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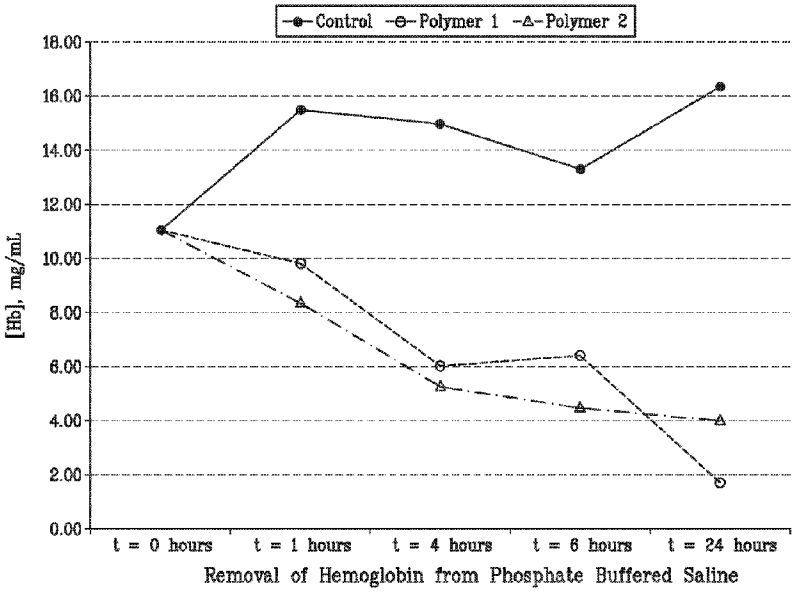
(54) **Titre : SORBANT POLYMERE PERMETTANT D'ELIMINER LES IMPURETES PRESENTES DANS LE SANG ENTIER ET LES PRODUITS SANGUINS**
(54) **Title: POLYMERIC SORBENT FOR REMOVAL OF IMPURITIES FROM WHOLE BLOOD AND BLOOD PRODUCTS**



(57) **Abrégé/Abstract:**
Methods of treating blood, blood products or physiologic fluid maximize shelf life and/or minimize transfusion related complications such as non-hemolytic transfusion reactions such as fever, transfusion-related acute lung injury (TRALI), transfusion associated dyspnea (TAD), and allergic reactions by removing undesirable molecules in the blood, blood product or physiologic fluid milieu through use of a sorbent. The blood purification devices comprise: (a) a compliant container suitable for the storage of blood, blood product or physiologic fluid; (b) sorbent comprising hemocompatible material suitable for treating blood, blood product or physiologic fluid, the sorbent performing at least one of (i) increasing shelf life of the blood, blood product or physiologic fluid, (ii) maintaining freshness of new blood, blood product or physiologic fluid, and (iii) removing undesirable molecules from the blood, blood product or physiologic fluid; where the sorbent is contained within the compliant container.

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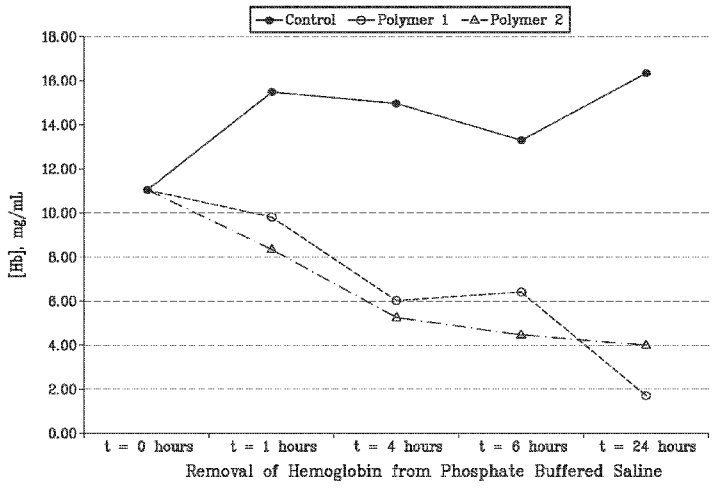

FIG. 4

(57) **Abstract**: Methods of treating blood, blood products or physiologic fluid maximize shelf life and/or minimize transfusion related complications such as non-hemolytic transfusion reactions such as fever, transfusion-related acute lung injury (TRALI), transfusion associated dyspnea (TAD), and allergic reactions by removing undesirable molecules in the blood, blood product or physiologic fluid milieu through use of a sorbent. The blood purification devices comprise: (a) a compliant container suitable for the storage of blood, blood product or physiologic fluid; (b) sorbent comprising hemocompatible material suitable for treating blood, blood product or physiologic fluid, the sorbent performing at least one of (i) increasing shelf life of the blood, blood product or physiologic fluid, (ii) maintaining freshness of new blood, blood product or physiologic fluid, and (iii) removing undesirable molecules from the blood, blood product or physiologic fluid; where the sorbent is contained within the compliant container.

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POLYMERIC SORBENT FOR REMOVAL OF IMPURITIES FROM WHOLE BLOOD AND BLOOD PRODUCTS

RELATED APPLICATIONS

[0001] This application claims priority to U.S. Patent Application No. 13/344,166, filed January 5, 2012, and also claims benefit to U.S. Provisional Application Serial No. 61/430,374.

TECHNICAL FIELD

[0002] The present invention concerns compositions and methods useful in the removal of cytokines, bioactive lipids, free hemoglobin, membrane or cellular degradation products, inflammatory mediators, vasoactive substances, foreign antigens, drugs, antibodies from blood and blood products, and other substances that can cause unwanted transfusion reactions.

BACKGROUND

[0003] The transfusion of whole blood or derivatives of whole blood ("blood products") are literally the lifeblood of patients with a range of conditions from severe trauma to surgery to cancer. According to the American Red Cross, there are more than 14 million packed red blood cell (pRBC) transfusions per year in the United States with 1 in every ten admissions to US hospitals requiring a blood transfusion on average. A similar number of transfusions of other fractions of whole blood, or blood products, such as platelets, white blood cells, plasma, albumin, immunoglobulins, clotting factors and cryoprecipitate, are administered each year. The critical need for blood extends to the military, where logistics of blood transport and storage are complicated and 8% of all hospital admissions during Operation Iraqi Freedom required massive transfusions, defined as more than 10 units of blood in the first 24 hours. Whole blood and blood products will be collectively referred to herein as "blood".

[0004] Blood has a limited life span. A typical pRBC unit has a usable life of only 42 days while platelets must be used within 5 days of donation. This, coupled with

the high demand for blood, has led to periodic blood shortages. But many medical experts believe fresh blood should be used even sooner, within 2–4 weeks. Retrospective studies have implicated transfusions of "older" blood with an increased risk of non-hemolytic transfusion reactions such as fever, transfusion related acute lung injury (TRALI), transfusion associated dyspnea (TAD), allergic reactions, infection, death and other complications. In one of these studies, the risk of in-hospital death increased by 2% for each day a packed red cell unit aged. Because of this, extending the useful life of blood products and improving the quality of blood would be helpful.

SUMMARY

[0005] In some aspects, the invention concerns blood purification devices comprising: (a) a compliant container suitable for the storage of blood, blood product or physiologic fluid; (b) sorbent comprising hemocompatible material suitable for treating blood, blood product or physiologic fluid, the sorbent performing at least one of (i) increasing shelf life of the blood, blood product or physiologic fluid, (ii) maintaining freshness of new blood, blood product or physiologic fluid, and (iii) removing undesirable molecules from the blood, blood product or physiologic fluid; where the sorbent is contained within the compliant container.

[0006] In certain aspects, the invention concerns sorbent compositions, comprising a plurality of particles characterized as having a diameter in the range of from about 0.1 micron meters to about 2 centimeters, the particles comprising a hemocompatible porous polymer characterized as having a total pore volume of pore sizes in the range of from 10 Å to 10,000 Å, the total pore volume being in the range of from about 0.5 cc/g to about 3.0 cc/g based on dry polymer weight.

[0007] The invention also concerns methods of treating blood, blood product or physiologic fluid that (i) increase shelf life, (ii) maintain freshness of new blood, and/or (iii) remove undesirable molecules by use of a sorbent, the sorbent being contained within a compliant container suitable for the storage of blood, blood product or physiologic fluid and the sorbent being in a plurality of solid forms that are substantially free-flowing within the compliant container. In some embodiments the blood, blood product or physiologic fluid is a stored blood, blood product or physiologic fluid. In

some embodiments, the blood, blood product or physiologic fluid is treated prior to storage.

[0008] Certain aspects of the invention concern methods of making a blood, blood product or physiologic fluid purification device comprising placing sorbent comprising hemocompatible material in a compliant container suitable for the storage of blood, blood products, or physiological fluid; wherein the hemocompatible material suitable for treating blood, blood product, or physiologic fluid, the sorbent performing at least one of (i) increasing shelf life of the blood, blood product or physiologic fluid, (ii) maintaining freshness of new blood, blood product or physiologic fluid, and (iii) removing undesirable molecules from the blood, blood product or physiologic fluid; and the sorbent being contained within said compliant container and said sorbent being in a plurality of solid forms that are substantially free-flowing within said compliant container.

[0009] The invention also concerns methods of treating blood, blood product, or physiologic fluid, said method comprising: (a) contacting the blood, blood product, or physiologic fluid with a sorbent, the sorbent performing at least one of (i) increasing shelf life, (ii) maintaining freshness of new blood, and/or (iii) removing undesirable molecules; and (b) placing the blood, blood product, or physiologic fluid from step (b) in a container for storage or into an animal. In some embodiments, the animal is a human. In some embodiments, the contacting takes place in a filter device. The filter may be used when administering blood to a patient between the blood bag (or potentially integrated into the blood bag) and the patient. The filter may also be used between a blood donor and the whole blood collection bag. In another embodiment, the filter may be used between the whole blood, collection bag and the blood storage bag.

[0009a] The invention also concerns a blood, blood product or physiologic fluid storage bag comprising: (a) a bag configured for the storage of blood, blood products or physiologic fluids; (b) a sorbent comprising hemocompatible material configured for treating blood, blood product or physiologic fluid, said sorbent increasing shelf life of the blood, blood product or physiologic fluid; said sorbent being contained within said bag; wherein said sorbent is free-flowing within said bag; wherein said sorbent being a plurality of solid forms; and wherein said hemocompatible material is a crosslinked polymer produced using one or

more polymerizable monomer, a cross-linking agent and a porogen, wherein the polymerizable monomers comprise one or more monomers selected from the group consisting of divinylbenzene, ethylvinylbenzene, styrene, ethylstyrene, acrylonitrile, butyl methacrylate, octyl methacrylate, butyl acrylate, octyl acrylate, cetyl methacrylate, cetyl acrylate, ethyl methacrylate, ethyl acrylate, vinyltoluene, vinylnaphthalene, vinylbenzyl alcohol, vinylformamide, methyl methacrylate, methyl acrylate, trivinylbenzene, divinylnaphthalene, trivinylcyclohexane, divinylsulfone, trimethylolpropane trimethacrylate, trimethylolpropane dimethacrylate, trimethylolpropane triacrylate, trimethylolpropane diacrylate, pentaerythritol dimethacrylate, pentaerythritol trimethacrylate, pentaerythritol tetramethacrylate, pentaerythritol diacrylate, pentaerythritol triacrylate, pentaerythritol tetraacrylate, dipentaerythritol dimethacrylate, dipentaerythritol trimethacrylate, dipentaerythritol tetramethacrylate, dipentaerythritol diacrylate, dipentaerythritol triacrylate, dipentaerythritol tetraacrylate, and divinylformamide.

[0009b] The invention also concerns a sorbent composition, comprising a plurality of particles having a diameter in the range of from 0.1 micron meters to 2 centimeters, the particles comprising a hemocompatible porous polymer having a total volume of pore sizes in the range of from 10 Å to 10,000 Å of from about 0.5 cc/g to about 3.0 cc/g based on dry polymer weight, wherein the sorbent composition is free-flowing.

[0009c] The invention also concerns a method of treating blood, blood products, or physiologic fluids to provide at least one of increasing shelf life of the bloods, blood products or physiologic fluids and removing undesirable molecules from the blood, blood products or physiologic fluids, the method comprising contacting the bloods, blood products, or physiologic fluids with a sorbent, wherein said sorbent is contained within a bag configured for the storage of blood, blood products or physiologic fluid, wherein said sorbent is free-flowing within said bag, and wherein said hemocompatible material is a crosslinked polymer produced using one or more polymerizable monomer, a cross-linking agent and a porogen, wherein the polymerizable monomers comprise one or more monomers selected from the group consisting of divinylbenzene, ethylvinylbenzene, styrene, ethylstyrene, acrylonitrile, butyl methacrylate, octyl methacrylate, butyl acrylate, octyl acrylate, cetyl methacrylate, cetyl acrylate, ethyl methacrylate, ethyl acrylate, vinyltoluene, vinylnaphthalene, vinylbenzyl

alcohol, vinylformamide, methyl methacrylate, methyl acrylate, trivinylbenzene, divinylnaphthalene, trivinylcyclohexane, divinylsulfone, trimethylolpropane trimethacrylate, trimethylolpropane dimethacrylate, trimethylolpropane triacrylate, trimethylolpropane diacrylate, pentaerythritol dimethacrylate, pentaerythritol trimethacrylate, pentaerythritol tetramethacrylate, pentaerythritol diacrylate, pentaerythritol triacrylate, pentaerythritol tetraacrylate, dipentaerythritol dimethacrylate, dipentaerythritol trimethacrylate, dipentaerythritol tetramethacrylate, dipentaerythritol diacrylate, dipentaerythritol triacrylate, dipentaerythritol tetraacrylate, and divinylformamide.

[0009d] The invention also concerns the method as described herein, wherein said sorbent is in container configured to hold blood, wherein said container comprises a permeable membrane or barrier, and wherein said sorbent is separated from the blood by the permeable membrane or barrier, the permeable membrane or barrier allowing fluid but not cells to interact with the sorbent.

[0009e] The invention also concerns a method of treating blood, blood products, or physiologic fluids, said method comprising: (a) contacting said blood, blood products, or physiologic fluids with a sorbent in a first bag, said sorbent performing at least one of increasing shelf life, and removing undesirable molecules; and (b) placing the blood, blood products, or physiologic fluids from step (a) into a second bag for storage; wherein said sorbent is free-flowing within said first bag; wherein said sorbent comprises a hemocompatible material, wherein said hemocompatible material is a crosslinked polymer produced using one or more polymerizable monomer, a cross-linking agent and a porogen, wherein the polymerizable monomers comprise one or more monomers selected from the group consisting of divinylbenzene, ethylvinylbenzene, styrene, ethylstyrene, acrylonitrile, butyl methacrylate, octyl methacrylate, butyl acrylate, octyl acrylate, cetyl methacrylate, cetyl acrylate, ethyl methacrylate, ethyl acrylate, vinyltoluene, vinylnaphthalene, vinylbenzyl alcohol, vinylformamide, methyl methacrylate, methyl acrylate, trivinylbenzene, divinylnaphthalene, trivinylcyclohexane, divinylsulfone, trimethylolpropane trimethacrylate, trimethylolpropane dimethacrylate, trimethylolpropane triacrylate, trimethylolpropane diacrylate, pentaerythritol dimethacrylate, pentaerythritol trimethacrylate, pentaerythritol tetramethacrylate, pentaerythritol diacrylate, pentaerythritol triacrylate, pentaerythritol

tetraacrylate, dipentaerythritol dimethacrylate, dipentaerythritol trimethacrylate, dipentaerythritol tetramethacrylate, dipentaerythritol diacrylate, dipentaerythritol triacrylate, dipentaerythritol tetraacrylate, and divinylformamide.

[0009f] The invention also concerns use of a sorbent for the treatment of blood, blood products, or physiological fluids for administration to an animal, said sorbent performing at least one of increasing shelf life, and removing undesirable molecules; wherein said sorbent is free-flowing, and wherein said sorbent comprises a hemocompatible material, wherein said hemocompatible material is a crosslinked polymer produced using one or more polymerizable monomer, a cross-linking agent and a porogen, wherein the polymerizable monomers comprise one or more monomers selected from the group consisting of divinylbenzene, ethylvinylbenzene, styrene, ethylstyrene, acrylonitrile, butyl methacrylate, octyl methacrylate, butyl acrylate, octyl acrylate, cetyl methacrylate, cetyl acrylate, ethyl methacrylate, ethyl acrylate, vinyltoluene, vinylnaphthalene, vinylbenzyl alcohol, vinylformamide, methyl methacrylate, methyl acrylate, trivinylbenzene, divinylnaphthalene, trivinylcyclohexane, divinylsulfone, trimethylolpropane trimethacrylate, trimethylolpropane dimethacrylate, trimethylolpropane triacrylate, trimethylolpropane diacrylate, pentaerythritol dimethacrylate, pentaerythritol trimethacrylate, pentaerythritol tetramethacrylate, pentaerythritol diacrylate, pentaerythritol triacrylate, pentaerythritol tetraacrylate, dipentaerythritol dimethacrylate, dipentaerythritol trimethacrylate, dipentaerythritol tetramethacrylate, dipentaerythritol diacrylate, dipentaerythritol triacrylate, dipentaerythritol tetraacrylate, and divinylformamide.

[0009g] The invention also concerns a sorbent for use in the treatment of blood, blood products, or physiological fluids for administration to an animal, said sorbent performing at least one of increasing shelf life, and removing undesirable molecules; wherein said sorbent is free-flowing, and wherein said sorbent comprises a hemocompatible material, wherein said hemocompatible material is a crosslinked polymer produced using one or more polymerizable monomer, a cross-linking agent and a porogen, wherein the polymerizable monomers comprise one or more monomers selected from the group consisting of divinylbenzene, ethylvinylbenzene, styrene, ethylstyrene, acrylonitrile, butyl methacrylate, octyl methacrylate, butyl acrylate, octyl acrylate, cetyl methacrylate, cetyl acrylate, ethyl

methacrylate, ethyl acrylate, vinyltoluene, vinylnaphthalene, vinylbenzyl alcohol, vinylformamide, methyl methacrylate, methyl acrylate, trivinylbenzene, divinylnaphthalene, trivinylcyclohexane, divinylsulfone, trimethylolpropane trimethacrylate, trimethylolpropane dimethacrylate, trimethylolpropane triacrylate, trimethylolpropane diacrylate, pentaerythritol dimethacrylate, pentaerythritol trimethacrylate, pentaerythritol tetramethacrylate, pentaerythritol diacrylate, pentaerythritol triacrylate, pentaerythritol tetraacrylate, dipentaerythritol dimethacrylate, dipentaerythritol trimethacrylate, dipentaerythritol tetramethacrylate, dipentaerythritol diacrylate, dipentaerythritol triacrylate, dipentaerythritol tetraacrylate, and divinylformamide.

[009h] The invention also concerns a method of making a blood purification device comprising placing a sorbent comprising a hemocompatible material in a container configured for the storage of blood, blood products, or physiological fluids; wherein said hemocompatible material is configured for treating stored blood, blood products, and physiological fluids, wherein said sorbent performs at least one of increasing shelf life of the blood, blood products or physiologic fluids, and removing undesirable molecules from the blood, blood products or physiologic fluids; wherein said sorbent being contained within said container and said sorbent being free-flowing within said container; and wherein said hemocompatible material comprises residues from one or more monomers selected from the group consisting of divinylbenzene, ethylvinylbenzene, styrene, ethylstyrene, acrylonitrile, butyl methacrylate, octyl methacrylate, butyl acrylate, octyl acrylate, cetyl methacrylate, cetyl acrylate, ethyl methacrylate, ethyl acrylate, vinyltoluene, vinylnaphthalene, vinylbenzyl alcohol, vinylformamide, methyl methacrylate, methyl acrylate, trivinylbenzene, divinylnaphthalene, trivinylcyclohexane, divinylsulfone, trimethylolpropane trimethacrylate, trimethylolpropane dimethacrylate, trimethylolpropane triacrylate, trimethylolpropane diacrylate, pentaerythritol dimethacrylate, pentaerythritol trimethacrylate, pentaerythritol tetramethacrylate, pentaerythritol diacrylate, pentaerythritol triacrylate, pentaerythritol tetraacrylate, dipentaerythritol dimethacrylate, dipentaerythritol trimethacrylate, dipentaerythritol tetramethacrylate, dipentaerythritol diacrylate, dipentaerythritol triacrylate, dipentaerythritol tetraacrylate, and divinylformamide.

[0010] Hemocompatible material suitable for treating stored blood and blood products include polymeric material, pyrolyzed polymeric material, ceramic material, sol-gel material, metal, hybrid material, biological material, coated materials, Y-Carbon Products (Hemocompatible activated pyrolyzed carbon beads), CarboRx (activated carbon), hemosorbent, enterosorbent, NanoTube X (Biocompatible sorbent carbon material), Gambro (activated carbon filter device), Adsorba 150 & 300, Jafron Biomedical Co. (neutral porous polymer resin-pyrolyzed), HA330 Hemoperfusion

Cartridge, HA130 (uremic toxins), the HA230 (drugs, lipophilic, hydrophobic or protein binding drugs), HA 280 (immunoadsorption), HA330 (cytokines, endotoxin for sepsis and SIRS), HA330-II (toxins related to hepatic failure), Kaneka (modified cellulosic porous beads), Lixelle CTR, Ube Industries (Cellulosic bead crosslinked with hexamethylene-di-isocyanate) CF-X, ExThera Medical (Heparin coated polyurethane solid beads), Seraph, Toray industries, Inc. CYT-860 (polystyrene-based conjugated fiber reinforced with polypropylene) and silica based mesoporous materials.

[0011] In one embodiment of the invention, transfusion related complications such as non-hemolytic transfusion reactions such as fever, transfusion related acute lung injury (TRALI), transfusion associated dyspnea (TAD), allergic reactions are mitigated by removing undesirable molecules from blood through use of a sorbent. Use of the sorbent to remove undesirable products from transfusable blood can also extend the useful shelf life of this blood by, for example, removing undesirable products that accumulate during storage. These undesirable products found in blood are herein collectively referred to as Biologically Active Molecules (BAM)s. BAMs are defined as any substance or molecule that can, by itself or in combination with other BAMs, cause a biological, cellular or physiologic process. During blood transfusions, BAMs can elicit an undesirable physiologic response in the recipient of the transfused blood, such as TRALI, TAD, and others. For example, anti-human leukocyte antigen antibodies are BAMs linked to severe cases of TRALI. Prions, another example of a BAM, can cause Creutzfeldt-Jakob disease or subacute spongiform encephalopathy. A subset of BAMs are biological response modifiers (BRMs), that are substances that have an effect on the immune system. These include, for example, cytokines, chemokines, antibodies, glycoproteins, and growth factors. Cytokines found in transfusable blood can cause fever in the recipient.

[0012] In another embodiment, BAMs present in blood and blood products such as drugs, inflammatory mediators and stimulators such as cytokines, chemokines, interferons, nitric oxide, thromboxanes, leukotrienes, platelet,-activating factor, prostaglandins, glycoproteins, kinins, kininogens, complement factors, cell-adhesion molecules, superantigens, monokines, free radicals, proteases, arachidonic acid metabolites, prostacyclins, beta endorphins, myocardial depressant factors, anandimide,

2-arachadonylglycerol, tetrahydrobiopterin, histamine, bradykinin, soluble CD40 ligand, serotonin, hemoglobin, bioactive lipids, antibodies, antigens, prions, toxins, endotoxins, membrane or cellular components, and other BRMs are removed by the sorbent. These BAMs may have been present in the donor's blood at the time the blood donation was made or may develop over time as the blood is processed, or is in storage, or as part of the aging process.

[0013] In another embodiment the donated blood is treated with a sorbent to remove undesirable antibodies such as anti-leukocyte antibodies, and anti-human leukocyte antigen antibodies, at the time of donation, during storage, or at the point of use.

[0014] In another embodiment, polymers comprise particles having a diameter in the range for 0.1 micron meters to 2 centimeters. Certain polymers are in the form of powder, beads or other regular or irregularly shaped particulates. The pore structure of some polymers is such that the total pore volume of pore size in the range of 10 Å to 10,000 Å is greater than 0.5 cc/g to 3.0 cc/g dry polymer and a preferred embodiment of >50% pore volume between 10 Å to 6,000 Å. In some embodiments, the polymer has a pore structure such that the total pore volume of pore size in the range of 10 Å to 10,000 Å is greater than 0.5 cc/g to 3.0 cc/g dry polymer; wherein the ratio of pore volume between 10Å to 10,000Å (pore diameter) to pore volume between 500Å to 3,000Å (pore diameter) of the polymer is smaller than 7:1; and the ratio of pore volume between 10Å to 10,000Å (pore diameter) to pore volume between 10 Å to 6,000Å (pore diameter) of the polymer is $\leq$ 2:1.

[0015] Certain polymers have a pore structure such that the total pore volume of pore size in the range of 20 Å to 10,000 Å is greater than 0.5 cc/g to 3.0 cc/g dry polymer and a preferred embodiment of >50% pore volume between 20 Å to 6,000 Å. In some embodiments, the polymer has a pore structure such that the total pore volume of pore size in the range of 20 Å to 10,000 Å is greater than 0.5 cc/g to 3.0 cc/g dry polymer; wherein the ratio of pore volume between 20Å to 10,000Å (pore diameter) to pore volume between 500Å to 3,000Å (pore diameter) of the polymer is smaller than 7:1; and the ratio of pore volume between 20Å to 10,000Å (pore diameter) to pore volume between 20 Å to 6,000Å (pore diameter) of the polymer is $\leq$ 2:1.

[0016] In yet other embodiments, the pore structure of some polymers is such that the total pore volume of pore size in the range of 50 Å to 10,000 Å is greater than 0.5 cc/g to 3.0 cc/g dry polymer and a preferred embodiment of >50% pore volume between 50 Å to 6,000 Å. In some embodiments, the polymer has a pore structure such that the total pore volume of pore size in the range of 50 Å to 10,000 Å is greater than 0.5 cc/g to 3.0 cc/g dry polymer; wherein the ratio of pore volume between 50Å to 10,000Å (pore diameter) to pore volume between 500Å to 3,000Å (pore diameter) of the polymer is smaller than 7:1; and the ratio of pore volume between 50Å to 10,000Å (pore diameter) to pore volume between 50 Å to 6,000Å (pore diameter) of the polymer is ≤ 2:1.

[0017] Some preferred polymers comprise residues from one or more monomers selected from divnylbenzene and ethylvinylbezene, styrene, ethylstyrene, acrylonitrile, butyl methacrylate, octyl methacrylate, butyl acrylate, octyl acrylate, cetyl methacrylate, cetyl acrylate, ethyl methacrylate, ethyl acrylate, vinyltoluene, vinylnaphthalene, vinylbenzyl alcohol, vinylformamide, methyl methacrylate, methyl acrylate, trivinylbenzene, divinylnaphthalene, trivinylcyclohexane, divinylsulfone, trimethylolpropane trimethacrylate, trimethylolpropane dimethacrylate, trimethylolpropane triacrylate, trimethylolpropane diacrylate, pentaerythritol dimethacrylate, pentaerythritol trimethacrylate, pentaerythritol tetramethacrylate, pentaerythritol diacrylate, pentaerythritol triiacrylate, pentaerythritol tetraacrylate, dipentaerythritol dimethacrylate, dipentaerythritol trimethacrylate, dipentaerythritol tetramethacrylate, dipentaerythritol diacrylate, dipentaerythritol triacrylate, dipentaerythritol tetraacrylate, divinylformamide and mixtures thereof.

[0018] Certain polymers useful in the invention are macroporous polymers prepared from the polymerizable monomers of styrene, divinylbenzene, ethylvinylbenzene, and the acrylate and methacrylate monomers such as those listed below by manufacturer. Rohm and Haas Company, (now part of Dow Chemical Company): (i) macroporous polymeric absorbents such as Amberlite™ XAD-1, Amberlite™ XAD-2, Amberlite™ XAD-4, Amberlite™ XAD-7, Amberlite™ XAD-7HP, Amberlite™ XAD-8, Amberlite™ XAD-16, Amberlite™ XAD-16 HP, Amberlite™ XAD-18, Amberlite™ XAD-200, Amberlite™ XAD-1180, Amberlite™ XAD-2000, Amberlite™ XAD-2005, Amberlite™ XAD-2010, Amberlite™ XAD-761,

and Amberlite™ XE-305, and chromatographic grade adsorbents such as Amberchrom™ CG 71,s,m,c, Amberchrom™ CG 161,s,m,c, Amberchrom™ CG 300,s,m,c, and Amberchrom™ CG 1000,s,m,c. Dow Chemical Company: Dowex® Optipore™ L-493, Dowex® Optipore™ V-493, Dowex® Optipore™ V-502, Dowex® Optipore™ L-285, Dowex® Optipore™ L-323, and Dowex® Optipore™ V-503. Lanxess (formerly Bayer and Sybron): Lewatit® VPOC 1064 MD PH, Lewatit® VPOC 1163, Lewatit® OC EP 63, Lewatit® S 6328A, Lewatit® OC 1066, and Lewatit® 60/150 MIBK. Mitsubishi Chemical Corporation: Diaion® HP 10, Diaion® HP 20, Diaion® HP 21, Diaion® HP 30, Diaion® HP 40, Diaion® HP 50, Diaion® SP70, Diaion® SP 205, Diaion® SP 206, Diaion® SP 207, Diaion® SP 700, Diaion® SP 800, Diaion® SP 825, Diaion® SP 850, Diaion® SP 875, Diaion® HP 1MG, Diaion® HP 2MG, Diaion® CHP 55A, Diaion® CHP 55Y, Diaion® CHP 20A, Diaion® CHP 20Y, Diaion® CHP 2MGY, Diaion® CHP 20P, Diaion® HP 20SS, Diaion® SP 20SS, and Diaion® SP 207SS. Purolite Company: Purosorb™ AP 250 and Purosorb™ AP 400.

[0019] In some embodiments, the polymer may be porous or non-porous. In certain preferred embodiments, the polymer is porous. In some embodiments, the polymer may be pyrolyzed. The pyrolyzation may be performed by methods known to those skilled in the art.

[0020] In some embodiments, the polymer is a coated polymer comprising at least one crosslinking agent and at least one dispersing agent. The dispersing agents can be selected from chemicals, compounds or materials such as hydroxyethyl cellulose, hydroxypopyl cellulose, poly(hydroxyethyl methacrylate), poly(hydroxyethyl acrylate), poly(hydroxypropyl methacrylate), poly(hydroxypropyl acrylate), poly(dimethylaminoethyl methacrylate), poly(dimethylaminoethyl acrylate), poly(diethylamimoethyl methacrylate), poly(diethylaminoethyl acrylate), poly(vinyl alcohol), poly(N-vinylpyrrolidinone), salts of poly(methacrylic acid), and salts of poly(acrylic acid) and mixtures thereof; the crosslinking agent selected from a group consisting of divinylbenzene, trivinylbenzene, divinylnaphthalene, trivinylcyclohexane, divinylsulfone, trimethylolpropane trimethacrylate, trimethylolpropane dimethacrylate, trimethylolpropane triacrylate, trimethylolpropane diacrylate, pentaerythrital dimethacrylates, pentaerythrital trimethacrylates, pentaerythrital, tetramethacrylates,

pentaerythritol diacrylates, pentaerythritol triiacrylates, pentaerythritol tetraacrylates, dipentaerythritol dimethacrylates, dipentaerythritol trimethacrylates, dipentaerythritol tetramethacrylates, dipentaerythritol diacrylates, dipentaerythritol triacrylates, dipentaerythritol tetraacrylates, divinylformamide, heparin, polyethylene glycol, and mixtures thereof; and the polymer is developed simultaneously with the formation of the coating, wherein the dispersing agent is chemically bound to the surface of the polymer.

[0021] In yet another embodiment, the polymer is capable of sorbing protein molecules approximately 100 Daltons to about 1,000 Kilodaltons.

[0022] In some embodiments, the polymers may be derivatized. Some polymers may be modified with an antibody or ligand. Such polymer may be porous or solid.

[0023] For purposes of this invention, the term "total pore volume" is defined as the volume of all the pores in a polymer per unit mass and the term "effective pore volume" means any pore which selectively sorbs molecules. The term "capacity pore volume" is defined as the volume of the "capacity" of all the pores per unit mass of polymer and the term "effective pores" means the functional pores designed to sorb particular molecules. The term "capacity pore" is the total sum of the effective pores and transport pores. The term "transport pore" is defined as a pore that allows for a fast "transport" of the molecules to the effective pores and the term "transport pore volume" means the volume of the "transport" pores per unit mass of the polymer.

[0024] In some embodiments, the composition is contained in a suitable blood container with the blood or blood products. In certain embodiments, the invention concerns a blood storage bag comprising any of the compositions discussed herein. In some embodiments the composition is part of the storage container material that forms the container. In some embodiments, the composition is coated or deposited on the interior surface of the storage container and in direct contact with blood or blood products. In some embodiments the material is separated from the blood via membrane but fluid may pass through the membrane allowing BRMs to communicate with the composition but excluding cells such as white blood cells, red blood cells and platelets. Some methods further comprise separating the composition from the blood via filtration. In certain embodiments the filtration occurs while the blood is removed from the storage

bag during transfusion to a patient. In some embodiments the sorbent in the blood container is in direct contact with the blood. In some embodiments the container contains a mixture of different bead types.

[0025] Certain embodiments concern filters comprising any of the composition discussed herein. Some embodiments, concern a filter cartridge comprising any of the composition discussed herein. Some devices of the invention are blood filtration devices comprising a filter or filter cartridge comprising the any of the composition discussed herein.

[0026] In some embodiments the composition is contained in a filter and either the blood from the donor at the time of donation is passed through the filter before placement into a suitable blood container or the blood or blood products in the blood container pass through the filter during transfusion into the patient. For purposes of this invention, the term "sorb" is defined as "taking up and binding by absorption and adsorption".

BRIEF DESCRIPTION OF THE DRAWINGS

[0027] **Figure 1** presents a plot of pore volume as a function of the pore diameter.

[0028] **Figure 2** presents a polymer transfer adaptor for blood experiments

[0029] **Figure 3** presents a blood transfer adaptor for sample collection

[0030] **Figure 4**, presents a plot of adsorption of Hemoglobin from Phosphate Buffered Saline versus time

[0031] **Figure 5**, presents a plot of adsorption of Hemoglobin from New Human Blood versus time

[0032] **Figure 6** presents a plot of adsorption of human IgG from human blood versus time.

[0033] **Figure 7** presents a plot of LysoPC adsorption from human blood versus time.

[0034] **Figure 8** presents a plot of IL-7 adsorption from human blood versus time.

[0035] **Figure 9** presents a plot of IL-8 adsorption from human blood versus time.

[0036] **Figure 10** presents a plot of TNFα adsorption from human blood versus time.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[0037] As required, detailed embodiments of the present invention are disclosed herein; it is to be understood that the disclosed embodiments are merely exemplary of the invention that may be embodied in various forms. Therefore, specific structural and functional details disclosed herein are not to be interpreted as limits, but merely as a basis for teaching one skilled in the art to employ the present invention. The specific examples below will enable the invention to be better understood. However, they are given merely by way of guidance and do not imply any limitation.

[0038] Three porous polymeric sorbents are characterized for their pore structures and their syntheses are described in Example 1, 2, and 3. The pore structure characterization is given in Example 3.

[0039] The synthesis process consists of (1) preparing the aqueous phase, (2) preparing the organic phase, (3) carrying out the suspension polymerization, and (4) purifying the resulting porous polymeric sorbent product (work-up).

[0040] Remaining examples demonstrate removal of unwanted substances from blood.

Example 1 Sorbent 1-11 Synthesis

[0041] Reactor Setup, Kettle (0.5L) is fitted with over head stirrer, Multi-level stirrer blade, water cooled condenser, thermocouple, and bubbler. A gasket was installed between the top lid and bottom kettle. All unused ports are capped with the appropriate plug. Temperature is controlled with a heating mantle regulated by a temperature controller fitted with the above thermocouple.

[0042] Polymerization, The Polyvinyl Alcohol is dispersed in the water charge at room temperature (RT) and then heated to 70°C. The remaining salts (See **Table 1**,

MSP, DSP, TSP, & Sodium Nitrite) are then dissolved in the water charge. The PVA and Salts solutions are heated to 80°C with stirring. The pre-mixed organic phase listed in **Table 2** including the initiator is poured into the reactor onto the aqueous phase with the stirring speed set at the rpm for formation of the appropriate droplet size. Once temperature reaches the specified value start reaction timer (16 hours).

Table 1		
Aqueous Phase Charges		
Item		Charge, g
Ultrapure Water		231.26
Polyvinyl Alcohol (PVA)		0.68
Monosodium Phosphate (MSP)		0.71
Disodium Phosphate (DSP)		2.36
Trisodium Phosphate (TSP)		1.47
Sodium Nitrite		0.01
	Total	236.48

[0043] Work-up, Mark solvent level. After cooling the solvent is siphoned out to bead level. Reactor is filled to mark with (RT) water and heated to 50°C to 70°C and stirred for 30 minutes, allowed to settle for 3 to 5 minutes and then siphoned out to bead level. Beads are washed 5 times in this manner. For polymers using cyclohexanol as a porogen 3 additional methanol in pot washes are added. Polymer 1 uses 3 in pot IPA washes. If indicated, the polymer is extracted via a Soxhlet apparatus with per **Table 2** overnight. The polymer is steam stripped 6 hours and then dried in an oven overnight (~100°C). This process results in a clean, dry porous sorbent in the form of spherical, porous polymer beads, Sorbent Polymers 1 to 11.

Table 2	**Organic Charges, g**					

Sorbent/ Polymer #	Divinyl benzene (63%)	Divinyl benzene (80%)	Toluene	Isooctane	Cyclohexanol	Polyproplene glycol, PPG, Mw 3500
1	84.70		55.78	64.07		
2	83.03				151.00	
3		71.3			163.15	
4	129.55				77.11	25.70
5	106.38				107.80	19.02
6	106.38				114.14	12.68
7	106.38				115.73	11.10
8	94.73				130.21	8.68
9	106.38				109.07	17.76
10	124.05		88.6			
11	129.55				102.82	

Table 2 (continued)	**Organic Charges, g**			**Reaction Conditions**	**Work-up, Conditions**	
Sorbent/ Polymer #	Polystyrene, Mw 230,000	Benzoyl Peroxide (BPO) (97%)	Total, w/o BPO	Rxn Temp.°C	1st Soxhlet Solvent	2nd Soxhlet Solvent
1		0.64	236.48	80		
2		0.84	234.03	87	Methanol	
3		0.73	234.45	80	Methanol	
4		1.32	232.37	80	Acetone	
5		1.08	232.20	80	Acetone	
6		1.08	233.20	80	Acetone	
7		1.08	233.20	80	Acetone	
8		0.96	233.62	80	Acetone	
9		1.08	233.20	80	Acetone	
10	9.8	0.94	222.49	80	Toluene	Acetone
11		1.32	232.37	80	Methanol	

Example 2 Pore Structure Characterization

[0044] The pore structures of the sorbent polymers were analyzed with a either Micromeritics AutoPore IV 9500 V1.09 a Mercury Penetrometer (Hg Intrusion instrument). The results are provided in **Figure 1** where the pore volume is plotted as a

function of the pore diameter.

Example 3 Pore Structure comparison to biomolecule adsorbtion

[0045] The pore structures of the sorbent polymers were compared to Cytochrome C, Human Serum Albumin, and Immunoglobulin G (IgG). Cytochrome C, ~12 kDa, was used as a surrogate for middle molecular weight proteins such as cytokines, Human Serum Albumin (67 kDa) as a surrogate for Hemoglobin (64 kDa) and IgG representing antibodies. The comparisons are shown in **Table 3**.

Table 3

Sorbent/ Polymer #	Pore Diameter Based off Log Differential Plot maximum (Å)	Pore Volume between 50-10000Å (cc/g)	Pore Volume between 500-3000Å (cc/g)	Percent of total Pore Volume between 500-3000Å	Pore Volume Between 50-6000Å (cc/g)	Percent of total Pore Volume between 50-6000Å
1	1395	1.72	0.93	54	1.68	98
2	2,594	2.31	1.17	51	2.11	91
3	1,830	2.47	1.71	69	2.29	93
4	3,498	0.94	0.74	79	0.93	99
5	10,483	1.01	0.13	13	0.42	42
6	2,591	1.46	1.24	85	1.44	98
7	1,510	1.63	1.28	79	1.59	97
8	2,839	1.84	1.46	79	1.77	96
9	4,337	1.32	0.52	39	1.29	97

Sorbent/ Polymer #	Ratio of pore volume between 50-10000Å to pore volume between 500-3000Å	Ratio of pore volume between 50-10000Å to pore volume between 50-6000Å	3 hour Cytochrome C Removal (mg/g)	3 hour Human Serum Albumin Removal (mg/g)	3 hour Immunoglobulin G Removal (mg/g)
1	1.85	1.02	53	313.5	152.1
2	1.97	1.09	109.5	204.8	385.5
3	1.44	1.08	91.7	176.1	289.2
4	1.27	1.01	9.7	107	103.9
5	7.77	2.39	0.4	101.3	38.8
6	1.18	1.02	34.4	77.4	128.1
7	1.27	1.03	62.4	228.3	266.8
8	1.26	1.04	49.4	102.8	140
9	2.54	1.03	11.4	90.6	89.3

Example 4 Adsorbtion Experiments

Setup and Initial Sampling

Blood and Polymer Preparation

[0046] Each polymer tested was initially prepared as a 50% slurry in 0.9% Saline. Blood was prepared by pooling 8 bags of non-Leukoreduced packed red blood cells ~400 mL (human, <4 days old type AB+) each to an empty 3 L saline bag (PVC, NDC 0409-7983-03) and gently mixed by gently rocking 10 times. The pooled blood was aliquot to 8 empty x 500 mL saline bags, Part Number ND0409-7972-08, weighed and recorded for future reference. The test utilized 3 polymer and a no bead control:

Sorbent 1 (Polymer 1)

Sorbent 2 (Polymer 2)

Sorbent 3 (Polymer 3)

Control (No beads)

Blood/Polymer Charge

[0047] 80 mL of polymer slurry (50%) was charged to the empty 500 mL saline bags with a Modified Polystyrene 25 mL pipette **Figure 2** and the weight recorded. The pooled packed red blood cells were then transferred into emptied 500 mL saline bags that had been charged with the bead slurry (beads 10% of RBC volume) to be studied or no beads for the control and bag weights were recorded. Each bag was gently rocked back and forth 10 times to mix thoroughly. All blood stored at 5°C for the duration of the experiment.

Sampling Day 1

[0048] On Day One Hematocrit for each sample bag was taken to account for dilution due to polymer slurry charged into each sample bag. Approximately 5 mls of blood were sampled into a red top vacutainer (BD 366430) for Cytokine/IgG analysis and a second polystyrene tube (BD 352099) was sampled using 5 mls of blood for Lysophosphatidylcholine analysis (LPC). Both the red top and polystyrene collection tubes were spun for 20 minutes and the supernatant separated into polypropylene and polystyrene cryo tubes, respectively and frozen at -25 °C.

Sample Collection, Days 7, 14, 21, & 41

[0049] Sample bags were removed from the refrigerator. and gently mixed by inverting 10 times and sampled for hematocrit. Sampling for Cytokine/IgG and LPC was performed identical to Day 1 sampling. All samples collected were stored at -25 °C until analyzed.

Hemoglobin Absorption from Phosphate Buffered Saline

[0050] Solution of Hemoglobin in Phosphate Buffered Saline was prepared at a concentration of approximately 11.00 mg/mL. Individual 50 mL polypropylene

centrifuge tubes were used for each time point sampled, excluding the t = 0 time point (the t = 0 samples were taken directly from the Hemoglobin stock solution). 2.5 g of wet polymer with the interstitial saline removed and 22.5 mL of Hemoglobin solution were added to each centrifuge tube. The tubes were then placed on a platform rocker in a 4-8°C refrigerator. At the appropriate time points, the applicable centrifuge tubes were removed from the refrigerator. Four samples were removed from each centrifuge tube, labeled, and frozen at -20°C until analysis was performed.

Hemoglobin Absorption from "New" Human Blood – 14 day Aging Study

[0051] Three bags of freshly drawn blood were purchased. Upon receipt, the contents of the bags were pooled and approximately 350-400 mL of blood was distributed into two separate blood bags. 30 mL of 0.9% saline containing polymer beads (50% solids) was added to one of the bags (experiment), and 30 mL of 0.9% saline was added to the other (control). One blood sample was taken from the control bag, the result being used as the t = 0 (initial) sample value. At each time point, one hematocrit sample and one blood sample was taken. The hematocrit value was measured and recorded, the blood sample was appropriately centrifuged and plasma samples were removed and stored in polypropylene sample vials at -20°C until analysis was performed. The blood bags were placed on a platform rocker in a 4-8°C refrigerator. At the appropriate time points, the blood bags were removed from the refrigerator and sampled as previously described. Once sampled, the bags were returned to the refrigerator.

Analysis of Samples from the Hemoglobin in Phosphate Buffered Saline, Hemoglobin in "New" Human Blood (14 day Aging Study), and Real Time Aging (41-day) Study of Human Blood (IgG & LPC)

[0052] **Human Hemoglobin Analysis**; Analysis of Human Hemoglobin was conducted on the collected blood samples using Bethyl Laboratories Incorporated's Human Hemoglobin ELISA Kit, Catalog #E88-135. Analysis procedures were conducted according to the manual provided with the kit. See **Table 4** & **5** for the resultant data and **Figure 4 & 5** for a graphical representation.

[0053] This experiment represented a hemoglobin adsorption experiment under

controlled conditions with known starting concentrations of hemoglobin.

Table 4, Hemoglobin Data (Phosphate Buffered Saline)

Polymer ID	Sample Description	[Hb] (mg/mL)
Polymer 1	t = 0 hours	11.00
	t = 1 hour	9.79
	t = 4 hours	6.06
	t = 6 hours	6.41
	t = 24 hours	1.68
Polymer 2	t = 0 hours	11.00
	t = 1 hour	8.35
	t = 4 hours	5.24
	t = 6 hours	4.46
	t = 24 hours	4.03
Control	t = 0 hours	11.00
	t = 1 hour	15.50
	t = 4 hours	14.96
	t = 6 hours	13.30
	t = 24 hours	16.33

[0054] This test was designed to show the dynamic removal of hemoglobin by the test polymers in a model system where hemoglobin is constantly generated by gently rocking the blood in a bag causing red blood cell lysis and release of hemoglobin.

Table 5, Hemoglobin Data ("New" Human Blood – 14 day Aging Study)

Polymer ID	Sample Description	[Hb] (mg/mL) Corrected for Hematocrit
Polymer 1	t = 0 days	1.25
	t = 1 day	1.05
	t = 4 days	1.18
	t = 14 days	1.06
Control	t = 0 days	1.25
	t = 1 day	1.33

	t = 4 days	3.87
	t = 14 days	5.41

[0055] **Human Immunoglobulin G Analysis**; Analysis of Human Immunoglobulin G was conducted on the collected blood samples using ZeptoMetrix Corporation's Immunotek Quantitative Human IgG ELISA Kit, Catalog #0801182. Analysis procedures were conducted according to the manual provided with the kit. See **Table 6** for the resultant data and **Figure 6** for a graphical representation.

Table 6

Polymer ID	Sample Description	[IgG] (μg/mL) Corrected for Hematocrit
Polymer 1	t = 0	93.54
	t = 7 days	60.30
	t = 14 days	44.12
	t = 20 days	41.81
	t = 41 days	25.06
Polymer 2	t = 0	93.54
	t = 7 days	55.44
	t = 14 days	53.25
	t = 20 days	72.27
	t = 41 days	58.79
Polymer 3	t = 0	93.54
	t = 7 days	77.75
	t = 14 days	83.39
	t = 20 days	83.39
	t = 41 days	78.30
Control	t = 0	93.54
	t = 7 days	76.68
	t = 14 days	96.82
	t = 20 days	86.86
	t = 41 days	103.10

[0056] **Human Lysophosphatidylcholine Analysis;** Analysis of Human Lysophosphatidylcholine was conducted on the collected blood samples using Cosmo

Bio Company's AZWELL LPC Assay Kit, Catalog #ALF-274729843. Analysis procedures were conducted according to the manual provided with the kit (translated into English), with one exception: 700 nm filters are not currently available for the microplate reader in our facility (BioTek EL800). Therefore, we were unable to measure absorbance at this wavelength for avoidance of interference as recommended by the kit manufacturer. See **Table 7** for the resultant data and **Figure 7** for a graphical representation.

Table 7

Polymer ID	Sample Description	[LysoPC] (μmol/L) Corrected for Hematocrit
Polymer 1	t = 0	65.85
	t = 7 days	25.23
	t = 14 days	19.18
	t = 20 days	19.53
	t = 41 days	9.40
Polymer 2	t = 0	65.85
	t = 7 days	19.28
	t = 14 days	16.57
	t = 20 days	10.52
	t = 41 days	11.84
Polymer 3	t = 0	65.85
	t = 7 days	19.11
	t = 14 days	14.73
	t = 20 days	6.02
	t = 41 days	5.33
Control	t = 0	65.85
	t = 7 days	58.41
	t = 14 days	55.97
	t = 20 days	47.63
	t = 41 days	62.87

[0057] Human Cytokine Analysis; Analysis of thirteen Human Cytokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12(p70), IL-13, IFNγ,

GM-CSF, and TNFα) was conducted on the collected blood samples using Millipore's Milliplex MAP High Sensitivity Human Cytokine Magnetic Bead Kit, Catalog #HSCYTMAG-60SK. Analysis procedures were conducted according to the manual provided with the kit. Several analytes returned values below the lower limit of quantitation for the assay, and thus are not reported. See **Table 8** for the resultant data and **Figures 8, 9, & 10** for a graphical representation of each reported cytokine.

Table 8

Polymer ID	Sample Description	[IL-7] (pg/mL) Corrected for Hematocrit	[IL-8] (pg/mL) Corrected for Hematocrit	[TNFα] (pg/mL) Corrected for Hematocrit
Polymer 1	t = 0	0.89	7.17	3.03
	t = 7 days	0.53	3.14	0.98
	t = 14 days	0.56	2.54	0.51
	t = 20 days	0.25	2.11	0.32
	t = 41 days	0.00	3.44	0.09
Polymer 2	t = 0	0.89	7.17	3.03
	t = 7 days	0.56	2.59	1.25
	t = 14 days	0.37	1.74	0.38
	t = 20 days	0.07	2.92	0.04
	t = 41 days	0.15	1.46	0.06
Polymer 3	t = 0	0.89	7.17	3.03
	t = 7 days	0.48	3.37	1.16
	t = 14 days	0.53	3.21	0.60
	t = 20 days	0.44	4.44	0.22
	t = 41 days	0.51	3.79	0.07
Control	t = 0	0.89	7.17	3.03
	t = 7 days	0.99	12.04	3.70
	t = 14 days	1.34	13.76	3.94
	t = 20 days	1.52	16.89	4.11
	t = 41 days	1.98	40.70	5.49

CLAIMS:

1. A blood, blood product or physiologic fluid storage bag comprising:

(a) a bag configured for the storage of blood, blood products or physiologic fluids;

(b) a sorbent comprising hemocompatible material configured for treating blood, blood product or physiologic fluid, said sorbent increasing shelf life of the blood, blood product or physiologic fluid;

said sorbent being contained within said bag;

wherein said sorbent is free-flowing within said bag;

wherein said sorbent being a plurality of solid forms; and

wherein said hemocompatible material is a crosslinked polymer produced using one or more polymerizable monomer, a cross-linking agent and a porogen, wherein the polymerizable monomers comprise one or more monomers selected from the group consisting of divinylbenzene, ethylvinylbenzene, styrene, ethylstyrene, acrylonitrile, butyl methacrylate, octyl methacrylate, butyl acrylate, octyl acrylate, cetyl methacrylate, cetyl acrylate, ethyl methacrylate, ethyl acrylate, vinyltoluene, vinylnaphthalene, vinylbenzyl alcohol, vinylformamide, methyl methacrylate, methyl acrylate, trivinylbenzene, divinylnaphthalene, trivinylcyclohexane, divinylsulfone, trimethylolpropane trimethacrylate, trimethylolpropane dimethacrylate, trimethylolpropane triacrylate, trimethylolpropane diacrylate, pentaerythritol dimethacrylate, pentaerythritol trimethacrylate, pentaerythritol tetramethacrylate, pentaerythritol diacrylate, pentaerythritol triacrylate, pentaerythritol tetraacrylate, dipentaerythritol dimethacrylate, dipentaerythritol trimethacrylate, dipentaerythritol tetramethacrylate, dipentaerythritol diacrylate, dipentaerythritol triacrylate, dipentaerythritol tetraacrylate, and divinylformamide.

2. The storage bag of claim 1, wherein said hemocompatible material comprises one or more monomers selected from the group consisting of divinylbenzene, ethylvinylbenzene and styrene.

3. The storage bag of claim 1 or 2, wherein said bag comprises a polymeric material comprising one or more types of polymers selected from the group consisting of polyvinyl

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chloride (PVC), polyolefin (PO), poly(ethylene-co-vinyl acetate) (EVA), and fluorinated polyethylene propylene (FEP).

4. The storage bag of claim 3, wherein the polymeric material further comprises a biocompatible plasticizer.

5. The storage bag of any one of claims 1 to 4, wherein said sorbent removes undesirable molecules related to non-hemolytic transfusion reactions and result in one or more of fever, transfusion related acute lung injury (TRALI), transfusion associated dyspnea (TAD), allergic reactions, and infection; such undesirable molecules comprising one or more of cytokines, chemokines, antibodies, glycoproteins, growth factors, interferons, nitric oxide, thromboxanes, leukotrienes, platelet-activating factor, prostaglandins, glycoproteins, kinins, kininogens, complement factors, cell-adhesion molecules, superantigens, monokines, free radicals, proteases, arachidonic acid metabolites, prostacyclins, beta endorphins, myocardial depressant factors, anandimide, 2-arachadonylglycerol, tetrahydrobiopterin, histamine, bradykinin, soluble CD40 ligand, serotonin, hemoglobin, bioactive lipids, antibodies, antigens, prions, toxins, endotoxins, membrane and cellular components.

6. The storage bag of any one of claims 1 to 5, wherein said hemocompatible material comprises particles having a diameter in the range of 0.1 micrometers to 2 centimeters.

7. The storage bag of any one of claims 1 to 6, wherein said hemocompatible material is porous and has a pore structure having a total volume of pore sizes in the range of 50 Å to 10,000 Å greater than 0.5 cc/g to 3.0 cc/g dry polymer.

8. The storage bag of any one of claims 1 to 6, wherein said hemocompatible material has a pore structure having a total volume of pore sizes in the range of from 10 Å to 10,000 Å greater than 0.5 cc/g to 3.0 cc/g of dry polymer; wherein the ratio of pore volume between 10 Å to 3,000 Å in diameter to pore volume between 500 Å to 3,000 Å in diameter is smaller than 7:1, and wherein the ratio of pore volume between 10 Å to 3,000 Å in diameter to pore volume between 10 Å to 6,000 Å in diameter is less than 2:1.

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9. The storage bag of any one of claims 1 to 6, wherein said hemocompatible material has a pore structure having a total volume of pore sizes in the range of from 20 Å to 10,000 Å greater than 0.5 cc/g to 3.0 cc/g dry polymer; wherein the ratio of pore volume between 20 Å to 3,000 Å in diameter to pore volume between 500 Å to 3,000 Å in diameter is smaller than 7:1, and wherein the ratio of pore volume between 20 Å to 3,000 Å in diameter to pore volume between 20 Å to 6,000 Å in diameter is less than 2:1.

10. The storage bag of any one of claims 1 to 9, wherein said hemocompatible material has a pore structure having a total volume of pore sizes in the range of from 50 Å to 10,000 Å greater than 0.5 cc/g to 3.0 cc/g dry polymer; wherein the ratio of pore volume between 50 Å to 3,000 Å in diameter to pore volume between 500 Å to 3,000 Å in diameter is smaller than 7:1 and wherein the ratio of pore volume between 50 Å to 3,000 Å in diameter to pore volume between 50 Å to 6,000 Å in diameter is less than 2:1.

11. The storage bag of any one of claims 1 to 10, wherein the hemocompatible material can sorb molecules from about 100 Daltons to about 1,000 kDa.

12. The storage bag of claim 1, wherein the polymerizable monomers are selected from the group consisting of styrene, ethylstyrene, acrylonitrile, butyl methacrylate, octyl methacrylate, butyl acrylate, octyl acrylate, cetyl methacrylate, cetyl acrylate, ethyl methacrylate, ethyl acrylate, vinyltoluene, vinylnaphthalene, vinylbenzyl alcohol, vinylformamide, methyl methacrylate, and methyl acrylate.

13. The storage bag of claim 12, wherein said hemocompatible material is made hemocompatible by a hemocompatible surface comprising hydroxyethyl cellulose, hydroxypropyl cellulose, poly(hydroxyethyl methacrylate), poly(hydroxyethyl acrylate), poly(hydroxypropyl methacrylate), poly(hydroxypropyl acrylate), poly(dimethylaminoethyl methacrylate), poly(dimethylaminoethyl acrylate), poly(diethylaminoethyl methacrylate), poly-(diethylaminoethyl acrylate), poly(vinyl alcohol), heparin, polyethylene glycol, poly(N-vinylpyrrolidinone), salts of poly(methacrylic acid), salts of poly(acrylic acid), any copolymer

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thereof, or any mixture thereof, wherein said hemocompatible surface is chemically bound to the hemocompatible material.

14. The storage bag of claim 12 or 13, wherein said hemocompatible material is pyrolyzed.

15. The storage bag of claim 13, wherein said sorbent is pyrolyzed.

16. The storage bag of any one of claims 1 to 15, wherein said sorbent further comprises a dispersing agent.

17. A method of treating blood, blood products, or physiologic fluids to provide at least one of increasing shelf life of the blood, blood products or physiologic fluids and removing undesirable molecules from the blood, blood products or physiologic fluids, the method comprising contacting the blood, blood products, or physiologic fluids with a sorbent,

wherein said sorbent is contained within a bag configured for the storage of blood, blood products or physiologic fluid,

wherein said sorbent is free-flowing within said bag, and

wherein said sorbent comprises a hemocompatible material that is a crosslinked polymer produced using one or more polymerizable monomer, a cross-linking agent and a porogen, wherein the polymerizable monomers comprise one or more monomers selected from the group consisting of divinylbenzene, ethylvinylbenzene, styrene, ethylstyrene, acrylonitrile, butyl methacrylate, octyl methacrylate, butyl acrylate, octyl acrylate, cetyl methacrylate, cetyl acrylate, ethyl methacrylate, ethyl acrylate, vinyltoluene, vinylnaphthalene, vinylbenzyl alcohol, vinylformamide, methyl methacrylate, methyl acrylate, trivinylbenzene, divinylnaphthalene, trivinylcyclohexane, divinylsulfone, trimethylolpropane trimethacrylate, trimethylolpropane dimethacrylate, trimethylolpropane triacrylate, trimethylolpropane diacrylate, pentaerythritol dimethacrylate, pentaerythritol trimethacrylate, pentaerythritol tetramethacrylate, pentaerythritol diacrylate, pentaerythritol triacrylate, pentaerythritol tetraacrylate, dipentaerythritol dimethacrylate, dipentaerythritol trimethacrylate, dipentaerythritol tetramethacrylate, dipentaerythritol diacrylate, dipentaerythritol triacrylate, dipentaerythritol tetraacrylate, and divinylformamide.

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18. The method of claim 17, wherein said undesirable molecules comprise one or more molecules selected from the group consisting of biologically active molecules (BAMs) and biological response modifiers (BRMs).

19. The method of claim 18, wherein the biologically active molecules comprise inflammatory mediators and stimulators.

20. The method of claim 19, wherein said inflammatory mediators and stimulators comprise cytokines, nitric oxide, thromboxanes, leukotrienes, platelet-activating factor, prostaglandins, glycoproteins, kinins, kininogens, complement factors, cell-adhesion molecules, superantigens, monokines, chemokines, interferons, free radicals, proteases, arachidonic acid metabolites, prostacyclins, beta endorphins, myocardial depressant factors, anandimide, 2-arachadonylglycerol, tetrahydrobiopterin, serotonin, histamine, bradykinin, soluble CD40 ligand, bioactive lipids, oxidized lipids, hemoglobin, red cell particulates, membrane or cellular components, growth factors, endotoxins, vasoactive substances, or foreign antigens.

21. The method of claim 17 or 18, wherein the undesirable molecules are antibodies.

22. The method of any one of claims 17 to 21, wherein said hemocompatible material comprises one or more monomers selected from the group consisting of divinylbenzene, ethylvinylbenzene and styrene.

23. The method of any one of claims 17 to 22, wherein said sorbent is porous or non-porous.

24. The method of claim 23, wherein said hemocompatible material comprises particles having a diameter in the range of 0.1 micrometers to 2 centimeters.

25. The method of claim 23 or 24, wherein said hemocompatible material is supplied as a slurry, a suspension, a wettable dry powder, a wettable dry particulate, or within a semi-permeable container.

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26. The method of any one of claims 23 to 25, wherein said hemocompatible material is porous and has a pore structure having a total volume of pore sizes in the range of 50 Å to 10,000 Å greater than 0.5 cc/g to 3.0 cc/g dry polymer.

27. The method of any one of claims 23 to 25, wherein said hemocompatible material has a pore structure having a total volume of pore sizes in the range of from 10 Å to 10,000 Å greater than 0.5 cc/g to 3.0 cc/g dry polymer; wherein the ratio of pore volume between 10 Å to 3,000 Å in diameter to pore volume between 500 Å to 3,000 Å in diameter is smaller than 7:1 and wherein the ratio of pore volume between 10 Å to 3,000 Å in diameter to pore volume between 10 Å to 6,000 Å in diameter is less than 2:1.

28. The method of any one of claims 23 to 27, wherein said hemocompatible material can sorb molecules from about 100 Daltons to about 1,000 kDa.

29. The method of any one of claims 23 to 28, wherein said hemocompatible material is modified with ligands that specifically or non-specifically bind biomolecules.

30. The method of any one of claims 17 to 21, wherein the polymerizable monomers are selected from the group consisting of styrene, ethylstyrene, acrylonitrile, butyl methacrylate, octyl methacrylate, butyl acrylate, octyl acrylate, cetyl methacrylate, cetyl acrylate, ethyl methacrylate, ethyl acrylate, vinyltoluene, vinylnaphthalene, vinylbenzyl alcohol, vinylformamide, methyl methacrylate, and methyl acrylate.

31. The method of claim 30, wherein said sorbent comprises a hemocompatible surface comprising hydroxyethyl cellulose, hydroxypropyl cellulose, poly(hydroxyethyl methacrylate), poly(hydroxyethyl acrylate), poly(hydroxypropyl methacrylate), poly(hydroxypropyl acrylate), poly(dimethylaminoethyl methacrylate), poly(dimethylaminoethyl acrylate), poly(diethylaminoethyl methacrylate), poly(diethylaminoethyl acrylate), poly(vinyl alcohol), heparin, polyethylene glycol, poly(N-vinylpyrrolidinone), salts of poly(methacrylic acid), salts of poly(acrylic acid) or copolymers or mixtures thereof, wherein said hemocompatible surface is chemically bound to the hemocompatible material.

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32. The method of any one of claims 17 to 31, wherein said sorbent is in the bag, the bag configured to hold blood, and is in direct contact with blood or blood products, and is incapable of escaping from the bag.

33. The method of any one of claims 17 to 31, wherein said sorbent is in the bag, the bag configured to hold blood and comprising a permeable membrane or barrier, and wherein said sorbent is separated from the blood by the permeable membrane or barrier, the permeable membrane or barrier allowing fluid but not cells to interact with the sorbent.

34. A method of making a blood purification device comprising placing a sorbent comprising a hemocompatible material in a bag configured for the storage of blood, blood products, or physiological fluids;

wherein said hemocompatible material is configured for treating stored blood, blood products, and physiological fluids,

wherein said sorbent performs at least one of increasing shelf life of the blood, blood products or physiologic fluids, and removing undesirable molecules from the blood, blood products or physiologic fluids;

wherein said sorbent being contained within said bag and said sorbent being free-flowing within said bag; and

wherein said hemocompatible material is a crosslinked polymer produced using one or more polymerizable monomer, a cross-linking agent and a porogen, wherein the polymerizable monomers comprise one or more monomers selected from the group consisting of divinylbenzene, ethylvinylbenzene, styrene, ethylstyrene, acrylonitrile, butyl methacrylate, octyl methacrylate, butyl acrylate, octyl acrylate, cetyl methacrylate, cetyl acrylate, ethyl methacrylate, ethyl acrylate, vinyltoluene, vinylnaphthalene, vinylbenzyl alcohol, vinylformamide, methyl methacrylate, methyl acrylate, trivinylbenzene, divinylnaphthalene, trivinylcyclohexane, divinylsulfone, trimethylolpropane trimethacrylate, trimethylolpropane dimethacrylate, trimethylolpropane triacrylate, trimethylolpropane diacrylate, pentaerythritol dimethacrylate, pentaerythritol trimethacrylate, pentaerythritol tetramethacrylate, pentaerythritol diacrylate, pentaerythritol triacrylate, pentaerythritol tetraacrylate, dipentaerythritol dimethacrylate, dipentaerythritol trimethacrylate, dipentaerythritol

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tetramethacrylate, dipentaerythritol diacrylate, dipentaerythritol triacrylate, dipentaerythritol tetraacrylate, and divinylformamide.

35. A method of treating blood, blood products, or physiologic fluids, said method comprising:

(a) contacting said blood, blood products, or physiologic fluids with a sorbent in a first bag, said sorbent performing at least one of increasing shelf life, and removing undesirable molecules; and

(b) placing the blood, blood products, or physiologic fluids from step (a) into a second bag for storage;

wherein said sorbent is free-flowing within said first bag;

wherein said sorbent comprises a hemocompatible material, wherein said hemocompatible material is a crosslinked polymer produced using one or more polymerizable monomer, a cross-linking agent and a porogen, wherein the polymerizable monomers comprise one or more monomers selected from the group consisting of divinylbenzene, ethylvinylbenzene, styrene, ethylstyrene, acrylonitrile, butyl methacrylate, octyl methacrylate, butyl acrylate, octyl acrylate, cetyl methacrylate, cetyl acrylate, ethyl methacrylate, ethyl acrylate, vinyltoluene, vinylnaphthalene, vinylbenzyl alcohol, vinylformamide, methyl methacrylate, methyl acrylate, trivinylbenzene, divinylnaphthalene, trivinylcyclohexane, divinylsulfone, trimethylolpropane trimethacrylate, trimethylolpropane dimethacrylate, trimethylolpropane triacrylate, trimethylolpropane diacrylate, pentaerythritol dimethacrylate, pentaerythritol trimethacrylate, pentaerythritol tetramethacrylate, pentaerythritol diacrylate, pentaerythritol triacrylate, pentaerythritol tetraacrylate, dipentaerythritol dimethacrylate, dipentaerythritol trimethacrylate, dipentaerythritol tetramethacrylate, dipentaerythritol diacrylate, dipentaerythritol triacrylate, dipentaerythritol tetraacrylate, and divinylformamide.

36. Use of a sorbent for the treatment of blood, blood products, or physiological fluids for administration to an animal, said sorbent performing at least one of increasing shelf life, and removing undesirable molecules; wherein said sorbent is free-flowing, and wherein said sorbent comprises a hemocompatible material, wherein said hemocompatible material is a crosslinked polymer produced using one or more polymerizable monomer, a cross-linking agent and a

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porogen, wherein the polymerizable monomers comprise one or more monomers selected from the group consisting of divinylbenzene, ethylvinylbenzene, styrene, ethylstyrene, acrylonitrile, butyl methacrylate, octyl methacrylate, butyl acrylate, octyl acrylate, cetyl methacrylate, cetyl acrylate, ethyl methacrylate, ethyl acrylate, vinyltoluene, vinylnaphthalene, vinylbenzyl alcohol, vinylformamide, methyl methacrylate, methyl acrylate, trivinylbenzene, divinylnaphthalene, trivinylcyclohexane, divinylsulfone, trimethylolpropane trimethacrylate, trimethylolpropane dimethacrylate, trimethylolpropane triacrylate, trimethylolpropane diacrylate, pentaerythritol dimethacrylate, pentaerythritol trimethacrylate, pentaerythritol tetramethacrylate, pentaerythritol diacrylate, pentaerythritol triacrylate, pentaerythritol tetraacrylate, dipentaerythritol dimethacrylate, dipentaerythritol trimethacrylate, dipentaerythritol tetramethacrylate, dipentaerythritol diacrylate, dipentaerythritol triacrylate, dipentaerythritol tetraacrylate, and divinylformamide.

37. A sorbent for use in the treatment of blood, blood products, or physiological fluids for administration to an animal, said sorbent performing at least one of increasing shelf life, and removing undesirable molecules; wherein said sorbent is free-flowing, and wherein said sorbent comprises a hemocompatible material, wherein said hemocompatible material is a crosslinked polymer produced using one or more polymerizable monomer, a cross-linking agent and a porogen, wherein the polymerizable monomers comprise one or more monomers selected from the group consisting of divinylbenzene, ethylvinylbenzene, styrene, ethylstyrene, acrylonitrile, butyl methacrylate, octyl methacrylate, butyl acrylate, octyl acrylate, cetyl methacrylate, cetyl acrylate, ethyl methacrylate, ethyl acrylate, vinyltoluene, vinylnaphthalene, vinylbenzyl alcohol, vinylformamide, methyl methacrylate, methyl acrylate, trivinylbenzene, divinylnaphthalene, trivinylcyclohexane, divinylsulfone, trimethylolpropane trimethacrylate, trimethylolpropane dimethacrylate, trimethylolpropane triacrylate, trimethylolpropane diacrylate, pentaerythritol dimethacrylate, pentaerythritol trimethacrylate, pentaerythritol tetramethacrylate, pentaerythritol diacrylate, pentaerythritol triacrylate, pentaerythritol tetraacrylate, dipentaerythritol dimethacrylate, dipentaerythritol trimethacrylate, dipentaerythritol tetramethacrylate, dipentaerythritol diacrylate, dipentaerythritol triacrylate, dipentaerythritol tetraacrylate, and divinylformamide.

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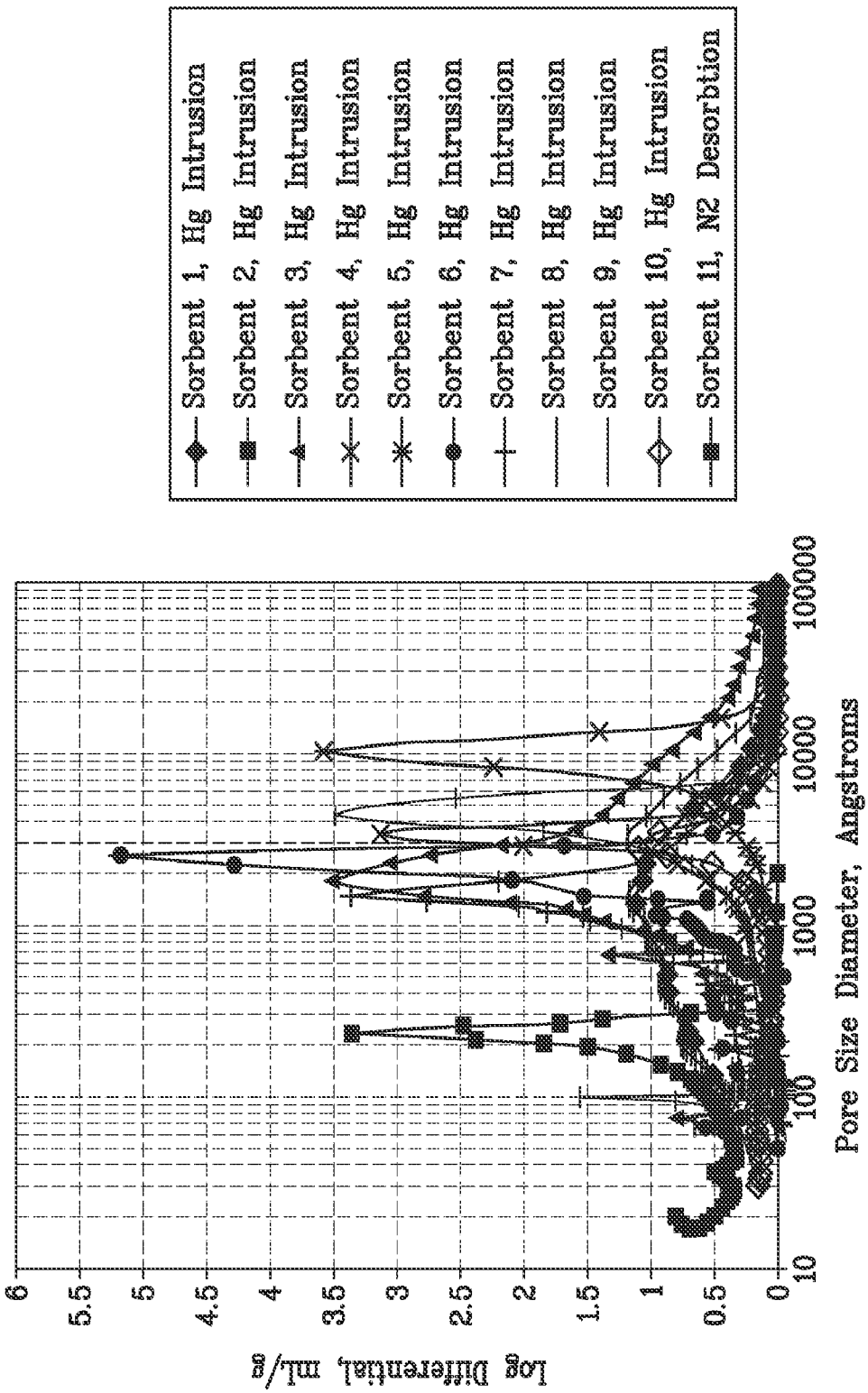
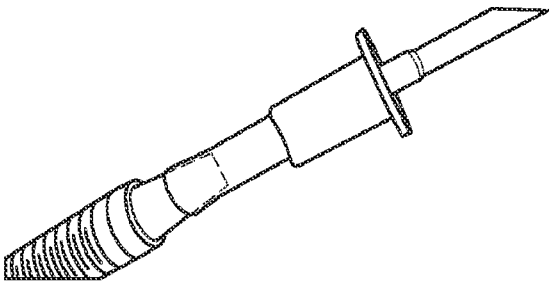


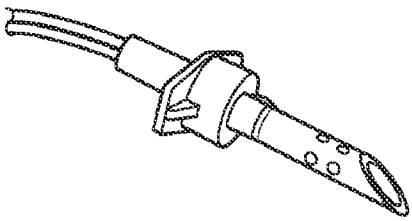
Plot of pore volume as a function of the pore diameter

FIG. 1



Modified Polystyrene 25 mL pipette for slurry transfer

FIG. 2



Modified Bag Spike

(Holes drilled in spike,
strip of 200 micron screen inserted in the end)

FIG. 3

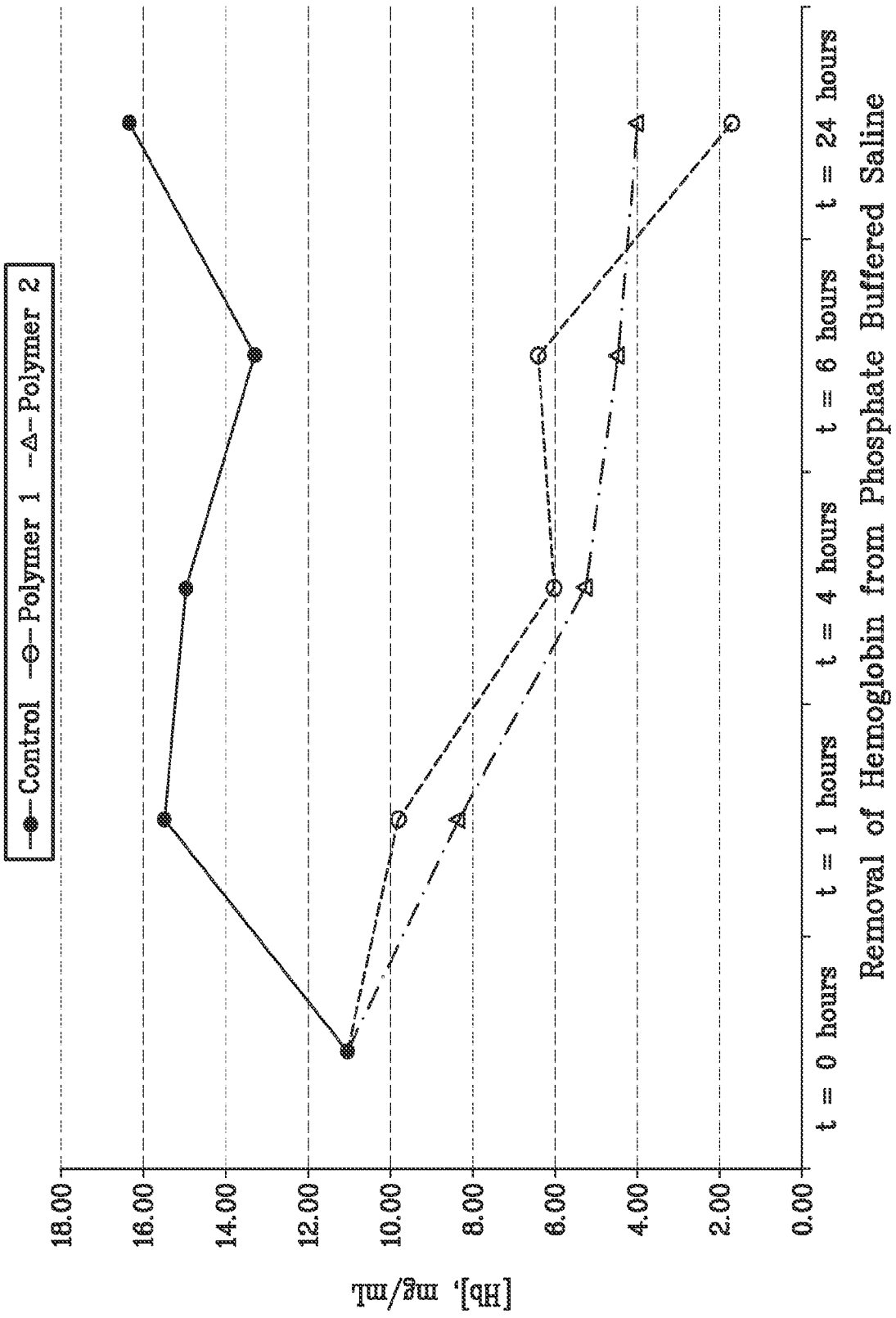
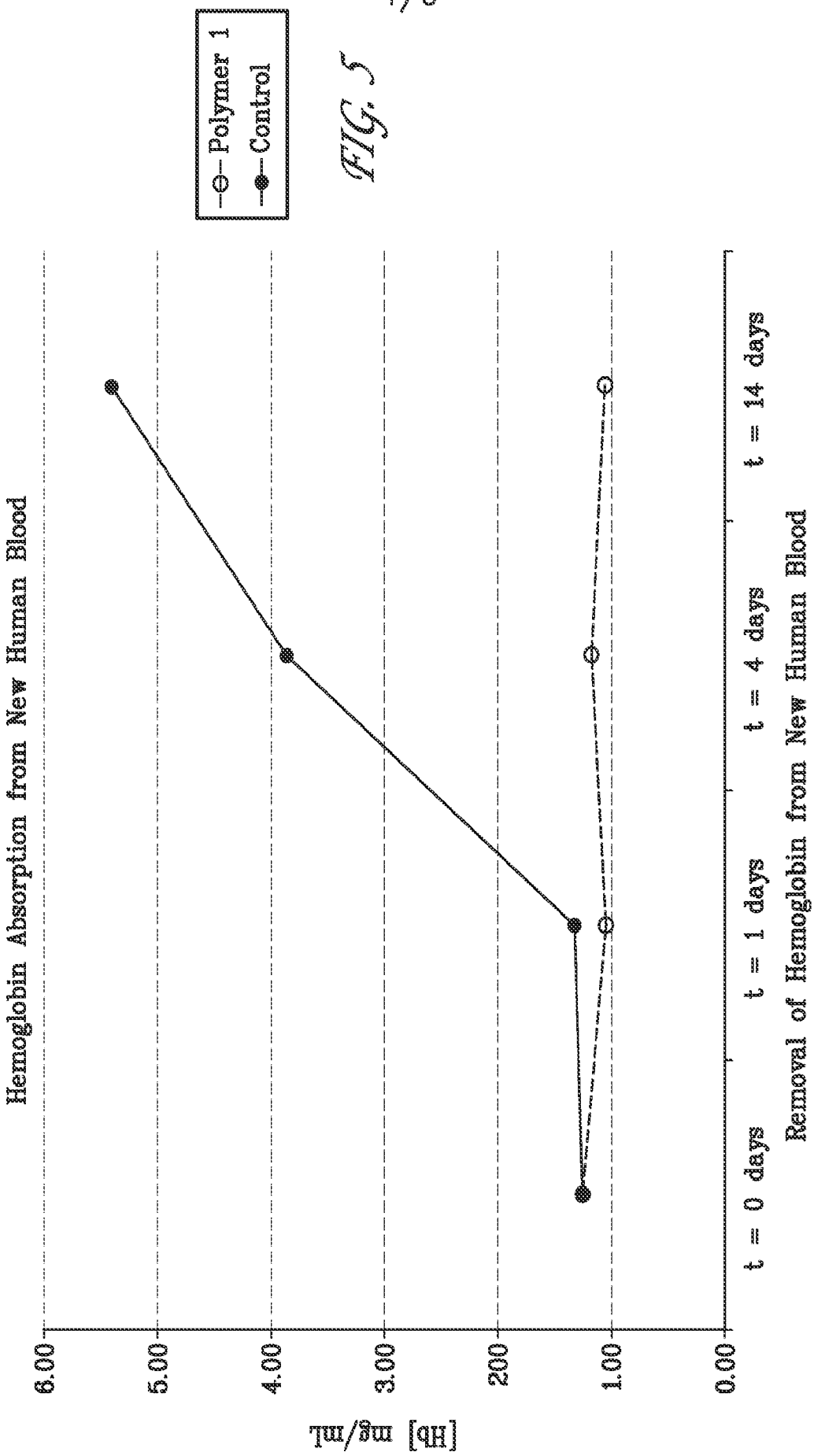

Control
Polymer 1
Polymer 2
[Hb], mg/mL
18.00
16.00
14.00
12.00
10.00
8.00
6.00
4.00
2.00
0.00
t = 0 hours
t = 1 hours
t = 4 hours
t = 6 hours
t = 24 hours
Removal of Hemoglobin from Phosphate Buffered Saline

FIG. 4

FIG. 5


Polymer 1
Control
Hemoglobin Absorption from New Human Blood
[Hb] mg/mL
6.00
5.00
4.00
3.00
200
1.00
0.00
t = 0 days
t = 1 days
t = 4 days
t = 14 days
Removal of Hemoglobin from New Human Blood

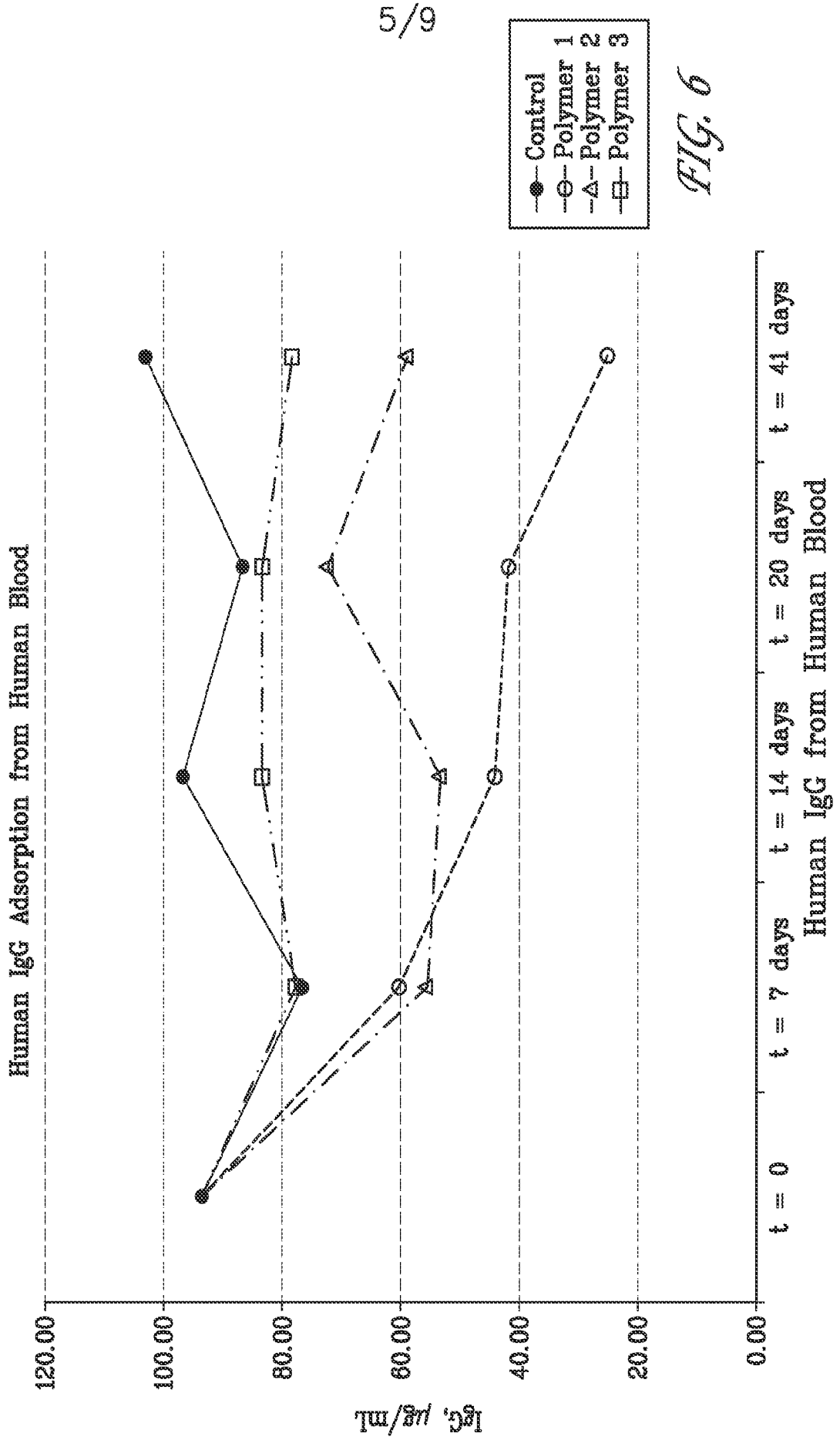

Human IgG Adsorption from Human Blood
IgG, μg/mL
120.00
100.00
80.00
60.00
40.00
20.00
0.00
t = 0
t = 7 days
t = 14 days
t = 20 days
t = 41 days
Human IgG from Human Blood
Control
Polymer 1
Polymer 2
Polymer 3

FIG. 6

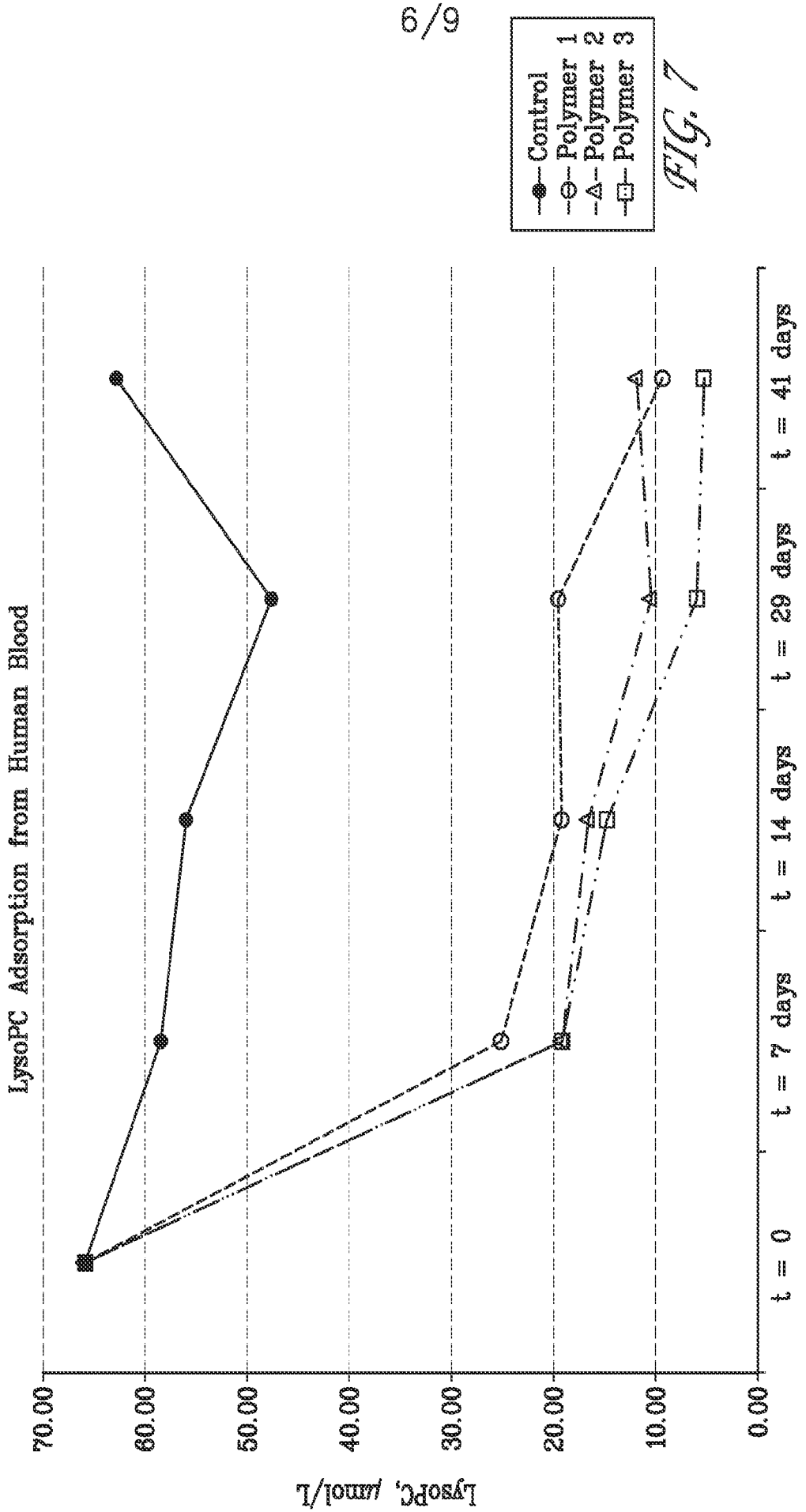

LysoPC Adsorption from Human Blood
LysoPC, μmol/L
70.00
60.00
50.00
40.00
30.00
20.00
10.00
0.00
t = 0
t = 7 days
t = 14 days
t = 29 days
t = 41 days
Control
Polymer 1
Polymer 2
Polymer 3

FIG. 7

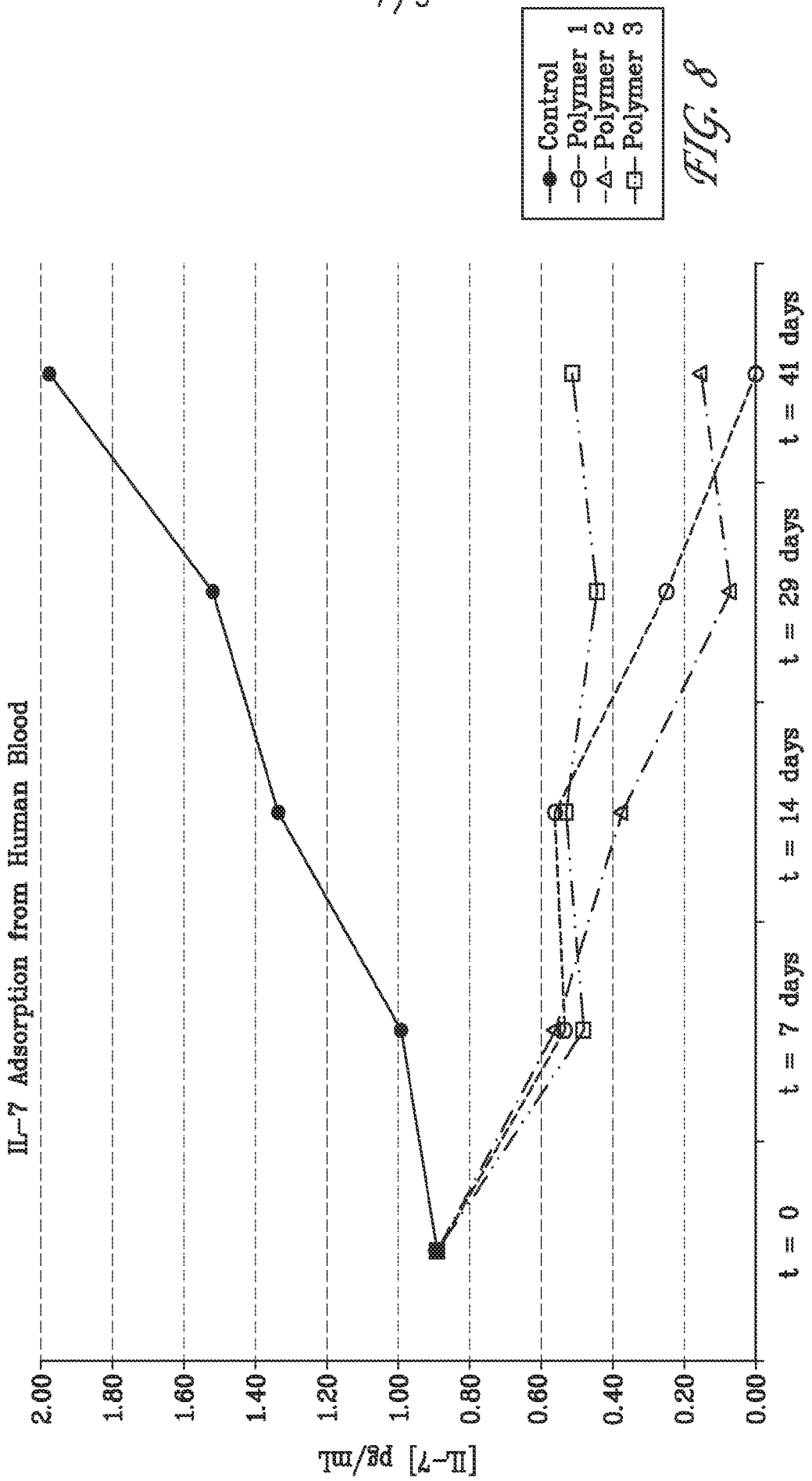

IL-7 Adsorption from Human Blood
[IL-7] pg/mL
2.00
1.80
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
t = 0
t = 7 days
t = 14 days
t = 29 days
t = 41 days
Control
Polymer 1
Polymer 2
Polymer 3

FIG. 8

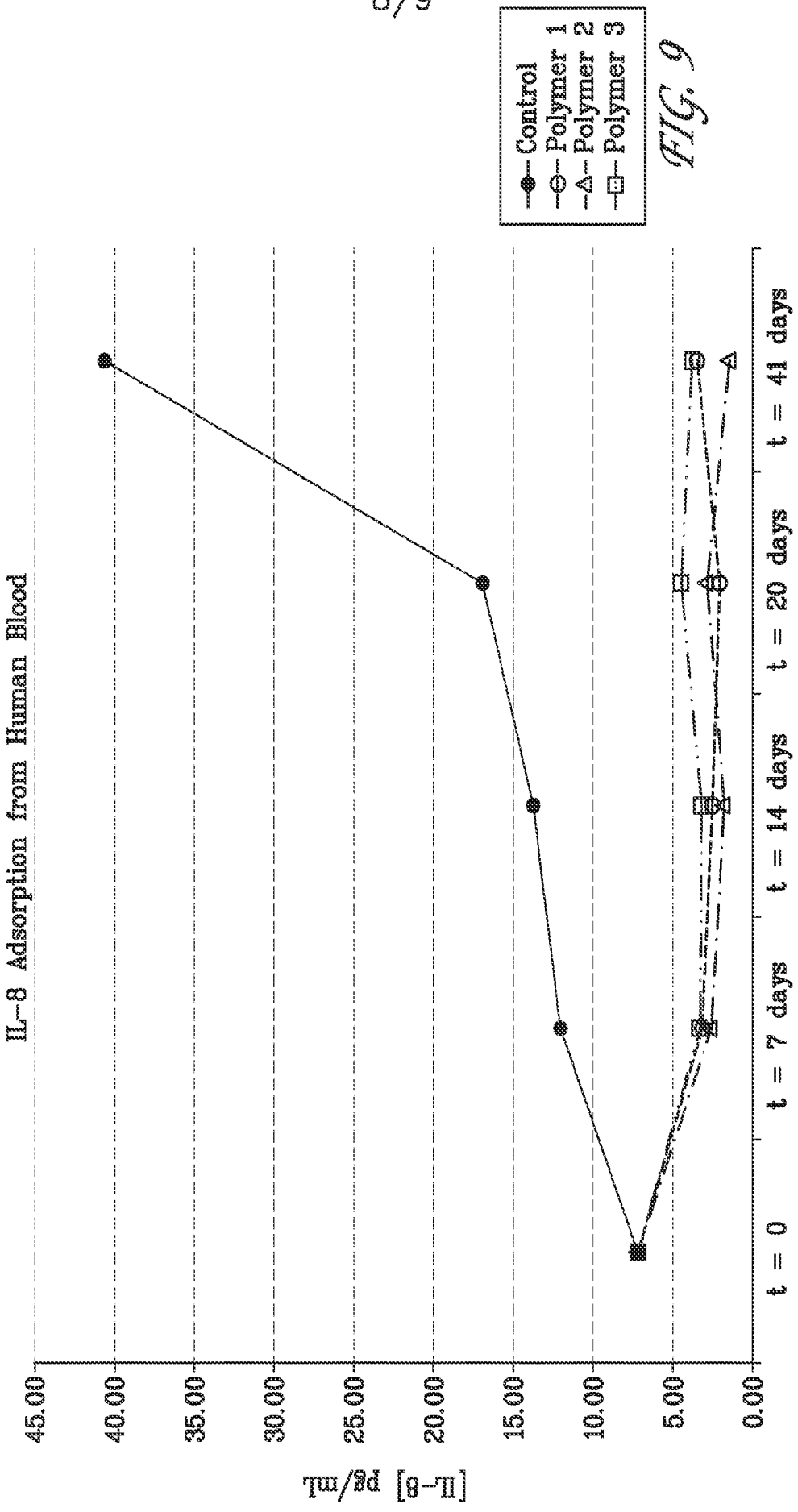

IL-8 Adsorption from Human Blood
[IL-8] pg/mL
45.00
40.00
35.00
30.00
25.00
20.00
15.00
10.00
5.00
0.00
t = 0
t = 7 days
t = 14 days
t = 20 days
t = 41 days
Control
Polymer 1
Polymer 2
Polymer 3

FIG. 9

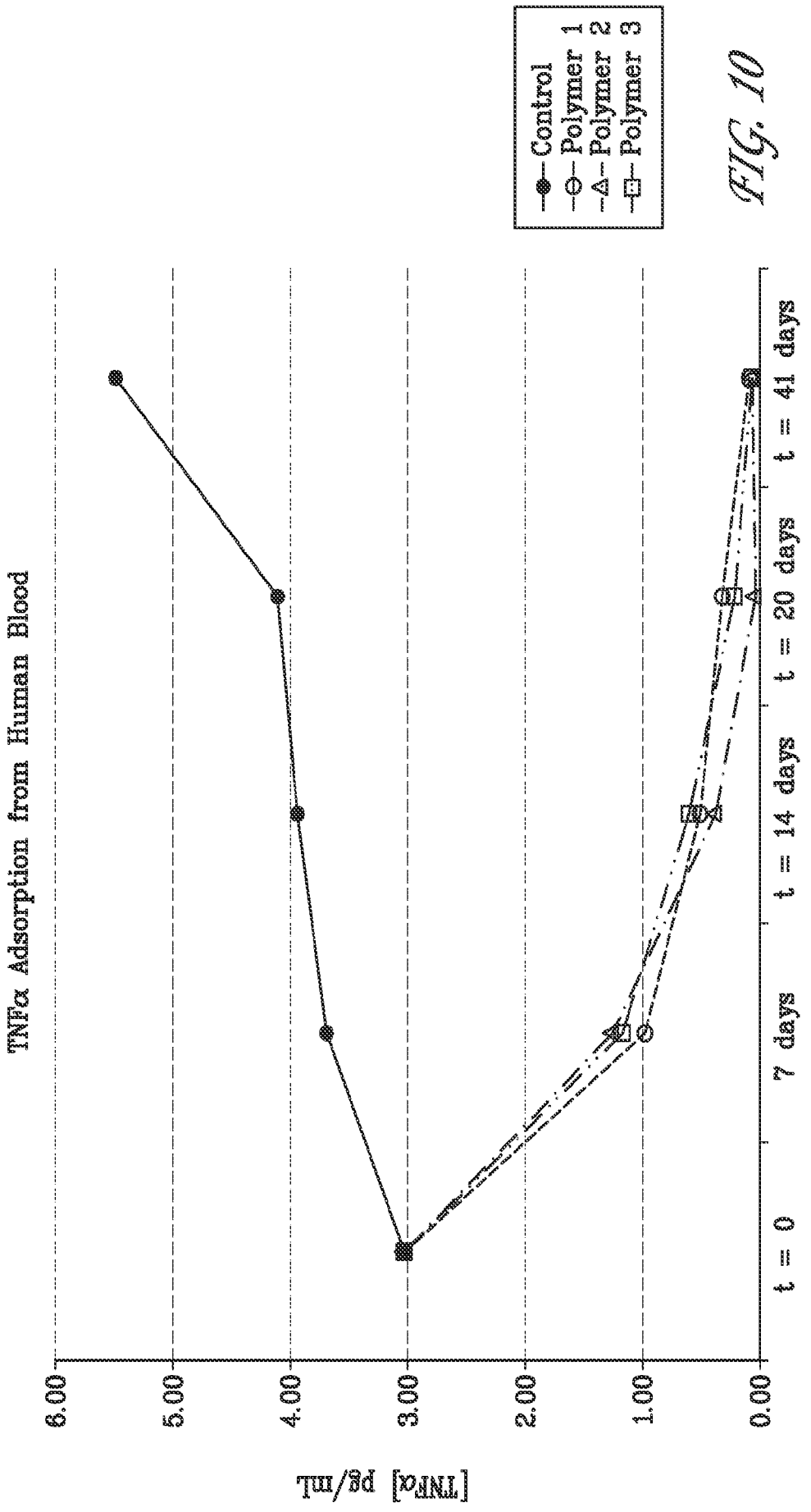
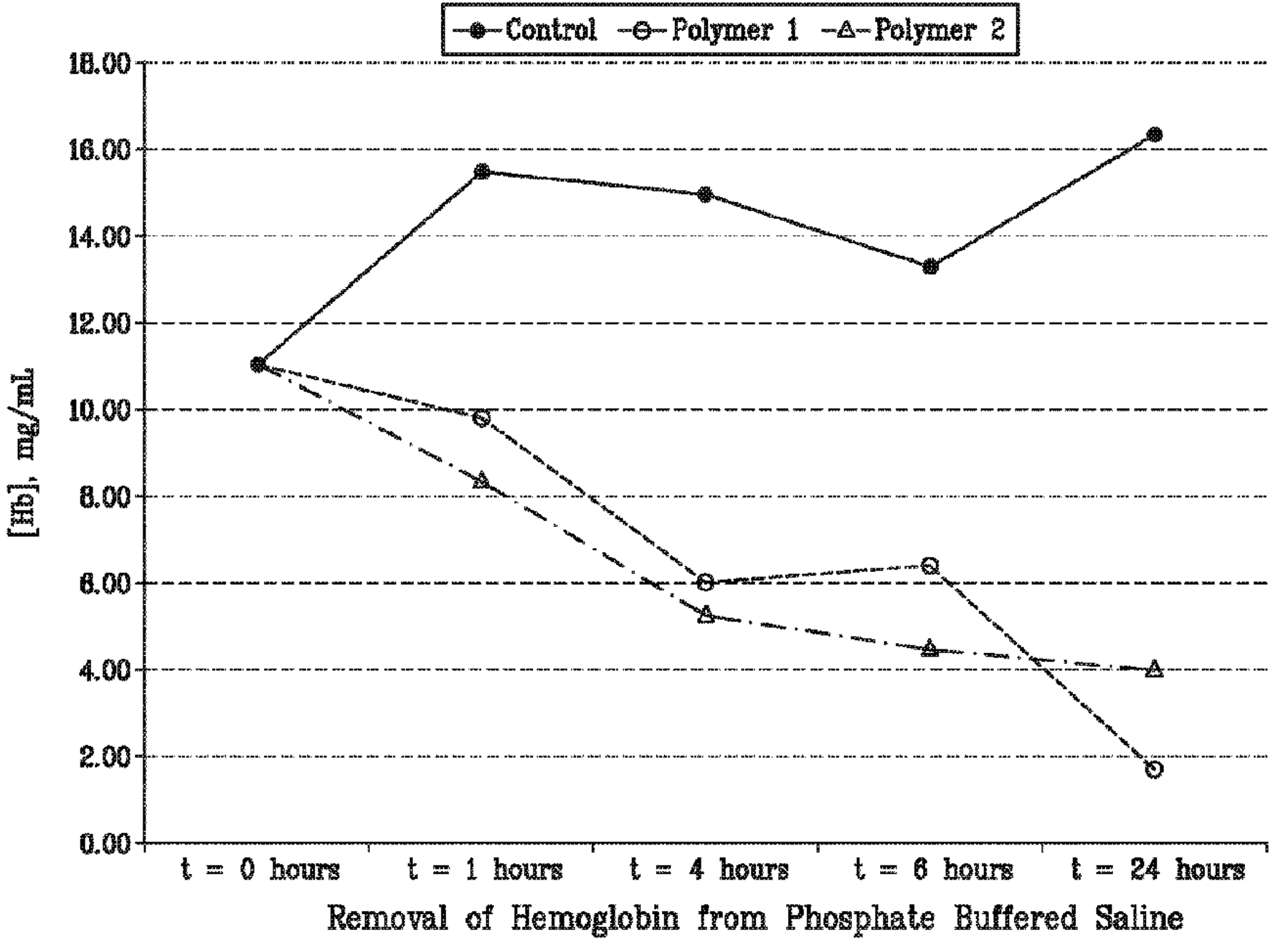

TNFα Adsorption from Human Blood
[TNFα] pg/mL
6.00
5.00
4.00
3.00
2.00
1.00
0.00
t = 0
7 days
t = 14 days
t = 20 days
t = 41 days
Control
Polymer 1
Polymer 2
Polymer 3

FIG. 10


Control
Polymer 1
Polymer 2
18.00
16.00
14.00
12.00
10.00
8.00
6.00
4.00
2.00
0.00
[Hb], mg/ml
t = 0 hours
t = 1 hours
t = 4 hours
t = 6 hours
t = 24 hours
Removal of Hemoglobin from Phosphate Buffered Saline