size distributions and number concentrations, total silicone oil surface area can be estimated.

[0069] In some non-limiting embodiments, the aqueous suspension further comprises at least one non-ionic surfactant. The non-ionic surfactant can reduce silicone oil coalescence rates. Thus, suspended oil droplets remain in solution longer when non-ionic surfactant is present.

[0070] Non-limiting examples of suitable non-ionic surfactants include acetylenic glycols, alkanolamides, alkanola-

mines, alkyl phenols, fatty acids, fatty alcohols, fatty esters, glycerol esters, monododecyl ethers, phenol derivatives, poloxamers, poloxamines, polyoxyethylene acyl ethers, polyoxyethyleneglycol dodecyl ethers, sorbitols, sorbitan derivatives and mixtures thereof. In some non-limiting embodiments, the non-ionic surfactant is a sorbitan derivative selected from the group consisting of sorbitan fatty acid esters, polyoxyethylene sorbitan fatty acid esters and mixtures thereof. In some non-limiting embodiments, the non-ionic surfactant is a polyoxyethylene sorbitan fatty acid ester, such as Tween 20® polyoxyethylene 20 sorbitan monolaurate, also known as Polysorbate 20. Other useful polyoxyethylene sorbitan fatty acid esters include Polysorbate 21, Polysorbate 40, Polysorbate 60, Polysorbate 61, Polysorbate 65, Polysorbate 80, Polysorbate 81, Polysorbate 85 or Polysorbate 120.

[0071] The amount of non-ionic surfactant in the solution can range from about 0.001 to about 0.5 weight percent on a basis of total weight of the aqueous solution.

[0072] In some non-limiting embodiments, the aqueous suspension further comprises at least one sugar. Sugar can enhance the rate of organopolysiloxane coalescence, such that less surface area of organopolysiloxane is available to attract proteinaceous material. Suitable sugars include monosaccharides, disaccharides, trisaccharides, oligosaccharides and mixtures thereof. Non-limiting examples of suitable sugars include sucrose, lactose, fructose, glucose, galactose, mannose, trehalose and mixtures thereof.

[0073] The amount of sugar in the solution can range from about 0.005 to about 10 weight percent on a basis of total weight of the aqueous solution.

[0074] The combined presence of sugar and non-ionic surfactant can further reduce aggregation of proteinaceous material. In some non-limiting embodiments, the solution can comprise at least one sugar and at least one non-ionic surfactant, such as polyoxyethylene sorbitan fatty acid ester and sucrose, in amounts or concentrations such as are describe above.

[0075] In some non-limiting embodiments, the method further comprises providing a plurality of aqueous suspensions of a fluorescently-labeled organopolysiloxane and a fluorescently-labeled proteinaceous material, wherein each aqueous suspension further comprises at least one aggregation inhibitor selected from the group consisting of non-ionic surfactants and sugars wherein a concentration of the at least one aggregation inhibitor is different in each aqueous suspension, measuring relative particle fluorescence intensity of the fluorescently-labeled organopolysiloxane and the fluorescently-labeled proteinaceous material in each aqueous suspension using fluorescence-activated particle sorting; and comparing the relative intensity of the fluorescently-labeled organopolysiloxane to the relative intensity of the fluorescently-labeled proteinaceous material for each aqueous suspension.

[0076] In some non-limiting embodiments, the method further comprises providing a plurality of aqueous suspensions of a fluorescently-labeled organopolysiloxane and a fluorescently-labeled proteinaceous material, wherein each aqueous suspension further comprises at least one aggregation inhibitor selected from the group consisting of non-ionic surfactants and sugars wherein the at least one aggregation inhibitor is different in each aqueous suspension, measuring relative particle fluorescence intensity of the fluorescently-labeled organopolysiloxane and the fluorescently-labeled proteinaceous material in each aqueous suspension using fluores-

cence-activated particle sorting; and comparing the relative intensity of the fluorescently-labeled organopolysiloxane to the relative intensity of the fluorescently-labeled proteinaceous material for each aqueous suspension. The aggregation inhibitor in each solution is chemically different or of a different type, for example different sugars and/or different non-ionic surfactants.

[0077] Referring to FIG. 10, there is shown a flow chart for a method for preparing and analyzing samples of organopolysiloxane solutions according to the present invention. The solutions can be prepared and analyzed as discussed above and in detail in Example A below.

[0078] In some non-limiting embodiments, the method further comprises selecting at least one aggregation inhibitor for use in a suspension comprising a proteinaceous material based upon the comparison of the relative intensity of the fluorescently-labeled organopolysiloxane to the relative intensity of the fluorescently-labeled proteinaceous material for each aqueous suspension.

[0079] In some non-limiting embodiments, the present invention provides a method for inhibiting the aggregation of a proteinaceous material in a suspension comprising an organopolysiloxane, comprising: (a) providing a plurality of aqueous suspensions of a fluorescently-labeled organopolysiloxane and a fluorescently-labeled proteinaceous material, wherein each aqueous suspension further comprises at least one aggregation inhibitor selected from the group consisting of non-ionic surfactants and sugars wherein (i) the at least one aggregation inhibitor is different in each aqueous suspension, or (ii) the amount of aggregation inhibitor is different in each aqueous solution; (b) measuring relative particle fluorescence intensity of the fluorescently-labeled organopolysiloxane and the fluorescently-labeled proteinaceous material in each aqueous suspension using fluorescence-activated particle sorting; (c) comparing the relative intensity of the fluorescently-labeled organopolysiloxane to the relative intensity of the fluorescently-labeled proteinaceous material for each aqueous suspension; and (d) selecting at least one aggregation inhibitor for use in a suspension comprising a proteinaceous material based upon the comparison of the relative intensity of the fluorescently-labeled organopolysiloxane to the relative intensity of the fluorescently-labeled proteinaceous material for each aqueous suspension.

[0080] By one or more of the above methods, a suitable combination of sugar and non-ionic surfactant (and suitable concentrations thereof) can be determined for use in medical articles which use an organopolysiloxane coating on surfaces in contact with a solution comprising proteinaceous material.

[0081] In some non-limiting embodiments, the present invention provides a medical article, comprising: (a) a container comprising a chamber for receiving a solution, wherein the inner surface of the chamber has a coating thereon prepared from a composition comprising an organopolysiloxane; and (b) a solution comprising: (i) at least one proteinaceous material; (ii) at least one non-ionic surfactant; and (iii) at least one sugar.

[0082] As used herein, "medical article" means an article or device that can be useful for medical treatment. Non-limiting examples of medical articles include syringe assemblies, drug cartridges, needleless injectors, liquid dispensing devices and liquid metering devices. In some embodiments, the medical article is a syringe assembly comprising a syringe chamber or barrel (for receiving the solution comprising proteinaceous material, for example) and a sealing member.

[0083] The chamber can be formed from glass, metal, ceramic, plastic, rubber, or combinations thereof. In some non-limiting embodiments, the chamber is prepared from one or more olefinic polymers, such as polyethylene, polypropylene, poly(1-butene), poly(2-methyl-1-pentene), and/or cyclic polyolefin. For example, the polyolefin can be a homopolymer or a copolymer of an aliphatic monoolefin, the aliphatic monoolefin preferably having about 2 to 6 carbon atoms, such as polypropylene. In some non-limiting embodiments, the polyolefin can be basically linear, but optionally may contain side chains such as are found, for instance, in conventional, low density polyethylene. In some non-limiting embodiments, the polyolefin is at least 50% isotactic. In other embodiments, the polyolefin is at least about 90% isotactic in structure. In some non-limiting embodiments, syndiotactic polymers can be used. In some embodiments, cyclic polyolefins can be used. Non-limiting examples of suitable cyclic polyolefins include norbornene polymers such as are disclosed in U.S. Pat. Nos. 6,525,144, 6,511,756, 5,599,882, and 5,034,482 (each of Nippon Zeon), U.S. Pat. Nos. 7,037,993, 6,995,226, 6,908,970, 6,653,424 and 6,486,264 (each of Zeon Corp.), U.S. Pat. Nos. 7,026,401 and 6,951,898 (Ticona), U.S. Pat. No. 6,063,886 (Mitsui Chemicals), U.S. Pat. Nos. 5,866,662, 5,856,414, 5,623,039 and 5,610,253 (Hoechst), U.S. Pat. Nos. 5,854,349 and 5,650,471 (Mitsui Petrochemical and Hoechst) and as described in "Polycyclic olefins", process Economics Program (July 1998) SRI Consulting, each of the foregoing references being incorporated by reference herein. Non-limiting examples of suitable cyclic polyolefins include ApelTM cyclic polyolefins available from Mitsui Petrochemical, TopasTM cyclic polyolefins available from Ticona Engineering Polymers, ZeonorTM or ZeonexTM cyclic polyolefins available from Zeon Corporation, and cyclic polyolefins available from Promerus LLC.

[0084] The polyolefin can contain a small amount, generally from about 0.1 to 10 percent, of an additional polymer incorporated into the composition by copolymerization with the appropriate monomer. Such copolymers may be added to the composition to enhance other characteristics of the final composition, and may be, for example, polyacrylate, polystyrene, and the like.

[0085] In some non-limiting embodiments, the chamber may be constructed of a polyolefin composition which includes a radiation stabilizing additive to impart radiation stability to the container, such as a mobilizing additive which contributes to the radiation stability of the container, such as for example those disclosed in U.S. Pat. Nos. 4,959,402 and 4,994,552, assigned to Becton, Dickinson and Company and both of which are incorporated herein by reference.

[0086] The other component of the medical article in contact with the chamber is the sealing member. The sealing member can be formed from any elastomeric or plastic material. Elastomers are used in many important and critical applications in medical devices and pharmaceutical packaging. As a class of materials, their unique characteristics, such as flexibility, resilience, extendability, and sealability, have proven particularly well suited for products such as catheters, syringe tips, drug vial articles, tubing, gloves, and hoses. Three primary synthetic thermoset elastomers typically are used in medical applications: polyisoprene rubber, silicone rubber, and butyl rubber. Of the three rubbers, butyl rubber has been the most common choice for articles due to its high cleanness and permeation resistance which enables the rubber to protect oxygen- and water-sensitive drugs.

[0087] Suitable butyl rubbers useful in the method of the present invention include copolymers of isobutylene (about 97-98%) and isoprene (about 2-3%). The butyl rubber can be halogenated with chlorine or bromine. Suitable butyl rubber vulcanizates can provide good abrasion resistance, excellent impermeability to gases, a high dielectric constant, excellent resistance to aging and sunlight, and superior shock-absorbing and vibration-damping qualities to articles formed therefrom. Non-limiting examples of suitable rubber stoppers include those available from West Pharmaceuticals, American Gasket Rubber, Stelmi, and Helvoet Rubber & Plastic Technologies BV.

[0088] Other useful elastomeric copolymers include, without limitation, thermoplastic elastomers, thermoplastic vulcanizates, styrene copolymers such as styrene-butadiene (SBR or SBS) copolymers, styrene-isoprene (SIS) block polymers or styrene-isoprene/butadiene (SIBS), in which the content of styrene in the styrene block copolymer ranges from about 10% to about 70%, and preferably from about 20% to about 50%. Non-limiting examples of suitable styrene-butadiene stoppers are available from Firestone Polymers, Dow, Reichhold, Kokoku Rubber Inc., and Chemix Ltd. Other suitable thermoplastic elastomers are available from GLS, Technor Apex, AES, Mitsubishi and Solvay Engineered Polymers, for example. The elastomer composition can include, without limitation, antioxidants and/or inorganic reinforcing agents to preserve the stability of the elastomer composition.

[0089] In some embodiments, the sealing member can be a stopper, O-ring, plunger tip, or piston, for example. Syringe plunger tips or pistons typically are made of a compressible, resilient material such as rubber, because of the rubber's ability to provide a seal between the plunger and interior housing of the syringe. Syringe plungers, like other equipment used in the care and treatment of patients, have to meet high performance standards, such as the ability to provide a tight seal between the plunger and the barrel of the syringe.

[0090] The organopolysiloxane coating is applied to at least a portion of the sliding surface(s) of the chamber and/or sealing member. In some embodiments, the chamber is coated with the coating described below and the sealing member is uncoated or coated with a polydimethylsiloxane coating. In other embodiments, the sealing member is coated with the coating described below and the chamber is uncoated or coated with a polydimethylsiloxane coating. In other embodiments, both the chamber and sealing member are coated with coatings as described below.

[0091] The chamber and/or sealing member is coated with a coating prepared from a composition comprising one or more organopolysiloxane(s). Application of a coating to the inner surface of the chamber or outer surface of the sealing member may be accomplished by any suitable method, as, for example, dipping, brushing, spraying, and the like. The composition may be applied neat or it may be applied in a solvent, such as low molecular weight silicone, non-toxic chlorinated or fluorinated hydrocarbons, for example, 1,1,2-trichloro-1,2,2-trifluoroethane, freon or conventional hydrocarbon solvents such as alkanes, toluene, petroleum ether, and the like where toxicology is not considered important. The solvent is subsequently removed by evaporation. The coating may be of any convenient thickness and, in practice, the thickness will be determined by such factors as the quantity applied, viscosity of the lubricant, and the temperature of application. For reasons of economy, the coating preferably is applied as thinly as practical, since no significant advantage is gained by

thicker coatings. The exact thickness of the coating does not appear to be critical and very thin coatings, i.e., one or two microns exhibit effective lubricating properties. While not necessary for operability, it is desirable that the thickness of the coating be substantially uniform throughout. The coating can be partially or fully crosslinked after application or partially crosslinked to attach to the substrate, and then fully crosslinked at a later time.

[0092] The coated chamber and/or coated sealing member can be subjected to oxidative treatment, for example, plasma treatment. The plasma treatment may be carried out in any common vacuum or atmospheric plasma generation equipment. Any suitable ionizing plasma may be used, as, for example, a plasma generated by a glow discharge or a corona discharge. The plasma may be generated from a variety of gases or mixtures thereof. Gases frequently used include air, hydrogen, helium, ammonia, nitrogen, oxygen, neon, argon, krypton, and xenon. Any gas pressure may be used, for example, atmospheric pressure or 5 mm of Hg or below, such as about 0.1 to about 1.0 mm of Hg. In some embodiments such as atmospheric oxidative methods, the ionizing plasma is introduced directly from a small port in the chamber or through the opening later sealed by the sealing member. The external surface of the coated sealing member can be treated directly similarly to current corona or plasma treatment methods. In other embodiments, such as vacuum based equipment, the plasma can be excited around the coated sealing member or coated chamber and allowed to diffuse into the chamber and sealing member features. Alternatively, the plasma may be excited within the interior of the open chamber by properly controlling electrode position. After oxidative treatment, the treated chamber and/or treated sealing member can be subjected to heat treatment or irradiation with an isotope (such as gamma radiation), electron beam, or ultraviolet radiation. Alternatively, the treated chamber and/or treated sealing member can be heat treated via oven or radio frequency (RF). In the case of oven crosslinking, temperatures can range from about 120° to about 140° C. and residence time in the oven is generally about 30 to about 40 seconds, depending on the precise formulation. If RF techniques are used, the coil should conduct enough heat to obtain a substrate surface temperature of about 150° to about 200° C. At these temperatures, only about 2 to about 4 seconds are required for cure.

[0093] In some embodiments, the coating is at least partially crosslinked by irradiation with an isotope, electron beam, or ultraviolet radiation. This technique has the advantage of sterilizing as well, which is useful in medical applications. Radiation sterilization in the form of ionizing radiation commonly is used in hospitals for medical devices such as catheters, surgical items, and critical care tools. Gamma irradiation exerts a microbicidal effect by oxidizing biological tissue, and thus provides a simple, rapid and efficacious method of sterilization. Gamma rays are used either from a cobalt-60 (⁶⁰Co) isotope source or from a machine-generated accelerated electron source. Sufficient exposures are achieved when the materials to be sterilized are moved around an exposed ⁶⁰Co source for a defined period of time. The most commonly used dose for sterilizing medical articles is about 5 to about 100 kGy, for example, 5-50 kGy.

[0094] In some embodiments, a surface lubricant layer about 0.3 to 10, preferably about 0.8 to 4.0 microns thick may be applied over the crosslinked organopolysiloxane coating described above. The surface lubricant can be conventional silicone oil (organopolysiloxane) of viscosity about 100 to

1,000,000; 100 to 60,000; or preferably about 1,000 to 12,500 cSt. The surface lubricating layer may be applied by any of the conventional methods described above. The preferred methods for applying the surface lubricant are by spraying or dipping the syringe barrel into a solution, about 4% by weight, of the surface lubricant in a solvent such as chloroform, dichloromethane or preferably a chlorofluorocarbon, such as FREON™ TF. The surface lubricant may optionally be lightly crosslinked by oxidative treatment and/or radiation.

[0095] In some embodiments in which both the chamber and sealing member are coated with organopolysiloxanes, the viscosity of the organopolysiloxane coating the chamber can be greater than the viscosity of the organopolysiloxane coating the sealing member. For example, the viscosity of the organopolysiloxane coating the chamber can be 12,500 cSt, while the viscosity of the organopolysiloxane coating the sealing member can be 1,000 cSt. In other embodiments, the viscosity of the organopolysiloxane coating the chamber can be equal to or less than the viscosity of the organopolysiloxane coating the sealing member. For example, the viscosity of the organopolysiloxane coating the chamber can be 12,500 cSt, while the viscosity of the organopolysiloxane coating the sealing member can be 100,000 cSt.

[0096] In some embodiments, the coated articles are subjected to a sterilization treatment. Many sterilization techniques are available today to sterilize medical devices to eliminate living organisms such as bacteria, yeasts, mold and viruses. Commonly used sterilization techniques used for medical devices include autoclaving, ethylene oxide (EtO) or gamma irradiation, as well as more recently introduced systems that involve low-temperature gas plasma and vapor phase sterilants.

[0097] The chamber of the medical article is at least partially filled with the solution comprising: (i) at least one proteinaceous material; (ii) at least one non-ionic surfactant; and (iii) at least one sugar. The components and amounts of the solution are described in detail above. Generally, the solution can be filtered prior to filling the chamber, for example by filtration through a 0.22 μm filter and distributed into the sterile chamber under aseptic conditions well known to those skilled in the art.

[0098] The present invention is more particularly described in the following examples, which are intended to be illustrative only, as numerous modifications and variations therein will be apparent to those skilled in the art.

EXAMPLES

Example A

[0099] This example studies the effects of sucrose and a non-ionic surfactant (Tween 20® polyoxyethylene 20 sorbitan monolaurate non-ionic surfactant) on aggregation of Herceptin® trastuzumab monoclonal antibody (mAb) and on silicone oil droplet characteristics. In this investigation, no attempt was made to distinguish mAb adsorption to silicone oil from mAb aggregation nucleated by silicone oil. Instead, any irreversible association between silicone oil and mAb is simply referred to as "aggregation".

[0100] Four formulations were analyzed in this study, as detailed in Table 1. Each formulation was analyzed by fluorescence activated particle scanning to determine particle composition. For a subset of these formulations, fuller analysis was performed. Suspension turbidity, silicone oil droplet number concentration, and silicone oil droplet size distribu-

tion were measured. After filtration, Herceptin® trastuzumab concentrations were measured in aqueous filtrate.

[0101] A solution of the recombinant humanized monoclonal antibody (rh-mAb) Herceptin® (trastuzumab, Genentech, Inc.) was exchanged into 10 mM sodium acetate, pH 5.0, by extensive dialysis (Pierce Slide-A-Lyzer, 3500 MWCO). Appropriate volumes of separate solutions of sucrose and/or polysorbate 20 (Tween 20) were mixed with purified Herceptin® solutions to a final mAb concentration of 1 mg/mL. Concentrations of formulation additives (sucrose, NaCl and surfactants) were systematically varied as described in appropriate results sections. All chemicals were of reagent grade or higher.

TABLE 1

Formulation No.	Formulation Component			
	Silicone oil (1% v/v)	mAb (1 mg/mL)	Sucrose (0.5M)	Tween 20® Non-ionic surfactant (0.005%)
A	x	x		
B	x	x	x	
C	x	x		x
D	x	x	x	x

[0102] Suspensions of medical grade silicone oil (ca. 0.5% v/v) in aqueous buffer (10 mM sodium acetate, pH 5.0) were created by high pressure homogenization. Polydimethylsiloxane medical fluid (Dow Corning 360, 1000 cSt) was added to an aqueous buffer and passed once through a high pressure homogenizer (Emulsiflex C5 Homogenizer commercially available from Avestin, Inc.). Final suspensions for analysis were created by mixing mAb solutions containing formulation additives with suspensions of silicone oil in buffer immediately following homogenization.

[0103] After varying periods of incubation, suspensions were filtered (Whatman Anotop 10, 0.02 µm syringe filter) to separate aqueous and oil phases. Just prior to filtration, suspensions were held for ca. 2 min. to allow oil droplets near the filter membrane to sediment. As a control to test the degree of phase separation, aqueous nitrate fluorescence was measured after labeling silicone oil with Nile red dye. Insignificant fluorescence measurements at 628 nm demonstrated adequate separation.

[0104] Optical densities of two sample types were measured with a PerkinElmer Lambda 35 spectrophotometer (Wellesley, Mass.). After brief and gentle agitation to deflocculate droplet agglomerates, homogeneous silicone oil suspension optical densities were measured at 660 nm as functions of time and formulation condition. In aqueous filtrate, mAb absorbance at 280 nm was measured to determine mAb concentrations. Alternatively, mAb concentrations were measured with a Coomassie dye binding assay (Coomassie Plus™ Better Bradford Assay Kit, Pierce Biotechnology, Rockford, Ill.).

[0105] Silicone oil droplet size distributions were measured using a Coulter LS230 laser diffraction particle size analyzer (Beckman Coulter, Fullerton, Calif.). Relative size distributions were measured for suspensions immediately after homogenization and as a function of time up to 2 weeks after suspension preparation. From silicone oil droplet relative size distributions and number concentrations, total silicone oil surface area was estimated.

[0106] Fluorescence activated particle scanning can be used to analyze particle size, morphology, and relative particle fluorescence. Only particles of a threshold size (>1 µm diameter) are analyzed by the technique. For scanned particles, forward light scattering (FSC, 1800 light scattering), side light scattering (SSC, 90° light scattering), green fluorescence intensity (FL1, 525-585 nm) and red fluorescence intensity (FL2, 585-600 nm) were measured. Herceptin® trastuzumab molecules were chemically labeled with Alexa Fluor® 488 dye (Invitrogen Corporation, Carlsbad, Calif.) according to well-documented protocols (MP 00143, Amine-Reactive Probes, Invitrogen Corporation). To label the silicone oil, Nile red dye was dissolved in silicone oil at 5 mg/mL. Nile red, 9-diethylamino-5-benzophenoxazine-5-one, is an extremely hydrophobic dye whose fluorescence is fully quenched in water. Alexa Fluor® 488 dye has an emission maximum of 519 nm, and Nile red dye has an emission maximum of 628 nm. Suspensions with chemically labeled mAb and dyed silicone oil were scanned with a BD FACScan™ Flow Cytometer analyzer (Becton, Dickinson and Company, Franklin Lakes, N.J.). The degree to which Herceptin® trastuzumab interacts with silicone oil droplets in suspension depends on the formulation environment and incubation time. FIGS. 1A and 1B illustrate the association of mAb with silicone oil. Symbols are arithmetic means of three replicates measured by difference between initial mAb concentration and mAb concentration in filtrate. Error bars represent ±1 standard deviation. In all series, mAb concentration is 1 mg/mL. In both panels, squares denote formulations with 0.5 M sucrose, mAb, and silicone oil. In FIG. 1A, triangles denote formulations with only mAb and oil. In FIG. 1B, triangles denote formulations with 0.5 M sucrose, 0.005% Tween 20® non-ionic surfactant, mAb, and oil.

[0107] After suspension, incubation and filtration, formulations with sucrose contained higher concentrations of mAb in aqueous filtrate than those without sucrose at sufficiently long incubation times. Thus, the presence of sucrose reduces mAb aggregation at long times, as shown in FIG. 1A. FIG. 1B compares the formulation with sucrose shown in panel A with a formulation containing sucrose and non-ionic surfactant. The addition of non-ionic surfactant further reduced mAb association with silicone oil.

[0108] By measuring fluorescence intensities of particles containing labeled mAb and labeled silicone oil, the effects of formulation additives on mAb aggregation can be better understood. FIGS. 2A-2D illustrate the fluorescence intensity scatter plots of two wavelength bands. In FIGS. 2A-2D, FL1 intensity is directly proportional to Alexafluor 488 labeled mAb concentration. FL2 fluorescence intensity is directly proportional to Nile red labeled silicone oil volume. FL1 and FL2 intensities scale roughly with particle size, encompassing a size range greater than one order of magnitude. Experimental settings were optimized such that the relative intensities of mAb and silicone oil would be equivalent in FIG. 2A. These settings were retained for all other formulations (FIGS. 2B-2D). Thus, trends within and comparisons between panels are meaningful; absolute intensity values are not. Axes units were arbitrary. Histograms represent particle intensity distributions. Histogram scales range from 0 to 0.5. FIGS. 2A-2D depict formulations of 1 mg/mL mAb and silicone oil with various combinations of sucrose and surfactants: A neither sucrose nor surfactant; B 0.5 M sucrose; C 0.005% Tween 20® non-ionic surfactant; and D 0.5 M sucrose and 0.005% Tween 20® non-ionic surfactant.

[0109] Each of FIGS. 2A-2D corresponds to the formulation with the same letter in Table 1. Thus, the two panels on the left (FIGS. 2A and 2C) represent formulations without sucrose. The two panels on the right (FIGS. 2B and 2D) represent formulations containing sucrose. From top to bottom, panels represent no surfactant (FIGS. 2A and 2B) and non-ionic surfactant (FIGS. 2C and 2D).

[0110] FIG. 2A shows particle intensities for a formulation containing only mAb and silicone oil. The scatter plot is linear across an order of magnitude in size (ca. 1-10 μm), indicating that the ratio of mAb concentration to silicone oil volume is constant for particles of different sizes. The addition of Tween 20[®] non-ionic surfactant (FIG. 2C) does not significantly affect FL1 or FL2 intensities. When sucrose is introduced to the formulation (right panels), ranges in fluorescence intensity are generally compressed. Moreover, the combined presence of sucrose and Tween 20[®] non-ionic surfactant greatly reduces mAb aggregation: more than half of the particles register negligible FL1 intensity (FIG. 2D). In FIG. 2B, multiple data trends suggest two or more distinct particle populations.

[0111] Deviations from linear in the scatter plot demonstrate that as oil droplets increase in size, regimes exist where particle growth is not linear. Instead, it appears that differences in surface roughness exist for particles of essentially the same size. While not intending to be bound by any theory, one plausible explanation of the non-linear, non-spherical particle growth is that particles grow by addition of smaller droplets without immediate coalescence. This "creaming" effect creates particles which are multi-droplet agglomerates. Fluorescence scanning allows measurement of antibody/oil contributions to particles as the particles agglomerate.

[0112] As particles grow in size (corresponding to an increase in red and green intensities) the ratio of antibody to oil remains generally constant. This supports the hypothesis that smaller oil droplets combine to form larger multi-droplet particles. It appears that antibody molecules adsorbed to the surface of small silicone oil droplets remain associated with the silicone oil as droplets agglomerate to form larger particles.

[0113] FIGS. 3A-3D are scatter plots of side light scattering (90° light scattering) versus forward light scattering (180° light scattering) of silicone oil droplets in aqueous mAb formulations (1 mg/mL) containing various combinations of sucrose and surfactants for the same four formulations A-D (see Table 1). Forward light scattering intensity is affected primarily by particle size, whereas side light scattering intensity is influenced by particle size and surface roughness. Axes units are arbitrary. Histograms represent particle distributions. Histogram scales range from 0 to 0.5. FIGS. 3A-3D depict formulations of 1 mg/mL mAb and silicone oil with various combinations of sucrose and surfactants: A neither sucrose nor surfactant, B 0.5 M sucrose, C 0.005% Tween 20[®] non-ionic surfactant, and D 0.5 M sucrose and 0.005% Tween 20[®] non-ionic surfactant. As shown in FIGS. 3B and 3D, the addition of sucrose greatly reduces average particle size α -axis) and surface roughness (y-axis).

[0114] Relative rates of silicone oil coalescence are plotted in FIGS. 4A and 4B. FIGS. 4A and 4B show time dependence of light obscuration in mAb formulations with suspended silicone oil. Samples of each formulation were analyzed after brief swirling to deflocculate and de-cream suspensions. The initial time point of each formulation was normalized to the same value. Symbols are arithmetic means of three replicates

and error bars represent ± 1 standard deviation. In each of FIGS. 4A and 4B, mAb concentration is 1 mg/mL. In FIGS. 4A and 4B, squares denote formulations with 0.5 M sucrose, mAb, and silicone oil. In FIG. 4A, triangles denote formulations with only mAb and oil. FIG. 4A compares formulations of mAb and silicone oil with and without sucrose. As shown in FIG. 4A, sucrose enhanced the rate of silicone oil coalescence. In FIG. 4B, triangles denote formulations with 0.5 M sucrose, 0.005% Tween 20[®] non-ionic surfactant, mAb, and oil. FIG. 4B compares formulations with sucrose to formulations with sucrose and a non-ionic surfactant. As shown in FIG. 4B, Tween 20[®] non-ionic surfactants reduced silicone oil coalescence rates. Thus, suspended oil droplets remain in solution longer when Tween 20[®] non-ionic surfactant was present and shorter when sucrose was present.

[0115] After estimating silicone oil surface area in each formulation at each time point, surface area normalized mAb aggregation can be calculated (FIGS. 5A-5B). Each of FIGS. 5A-5B corresponds to the same panel in FIG. 1, modified to account for silicone oil surface area. Symbols are arithmetic means of three replicates measured by difference between initial mAb concentration and mAb concentration in filtrate. Differences are divided by formulation- and time-specific silicone oil surface areas. Error bars represent ± 1 standard deviation. In each of FIGS. 5A and 5B, mAb concentration is 1 mg/mL. In all panels, dashed lines represent an estimate of monolayer coverage and squares denote formulations with 0.5 M sucrose, mAb, and silicone oil. In FIG. 5A, triangles denote formulations with only mAb and oil. In FIG. 5B, triangles denote formulations with 0.5 M sucrose, 0.005% Tween 20[®] non-ionic surfactant, mAb, and oil. Normalized by silicone oil surface area, mAb aggregation actually increases in the presence of sucrose at sufficiently long times, as shown in FIG. 5A. In formulations containing sucrose and Tween 20[®] non-ionic surfactant, mAb/oil association levels remain low and relatively constant (FIG. 5B).

[0116] As shown in the above Figures, formulation additives can influence silicone oil droplet coalescence, levels of mAb exposure to silicone oil, and mAb aggregation. Moreover, combined effects of two or more formulation additives are sometimes more significant than the separate effects of each. Specifically, formulations containing both sucrose and Tween 20[®] non-ionic surfactant effectively reduce association of mAb with silicone oil, and addition of sucrose to formulations of markedly alters silicone oil droplet characteristics.

[0117] While not intending to be bound by any theory, the mechanism whereby sucrose reduces association of mAb with silicone oil is believed to be coalescence driven. In the above example, sucrose increases the rate of silicone oil coalescence, as shown in FIG. 4A. As droplets coalesce, total silicone oil surface area decreases. Because reduced surface area is available in formulations with sucrose, mAb aggregation rates decline at sufficiently long times (FIG. 1A). Interestingly, sucrose increases the extent of mAb/silicone oil association per silicone oil surface unit (FIG. 5A). Even so, overall aggregation rates improve due to enhanced coalescence. Thus, the addition of sucrose to therapeutic mAb formulations is beneficial not only for mAb stabilization, but potentially to reduce its exposure to silicone oil surfaces.

[0118] The addition of Tween 20[®] non-ionic surfactant to formulations containing sucrose can further reduce mAb/oil association levels. This effect is especially evident at short times (FIG. 4B). Interestingly, Tween 20[®] non-ionic surfac-

tant's effectiveness in inhibiting mAb/oil association is enhanced by the co-presence of sucrose, as shown in FIGS. 2C and 2D. In the absence of sucrose, fluorescence intensity scatter plots for formulations with Tween 20® non-ionic surfactant (FIG. 2C) do not significantly differ from those without Tween 20® non-ionic surfactant (FIG. 2A). However, when the sugar and non-ionic surfactant are both present in the formulation (FIG. 2D), reduction in mAb/oil association is enhanced.

[0119] The mechanism by which sucrose and Tween 200 non-ionic surfactant together prevent mAb aggregation differs from that of sucrose alone. As evidenced in FIG. 4B, the addition of Tween 20® non-ionic surfactant to formulations containing sucrose slows oil coalescence rates. From droplet size and number concentration measurements, suspended silicone oil surface area remains relatively constant up to 2 weeks after homogenization. Formulations with sucrose and Tween 20® non-ionic surfactant inhibit mAb aggregation, exhibiting nearly a factor of 2 reduction in aggregation over the next best formulation with sucrose but without Tween 20® non-ionic surfactant (FIG. 5B).

[0120] Because light scattering dot plots of silicone oil suspensions without mAb appear nearly identical to those shown in FIGS. 3 and 4, the scatter plot profiles primarily reveal information about silicone oil droplet characteristics, namely flocculation and coalescence. Sucrose-driven increases in silicone oil coalescence and creaming rates influence these dot plots. In formulations with sucrose, droplets are smaller, have less surface complexity, and have a tighter size range than in formulations without sucrose.

[0121] In formulations without sucrose in FIG. 3, the constrained data trends are of interest. Hypothetically, perfectly smooth spherical particles of varying size would create a linear trend, provided that perpendicular light scattering is optimally calibrated. Variations from linear indicate shape deviation from spherical. While not intending to be bound by any theory, it is believed that deviations observed in this study result from droplet flocculation without immediate coalescence. Thus, large particles composed of smaller spherical droplets exhibit surface complexity that does not exist with spherical particles. FIG. 6 is hypothetical representation of silicone oil droplet and agglomerate distribution based on forward and side light scattering. A linear trend (dotted line) would result from spherical droplets of varying diameter. Deviations from linear in the scatter plot profile can be explained by droplet agglomeration without immediate coalescence.

[0122] The presence of persistent agglomerates of droplets (i.e., floc which does not coalesce rapidly) may explain other phenomena observed in this investigation. Particle size distributions measured by laminar flow light obscuration (likely inducing de-flocculation) consistently revealed tighter ranges in droplet size than measurements by fluorescence activated particle scanning. Additionally, in many formulations without sucrose, the ratio of mAb concentration to silicone oil volume was relatively constant over a wide range in particle size. With slow coalescence, adsorbed mAb is not necessarily expelled from silicone oil surfaces upon flocculation. MAb concentration can then grow linearly with silicone oil agglomerate volume instead of surface area.

[0123] Divided trends in FL1 versus FL2 scatter plots can be explained by the presence of separate populations of particles. These trends occur in formulations with sucrose (FIG. 2B). Depending on formulation conditions, combinations of

several particle populations may exist: mAb aggregates without silicone oil, mAb aggregates with a silicone oil nucleus, and silicone oil droplet agglomerates with mAb adsorbed to droplet surfaces. It is possible that hydrophobic pockets of mAb aggregates strip Nile red dye from silicone oil. Alternately, a silicone oil droplet could act as a nucleus for mAb aggregation.

[0124] Therapeutic mAb formulations containing sucrose and Tween 20® non-ionic surfactant notably reduce mAb aggregation in the presence of silicone oil. To a smaller extent, formulations with only sucrose reduce mAb aggregation, likely due to increased silicone oil coalescence rates. Because silicone oil contamination has been shown to induce protein aggregation, successful formulation strategies to reduce protein aggregation can be important for products exposed to silicone oil. The addition of sucrose to therapeutic protein formulations may reduce protein exposure to silicone oil surfaces. As shown in the above Example, formulations containing sucrose and a non-ionic surfactant can inhibit silicone oil induced protein aggregation.

Example B

Effect of Oil Viscosity on Oil Loading in Suspension

[0125] Medical grade silicone oil was added to aqueous solutions with and without non-ionic surfactant as shown in Table 2. Concentration and viscosity of silicone oil in each sample is set forth in Table 2 below. FIG. 7 shows the influence of oil viscosity on oil loading indirectly by measurement of optical density at 600 nm. Optical density at 600 nm (OD_{600}) is an indirect measure of suspended oil concentration. As shown in FIG. 7 and Table 2, lower oil viscosity reflects higher initial OD_{600} , which in turn permits higher oil loading. As shown in FIGS. 8 and 9, there was no qualitative difference in coalescence behavior of suspended oil droplets of differing viscosity (1,000 cSt vs. 12,500 cSt) polydimethylsiloxane for the samples tested.

TABLE 2

Oil Type ($c_{oil}=0.5\%$)	Initial OD_{600} (au)
350 cSt	0.21
1000 cSt	0.12
12500 cSt	0.04
350 cSt 0.1% Tween 20 ®	0.53
1000 cSt 0.1% Tween 20 ®	0.13
12500 cSt 0.1% Tween 20 ®	0.16

[0126] The present invention has been described with reference to specific details of particular embodiments thereof. It is not intended that such details be regarded as limitations upon the scope of the invention except insofar as and to the extent that they are included in the accompanying claims.

What is claimed is:

1. A medical article, comprising:

- (a) a container comprising a chamber for receiving a solution, wherein the inner surface of the chamber has a coating thereon prepared from a composition comprising an organopolysiloxane; and

- (b) a solution comprising:
 - (i) at least one proteinaceous material;
 - (ii) at least one non-ionic surfactant; and
 - (iii) at least one sugar.
- 2. The medical article according to claim 1, wherein the chamber is selected from the group consisting of a syringe barrel, drug cartridge container, needleless injector container, liquid dispensing device container, and liquid metering device container.
- 3. The medical article according to claim 2, wherein the chamber is a syringe barrel.
- 4. The medical article according to claim 1, wherein the chamber is formed from glass, metal, ceramic, plastic, rubber, or combinations thereof.
- 5. The medical article according to claim 1, wherein the chamber is prepared from an olefinic polymer selected from the group consisting of polyethylene, polypropylene, poly(1-butene), poly(2-methyl-1-pentene), and cyclic polyolefins.

- 6. The medical article according to claim 1, wherein the organopolysiloxane is polydimethylsiloxane.
- 7. The medical article according to claim 1, further comprising a sealing member having an exterior surface in sliding engagement with at least a portion of the interior surface of the chamber.
- 8. The medical article according to claim 1, wherein the sugar is selected from the group consisting of monosaccharides, disaccharides, trisaccharides, oligosaccharides and mixtures thereof.
- 9. A medical article, comprising:
 - (a) a container comprising a chamber for receiving a solution, wherein the inner surface of the chamber has a coating thereon prepared from a composition comprising an organopolysiloxane; and
 - (b) a solution comprising:
 - (i) at least one proteinaceous material; and
 - (ii) at least one non-ionic surfactant.

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