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(54) Title: MULTI-FUNCTIONAL HEMOCOMPATIBLE POROUS POLYMER BEAD SORBENT FOR REMOVING PROTEIN BASED TOXINS AN POTASSIUM FROM BIOLOGICAL FLUIDS

(57) Abstract: The invention concerns biocompatible polymer systems comprising at least one polymer with a plurality of pores, said polymer comprising a sulfonic acid salt functionality designed to adsorb a broad range of protein based toxins from less than 0.5 kDa to 1,000 kDa and positively charged ions including but not limited to potassium.

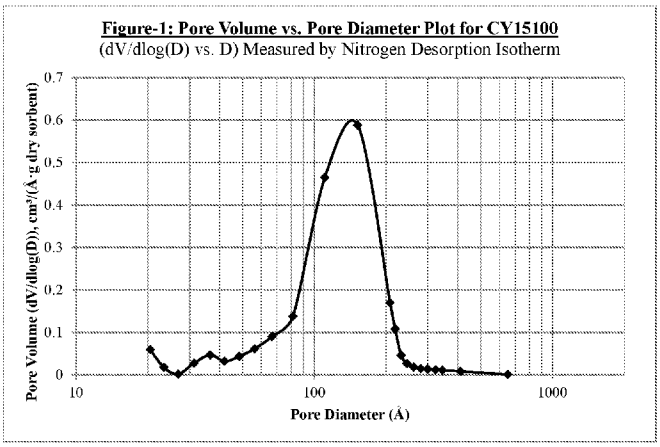

Figure 1

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MULTI-FUNCTIONAL HEMOCOMPATIBLE POROUS POLYMER BEAD SORBENT FOR REMOVING PROTEIN BASED TOXINS AN POTASSIUM FROM BIOLOGICAL FLUIDS

GOVERNMENT RIGHTS

[0001] The subject matter disclosed herein was made with government support under contract number HHSN268201600006C, awarded by The National Heart, Lung, and Blood Institute (NHLBI). The subject matter disclosed herein was also made with government support under contract number W81XWH-12-C-0038, awarded by The Department of Defense Small Business Innovation Research (DOD-SBIR). The government has certain rights in the herein disclosed subject matter.

CROSS-REFERENCE TO RELATED APPLICATIONS

[0002] The present application claims priority to U.S. Provisional Patent Application No. 62/245,071 filed on October 22, 2015. The contents of that application are hereby incorporated by reference.

TECHNICAL FIELD

[0003] The disclosed inventions are in the field of porous polymeric sorbents. The disclosed inventions are also in the field of broadly reducing contaminants in blood and blood products that can cause transfusion reactions; including, but not limited to, potassium, free hemoglobin, cytokines, bioactive lipids, and immunoglobulins. Additionally, the disclosed inventions are in the field of broadly removing contaminants by perfusion or hemoperfusion after tissue destruction; including, but not limited to, potassium, free hemoglobin, free myoglobin, cytokines, bioactive lipids, and immunoglobulins.

BACKGROUND

[0004] Packed red blood cell (pRBC) units contain reactive donor antibodies, free hemoglobin, high extracellular potassium levels, and biologically active inflammatory mediators that have the potential to cause adverse effects during blood transfusions. Such adverse effects can include non-hemolytic febrile and allergic transfusion reactions, atypical infections, allo-immunization, and potentially fatal reactions, like transfusion related acute lung injury (TRALI).

Furthermore, transfusion risk increases in patients receiving multiple pRBCs, such as those involved in trauma or undergoing surgery, and in primed susceptible patients, such as those in critical care or undergoing high-risk surgery.

[0005] The likelihood of adverse effects increases over time for stored blood or blood products, as concentrations of many biological response modifiers, such as potassium, free hemoglobin, and cytokines, increase with storage duration. Cytokines are produced by residual leukocytes during storage of platelets and pRBCs, and can cause inflammation, fever, and direct vascular and organ injury. Erythrocytes contain phosphatidyl choline, and cytosolic and membrane phospholipase A2, contributing increasing levels of lysophosphatidylcholine (lysoPC) during storage. Structural and biochemical changes that RBCs undergo are described as "storage lesion" and lead to a progressive loss of hemoglobin, and potassium. Plasma free hemoglobin can rapidly overwhelm the scavenging capability of haptoglobin, resulting in oxidative damage to lipids, proteins, endothelial cells, tissues, and renal proximal tubules, and in depletion of nitric oxide (NO) upon transfusion. Increases in extracellular potassium during storage lead to an increased risk of hyperkalemia and arrhythmia, particularly for large volume or "massive" transfusions and transfusions in newborns and infants.

[0006] Hyperkalemia describes a condition in which the potassium level in the blood exceeds a concentration of 5mEq/L, where concentrations exceeding 7mEq/L are considered severe cases. The electrical rhythm of the heart can be altered by moderate hyperkalemia, while severe conditions may cause the heart to stop beating. In addition to blood transfusions, another major cause of hyperkalemia is tissue destruction that causes dying cells to release potassium into blood circulation. Tissue destruction typically results from trauma, burns, hemolysis, massive lysis of tumor cells, rhabdomyolysis, or major surgery, such as cardiac surgery or cardiopulmonary bypass (CPB), where severe tissue destruction leads to more severe cases of hyperkalemia. In addition to the release of potassium into blood circulation, massive tissue injury is characterized by release of a large amount of myoglobin from damaged muscle tissue, plasma free hemoglobin from hemolyzed red blood cells, damage associated molecular pattern (DAMP) factors from damaged cells, and an upregulation of pro- and anti-inflammatory mediators, such as cytokines. Excessive free myoglobin, free hemoglobin, and other inflammatory mediators, can lead to complications such as renal failure or even death.

Abnormal regulation of cytokines, or release of DAMPS, may lead to systemic inflammatory response syndrome (SIRS) and multi-organ dysfunction (MODs).

[0007] Currently, there are existing technologies for potassium removal, or antibody removal, from stored blood or blood products. Kawasumi Laboratories has developed a single-pass in-line potassium adsorption filter to reduce the risk of hyperkalemia and improve safety for blood transfusions. The filter functions by exchanging potassium ions (K^+) for sodium ions (Na^+) to decrease the concentration of K^+ in stored RBC units. In an *in-vitro* study conducted by Yamada *et. al*, 10 filters were tested using each of three AS-3 RBC units via gravity filtration. The mean decrease in potassium was 97.5%, 91.2%, and 64.4% for the first, second, and third units, respectively. Accompanying the decrease in potassium were mean increases of sodium by 33%, magnesium by 151.4%, and total calcium by 116.1%. Plasma hemoglobin was unchanged after filtration.

[0008] A journal article published by Terai *et. al*., titled "Development of a Potassium-Specific Adsorbent for Direct Hemoperfusion", describes a study assessing the development of a sodium/calcium/magnesium exchange resin mixture that removes potassium without associated electrolyte abnormalities. At the time the article was written, direct hemoperfusion over an exchange resin was capable of lowering elevated serum potassium levels, but had not been used clinically due to subsequent electrolyte abnormalities. Prior to evaluating the exchange resin in an *in vivo* model, batch experiments were conducted *in vitro* to identify an effective ratio of sodium to calcium to magnesium for the resin mixture. Results from the study demonstrated a reduction of elevated plasma potassium levels from about 6.7 to about 3.5 mEq/L in anephric dogs, without any significant change in levels of sodium, calcium, magnesium, albumin, total protein, or cholesterol, after 2 hours of direct hemoperfusion through an exchange resin column. Pre- and post-hemoperfusion platelet counts and plasma free hemoglobin levels were also measured, where post-hemoperfusion platelet counts were only about 45% of pre-hemoperfusion levels, and there was no significant change in plasma free hemoglobin levels.

[0009] Patent WO 2012118735 A2, entitled "Removal of immunoglobulins and leukocytes from biological fluids," discloses devices, systems, and methods, for depleting biological fluids of immunoglobulins and leukocytes. It describes a system comprising immunoglobulin binding media and a leukocyte depletion filter element, where the binding media consist of cellulose beads and are placed into the pre-filtration blood bag. In one example,

30g dry weight cellulose beads, (4-MEP) HyperCel™ chromatography sorbent (Pall Corporation), were placed in a blood bag to which a unit of 5 day old AS-3 RBC was added, and the blood bag mixed on a rotamixer. The RBCs were gravity filtered through a downstream filter, where beads were trapped in an immunoglobulin binding media chamber and filtered cells passed through a fibrous leukocyte depletion filter before being collected and analyzed. Leukocyte content was reduced by 5.17 log, IgA reduced by 81%, IgG by 98%, and IgM by 42%. In another example, the ability of the leukocyte filter to remove cytokines was examined. Two units of 22-30 day old ABO compatible red cell concentrate were pooled together and then split into two lots. The first was placed in a blood bag containing about 25-33g dry weight cellulose beads, (4-MEP) HyperCel™ chromatography sorbent (Pall Corporation), with 10mL PBS and mixed for 45 minutes, and the second passed through a BPF4 High Efficiency leukocyte depletion filter (Pall Corporation) via gravity filtration. Afterwards, both lots were analyzed and it was found that in the aliquot placed in contact with the beads, interleukin 1-Beta (IL-1β) was reduced by 45.7%, interleukin-6 (IL-6) by 26.9%, interleukin-8 (IL-8) by 57.1% and tissue necrosis factor-alpha (TNF-α) by 49.9% For the aliquot passed through the filter, IL-1β was not reduced, IL-6 was not reduced, IL-8 was reduced by 35.0% and TNF-α reduced by 7.5%

[0010] In a journal article by Silliman *et. al.*, it was demonstrated that pre-storage filtration of packed RBCs removes HLA and HNA antibodies, reducing pro-inflammatory activity in RBC supernatant in an animal TRALI model. In the described study, plasma that contained antibodies to human lymphocyte antigen (HLA)-A2, or human neutrophil antigen (HNA)-3a, was filtered and priming activities of specific HNA-3a and HLA-2a were measured. OX27 antibodies were added to plasma and filtration was analyzed using a 2-event animal model for TRALI. RBC units from 31 donors, who were known to possess antibodies against HLA antigens, were filtered. In addition, 4 RBC units underwent standard leukoreduction. PMN priming activity, immunoglobulins, HLA antibodies, and ability to induce TRALI were measured. Filtration of the plasma was shown to remove more than 96% of IgG, and antibodies to HLA-A2 and HNA-3a, including their respective priming activity, and mitigated *in vivo* TRALI. Antibodies to HLA antigens were removed in experimental filtration of RBC units, accompanied by an inhibition of accumulation of lipid priming activity and lipid-mediated TRALI.

[0011] The sorbent material described herein is uniquely designed to efficiently remove free hemoglobin, antibodies, bioactive lipids, cytokines, and potassium, from blood and blood products. The polymer is multi-functional, retaining said biomolecules through tortuous path, sorption, pore capture, and ion exchange mechanisms. Novel chemistry is used to synthesize the polymer, utilizing a controlled sulfonation procedure that allows for the incorporation of sulfonic acid groups onto the aromatic rings without oxidizing all residual double bonds. This allows the polymeric matrix to maintain protein sorption and ion exchange capabilities, while still leaving residual functional groups available for hemocompatibility improvement modifications. The balance between sulfonation and retention of residual double bonds is crucial for preparation of an effective polymer sorbent.

[0012] Differentiating the multi-functional polymer from other filters that remove only reactive proteins or only potassium is its ability to remove both simultaneously without sacrificing binding capacity for either. Additionally, the sorbent is able to remove cytokines and inflammatory protein moieties simultaneously while removing potassium and antibodies. For hemoperfusion applications, it is a requirement that the polymer is hemocompatible. Using the unactivated partial thromboplastin time (uPTT) assay as a measure of thrombogenicity, the polymer described herein exhibits minimal activation, indicating a plasma-like interaction. This polymer is suited for a wide variety of applications, as many cases of trauma, burn, and major surgery, result in hyperkalemia, cytokine storm, and require blood transfusions. The ability to use one multi-application filter has many advantages over using many single-application filters. Given the value of blood and blood products, the use of a single, smaller filter that minimizes cell loss within the retained volume and reduces complexity of material quality assurance is very desirable.

SUMMARY

[0013] In some aspects, the invention concerns biocompatible polymer system comprising at least one polymer, said polymer comprising (i) a plurality of pores and (ii) a sulfonic acid salt functionality; the polymer system capable of adsorbing (i) a broad range of protein based toxins having a molecular weight of from less than about 0.5 kDa to about 1,000 kDa (or about 1 kDa to about 1,000 kDa in some embodiments) and (ii) positively charged ions. Some polymer systems have a polymer pore structure that has a total volume of pore sizes in the range of from 10 Å to 40,000 Å greater than 0.1 cc/g and less than 5.0 cc/g dry polymer. Some

preferred polymers are hemocompatible. The polymer system has the form of a solid support. Certain preferred polymer systems have a geometry of a spherical bead. Other polymer systems have the form of a fiber, monolithic column, film, membrane, or semi-permeable membrane.

[0014] In some embodiments, the toxins adsorbed comprise one or more of inflammatory mediators and stimulators comprised of one or more of cytokines, superantigens, monokines, chemokines, interferons, proteases, enzymes, peptides including bradykinin, soluble CD40 ligand, bioactive lipids, oxidized lipids, cell-free hemoglobin, cell-free myoglobin, growth factors, glycoproteins, prions, toxins, bacterial and viral toxins, endotoxins, drugs, vasoactive substances, foreign antigens, antibodies, and positively charged ions. In some preferred embodiments, the positively charged ion is potassium.

[0015] The polymers can be made by any means known in the art to produce a suitable porous polymer. In some embodiments, the polymer is made using suspension polymerization. Some polymers comprise a hypercrosslinked polymer. Certain spherical beads have a biocompatible hydrogel coating. In certain embodiments, the polymer is in the form of hypercrosslinked or a macroreticular porous polymer beads that have been sulfonated under mild conditions that retain residual functionality of any unreacted double bonds and chloromethyl groups. The unreacted double bonds or chloromethyl groups can be modified via free radical or S_N2 type chemistry to attach one or more of biocompatible and hemocompatible monomers, cross-linkers or low molecular weight oligomers.

[0016] In some embodiments, the porous polymer beads comprise sulfonic acid groups or a salt thereof, sulfonyl chloride, or sulfonate ester groups. The polymer beads comprising sulfonic acid groups or a salt thereof, sulfonyl chloride, or sulfonate ester groups can be produced by graft copolymerization of (i) premade porous polymer that contains unreacted double bonds with (ii) polymerizable vinyl monomers containing sulfonic acid groups or a salt thereof to form a mixture comprising hemocompatible vinyl monomers.

[0017] Some polymer systems are constructed from polymerizable vinyl monomers containing sulfonic acid groups or a salt thereof which are copolymerized in the presence of cross-linker, hemocompatible monomer, monomer and suitable porogen to yield porous polymeric polymer containing a sulfonic acid salt functionality.

[0018] Certain polymers are formed and subsequently modified to be biocompatible. Some modifications comprise forming a biocompatible surface coating or layer.

[0019] Other aspects include methods of perfusion comprising passing a physiologic fluid once through or by way of a suitable extracorporeal circuit through a device comprising the biocompatible polymer system described herein.

[0020] Yet another aspect concerns devices for removing (i) a broad range of protein based toxins from less than 0.5 kDa to 1,000 kDa and (ii) positively charged ions from physiologic fluid comprising the biocompatible polymer system described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] The accompanying drawings, which are included to provide a further understanding of the disclosure, are incorporated in and constitute a part of this specification, illustrate aspects of the disclosure and together with the detailed description serve to explain the principles of the disclosure. No attempt is made to show structural details of the disclosure in more detail than may be necessary for a fundamental understanding of the disclosure and the various ways in which it may be practiced. In the drawings:

[0022] **Figures 1, 2 and 3** present log differential pore volume plots for CY15100 and CY15102.

[0023] **Figures 4, 5 and 6** show plots of log differential pore volume for modified polymers.

[0024] **Figures 7 and 8** show plots of log differential pore volume for polymers CY15048 and CY15049.

[0025] **Figure 9** presents the percentage of initial free hemoglobin removed during single-pass filtration, averaged from three trials

[0026] **Figure 10** displays pre- and post- filtration potassium ion concentration in blood, averaged from three trials.

[0027] **Figure 11** presents dynamic recirculation data for CY14144, averaged from 7 trials.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[0028] 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.

[0029] The present invention may be understood more readily by reference to the following detailed description taken in connection with the accompanying figures and examples, which form a part of this disclosure. It is to be understood that this invention is not limited to the specific materials, devices, methods, applications, conditions or parameters described and/or shown herein, and that the terminology used herein is for the purpose of describing particular embodiments by way of example only and is not intended to be limiting of the claimed invention. The term "plurality", as used herein, means more than one. When a range of values is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another embodiment. All ranges are inclusive and combinable.

[0030] It is to be appreciated that certain features of the invention which are, for clarity, described herein in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention that are, for brevity, described in the context of a single embodiment, may also be provided separately or in any subcombination. Further reference to values stated in ranges includes each and every value within that range.

[0031] The following definitions are intended to assist in understanding the present invention:

[0032] The term "biocompatible" is defined to mean the sorbent is capable of coming in contact with physiologic fluids, living tissues, or organisms, without producing unacceptable clinical changes during the time that the sorbent is in contact with the physiologic fluids, living tissues, or organisms.

[0033] The term "hemocompatible" is defined as a condition whereby a biocompatible material when placed in contact with whole blood or blood plasma results in clinically acceptable physiologic changes.

[0034] As used herein, the term "physiologic fluids" are liquids that originate from the body and can include, but are not limited to, nasopharyngeal, oral, esophageal, gastric,

pancreatic, hepatic, pleural, pericardial, peritoneal, intestinal, prostatic, seminal, vaginal secretions, as well as tears, saliva, lung, or bronchial secretions, mucus, bile, blood, lymph, plasma, serum, synovial fluid, cerebrospinal fluid, urine, and interstitial, intracellular, and extracellular fluid, such as fluid that exudes from burns or wounds.

[0035] As used herein, the term “laboratory or manufacturing fluids” are defined as liquids that are used in life sciences applications that include, but are not limited to, tissue and cell culture media and additives, chemical or biologic assay media, sample preparation buffers, biologic manufacturing media, growth media, and bioreactor media.

[0036] As used herein, the term “sorbent” includes adsorbents and absorbents.

[0037] For purposes of this invention, the term “sorb” is defined as “taking up and binding by absorption and adsorption”.

[0038] For the purposes of this invention, the term “perfusion” is defined as passing a physiologic fluid, once through or by way of a suitable extracorporeal circuit, through a device containing the porous polymeric adsorbent to remove toxic molecules from the fluid.

[0039] The term “hemoperfusion” is a special case of perfusion where the physiologic fluid is blood.

[0040] The term “dispersant” or “dispersing agent” is defined as a substance that imparts a stabilizing effect upon a finely divided array of immiscible liquid droplets suspended in a fluidizing medium.

[0041] The term "heparin mimicking polymer" refers to any polymer that possesses the same anticoagulant and/or antithrombogenic properties as heparin.

[0042] The term “macroreticular synthesis” is defined as a polymerization of monomers into polymer in the presence of an inert precipitant which forces the growing polymer molecules out of the monomer liquid at a certain molecular size dictated by the phase equilibria to give solid nanosized microgel particles of spherical or almost spherical symmetry packed together to give a bead with physical pores of an open cell structure [U.S. Patent 4,297,220, Meitzner and Oline, October 27, 1981; R.L.Albright, Reactive Polymers, 4, 155-174(1986)].

[0043] The term “hypercrosslinked” describes a polymer in which the single repeating unit has a connectivity of more than two. Hypercrosslinked polymers are prepared by crosslinking swollen, or dissolved, polymer chains with a large number of rigid bridging spacers, rather than copolymerization of monomers. Crosslinking agents may include bis(chloromethyl)

derivatives of aromatic hydrocarbons, methylal, monochlorodimethyl ether, and other bifunctional compounds that react with the polymer in the presence of Friedel-Crafts catalysts [Tsyurupa, M. P., Z. K. Blinnikova, N. A. Proskurina, A. V. Pastukhov, L. A. Pavlova, and V. A. Davankov. "Hypercrosslinked Polystyrene: The First Nanoporous Polymeric Material." *Nanotechnologies in Russia* 4 (2009): 665-75.]

[0044] Some preferred polymers comprise residues from one or more monomers, or containing monomers, or mixtures thereof, selected from acrylonitrile, allyl ether, allyl glycidyl ether, butyl acrylate, butyl methacrylate, cetyl acrylate, cetyl methacrylate, 3,4-dihydroxy-1-butene, dipentaerythritol diacrylate, dipentaerythritol dimethacrylate, dipentaerythritol tetraacrylate, dipentaerythritol tetramethacrylate, dipentaerythritol triacrylate, dipentaerythritol trimethacrylate, divinylbenzene, divinylformamide, divinylnaphthalene, divinylsulfone, 3,4-epoxy-1-butene, 1,2-epoxy-9-decene, 1,2-epoxy-5-hexene, ethyl acrylate, ethyl methacrylate, ethylstyrene, ethylvinylbezene, glycidyl methacrylate, methyl acrylate, methyl methacrylate, octyl acrylate, octyl methacrylate, pentaerythritol diacrylate, pentaerythritol dimethacrylate, pentaerythritol tetraacrylate, pentaerythritol tetramethacrylate, pentaerythritol triacrylate, pentaerythritol trimethacrylate, styrene, trimethylolpropane diacrylate, trimethylolpropane dimethacrylate, trimethylolpropane triacrylate, trimethylolpropane trimethacrylate, trivinylbenzene, trivinylcyclohexane, vinyl acetate, vinylbenzyl alcohol, 4-vinyl-1-cyclohexene 1,2-epoxide, vinylformamide, vinylnaphthalene, 2-vinyloxirane, and vinyltoluene.

[0045] Some embodiments of the invention use an organic solvent and/or polymeric porogen as the porogen or pore-former, and the resulting phase separation induced during polymerization yield porous polymers. Some preferred porogens are selected from, or mixtures comprised of any combination of, benzyl alcohol, cyclohexane, cyclohexanol, cyclohexanone, decane, dibutyl phthalate, di-2-ethylhexyl phthalate, di-2-ethylhexylphosphoric acid, ethylacetate, 2-ethyl-1-hexanoic acid, 2-ethyl-1-hexanol, n-heptane, n-hexane, isoamyl acetate, isoamyl alcohol, n-octane, pentanol, poly(propylene glycol), polystyrene, poly(styrene-*co*-methyl methacrylate), tetraline, toluene, tri-n-butylphosphate, 1,2,3-trichloropropane, 2,2,4-trimethylpentane, xylene.

[0046] In yet another embodiment, the dispersing agent is selected from a group consisting of hydroxyethyl cellulose, hydroxypropyl cellulose, poly(diethylaminoethyl acrylate), poly(diethylaminoethyl methacrylate), poly(dimethylaminoethyl acrylate),

poly(dimethylaminoethyl methacrylate), poly(hydroxyethyl acrylate), poly(hydroxyethyl methacrylate), poly(hydroxypropyl acrylate), poly(hydroxypropyl methacrylate), poly(vinyl alcohol), salts of poly(acrylic acid), salts of poly(methacrylic acid) and mixtures thereof.

[0047] Preferred sorbents are biocompatible. In another further embodiment, the polymer is biocompatible. In yet another embodiment, the polymer is hemocompatible. In still a further embodiment, the biocompatible polymer is hemocompatible. In still a further embodiment, the geometry of the polymer is a spherical bead.

[0048] In another embodiment, the biocompatible polymer comprises poly(N-vinylpyrrolidone).

[0049] The coating/dispersant on the porous poly(styrene-*co*-divinylbenzene) resin will imbue the material with improved biocompatibility.

[0050] In still yet another embodiment, a group of cross-linkers consisting of dipentaerythritol diacrylates, dipentaerythritol dimethacrylates, dipentaerythritol tetraacrylates, dipentaerythritol tetramethacrylates, dipentaerythritol triacrylates, dipentaerythritol trimethacrylates, divinylbenzene, divinylformamide, divinylnaphthalene, divinylsulfone, pentaerythritol diacrylates, pentaerythritol dimethacrylates, pentaerythritol tetraacrylates, pentaerythritol tetramethacrylates, pentaerythritol triacrylates, pentaerythritol trimethacrylates, trimethylolpropane diacrylate, trimethylolpropane dimethacrylate, trimethylolpropane triacrylate, trimethylolpropane trimethacrylate, trivinylbenzene, trivinylcyclohexane and mixtures thereof can be used in formation of a hemocompatible hydrogel coating.

[0051] In some embodiments, the polymer is a polymer comprising at least one crosslinking agent and at least one dispersing agent. The dispersing agent may be biocompatible. The dispersing agents can be selected from chemicals, compounds or materials such as hydroxyethyl cellulose, hydroxypropyl cellulose, poly(diethylaminoethyl acrylate), poly(diethylaminoethyl methacrylate), poly(dimethylaminoethyl acrylate), poly(dimethylaminoethyl methacrylate), poly(hydroxyethyl acrylate), poly(hydroxyethyl methacrylate), poly(hydroxypropyl acrylate), poly(hydroxypropyl methacrylate), poly(vinyl alcohol), salts of poly(acrylic acid), salts of poly(methacrylic acid) and mixtures thereof; the crosslinking agent selected from a group consisting of dipentaerythritol diacrylates, dipentaerythritol dimethacrylates, dipentaerythritol tetraacrylates, dipentaerythritol tetramethacrylates, dipentaerythritol triacrylates, dipentaerythritol trimethacrylates,

divinylbenzene, divinylformamide, divinylnaphthalene, divinylsulfone, pentaerythritol diacrylates, pentaerythritol dimethacrylates, pentaerythritol tetraacrylates, pentaerythritol tetramethacrylates, pentaerythritol triacrylates, pentaerythritol trimethacrylates, trimethylolpropane diacrylate, trimethylolpropane dimethacrylate, trimethylolpropane triacrylate, trimethylolpropane trimethacrylate, trivinylbenzene, trivinylcyclohexane and mixtures thereof. Preferably, the polymer is developed simultaneously with the formation of the coating, wherein the dispersing agent is chemically bound or entangled on the surface of the polymer.

[0052] In still another embodiment, the biocompatible polymer coating is selected from a group consisting of poly(hydroxyethyl methacrylate), poly(hydroxyethyl acrylate), poly(dimethylaminoethyl methacrylate), salts of poly(acrylic acid), salts of poly(methacrylic acid), poly(diethylaminoethyl methacrylate), poly(hydroxypropyl methacrylate), poly(hydroxypropyl acrylate), poly(N-vinylpyrrolidone), poly(vinyl alcohol) and mixtures thereof. In another embodiment, the salts may be sodium and potassium salts and in still another embodiment, the salts are water-soluble salts.

[0053] In still another embodiment, the biocompatible oligomer coating is selected from a group consisting of poly(hydroxyethyl methacrylate), poly(hydroxyethyl acrylate), poly(dimethylaminoethyl methacrylate), salts of poly(acrylic acid), salts of poly(methacrylic acid), poly(diethylaminoethyl methacrylate), poly(hydroxypropyl methacrylate), poly(hydroxypropyl acrylate), poly(N-vinylpyrrolidone), poly(vinyl alcohol) and mixtures thereof. In another embodiment, the salts may be sodium and potassium salts and in still another embodiment, the salts are water-soluble salts.

[0054] The present biocompatible sorbent compositions are comprised of a plurality of pores. The biocompatible sorbents are designed to adsorb a broad range of toxins from less than 0.5 kDa to 1,000 kDa. While not intending to be bound by theory, it is believed the sorbent acts by sequestering molecules of a predetermined molecular weight within the pores. The size of a molecule that can be sorbed by the polymer will increase as the pore size of the polymer increases. Conversely, as the pore size is increased beyond the optimum pore size for adsorption of a given molecule, adsorption of said protein may or will decrease.

[0055] In certain methods, the solid form is porous. Some solid forms are characterized as having a pore structure having a total volume of pore sizes in the range of from 10 Å to 40,000 Å greater than 0.1 cc/g and less than 5.0 cc/g dry polymer.

[0056] In certain embodiments, the polymers can be made in bead form having a diameter in the range of 0.1 micrometers to 2 centimeters. Certain polymers are in the form of powder, beads or other regular or irregularly shaped particulates.

[0057] In some embodiments, the plurality of solid forms comprises particles having a diameter in the range for 0.1 micrometers to 2 centimeters.

[0058] In some methods, the undesirable molecules are inflammatory mediators and stimulators comprised of cytokines, superantigens, monokines, chemokines, interferons, proteases, enzymes, peptides including bradykinin, soluble CD40 ligand, bioactive lipids, oxidized lipids, cell-free hemoglobin, damage-associated molecular pattern (DAMPs), Pathogen-associated molecular pattern molecules (PAMPs), cell-free myoglobin, growth factors, glycoproteins, prions, toxins, bacterial and viral toxins, endotoxins, drugs, vasoactive substances, foreign antigens, antibodies, and positively charged ions, including, but not limited to, potassium.

[0059] In some methods, the antibodies can be immunoglobulin A (IgA), immunoglobulin D (IgD), immunoglobulin E (IgE), immunoglobulin D (IgG), immunoglobulin D (IgM) and/or immunoglobulin fragments or subunits.

[0060] DAMPs have been associated with countless syndromes and diseases. These include complications from trauma, burns, traumatic brain injury and invasive surgery, and also organ-specific illnesses like liver disease, kidney dialysis complications, and autoimmune diseases. DAMPs are host molecules that can initiate and perpetuate noninfectious SIRS and exacerbate infectious SIRS. DAMPs are a diverse family of molecules that are intracellular in physiological conditions and many are nuclear or cytosolic proteins. DAMPs can be divided into two groups: (1) molecules that perform noninflammatory functions in living cells (such as HMGB1) and acquire immunomodulatory properties when released, secreted, modified, or exposed on the cell surface during cellular stress, damage, or injury, or (2) alarmins, i.e., molecules that possess cytokine-like functions (such as β-Defensins and Cathelicidin), which can be stored in cells and released upon cell lysis, whereupon they contribute to the inflammatory response. When released outside the cell or exposed on the surface of the cell following tissue injury, they move from a reducing to an oxidizing milieu, which affects their activity. Also, following necrosis, mitochondrial and nuclear DNA fragments are released outside the cell becoming DAMPs.

[0061] DAMPs, such as HMGB-1, heat-shock and S100 proteins are normally found inside cells and are released by tissue damage. DAMPs act as endogenous danger signals to promote and exacerbate the inflammatory response. HMGB-1 is a non-histone nuclear protein that is released under stress conditions. Extracellular HMGB-1 is an indicator of tissue necrosis and has been associated with an increased risk of sepsis and multiple organ dysfunction syndrome (MODS). S100 A8 (granulin A, MRP8) and A9 (granulin B\, MRP14) homo and heterodimers bind to and signal directly via the TLR4/lipopolysaccharide receptor complex where they become danger signals that activate immune cells and vascular endothelium. Procalcitonin is a marker of severe sepsis caused by bacteria and its release into circulation is indicative of the degree of sepsis. Serum amyloid A (SAA), an acute-phase protein, is produced predominantly by hepatocytes in response to injury, infection, and inflammation. During acute inflammation, serum SAA levels may rise by 1000-fold. SAA is chemotactic for neutrophils and induces the production of proinflammatory cytokines. Heat shock proteins (HSP) are a family of proteins that are produced by cells in response to exposure to stressful conditions and are named according to their molecular weight (10, 20-30, 40, 60, 70, 90). The small 8-kilodalton protein ubiquitin, which marks proteins for degradation, also has features of a heat shock protein. Hepatoma-derived growth factor (HDGF), despite its name, is a protein expressed by neurons. HDGF can be released actively by neurons via a nonclassical pathway and passively by necrotic cells. Other factors, such as complement factors 3 and 5, are activated as part of the host defense against pathogens but can also contribute to the adverse outcomes in sepsis. Excessive, persistent circulating levels of cytokines and DAMPs contribute to organ injury and identify those patients who have the highest risk of multiple organ dysfunction (MODs) and death in community acquired pneumonia and sepsis.

[0062] PAMPs include lipopolysaccharides, lipopeptides, lipoteichoic acid, peptidoglycans, nucleic acids such as double-stranded RNA, toxins and flagellins nd can trigger an immune response in the host (e.g. the innate immune system) to fight the infection, leading to the production of high levels of inflammatory and anti-inflammatory mediators, such as cytokines. PAMPs and high cytokine levels, as well as direct tissue injury (trauma, burns, etc.), can damage tissue, causing the extracellular release of damage-associated molecular pattern (DAMPs) molecules into the bloodstream. DAMPs are a broad class of endogenous molecules,

which like PAMPs, trigger the immune response through pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs).

[0063] Preferred sorbents include cross-linked polymeric material derived from the reaction of a cross-linker with one or more of the following polymerizable monomers, then subsequently sulfonated to form a sulfonic acid salt: acrylonitrile, butyl acrylate, butyl methacrylate, cetyl acrylate, cetyl methacrylate, divinylbenzene, ethyl acrylate, ethyl methacrylate, ethylstyrene, methyl acrylate, methyl methacrylate, octyl acrylate, octyl methacrylate, styrene, vinylbenzyl alcohol, vinylformamide, vinylnaphthalene, or vinyltoluene.

[0064] In some embodiments, radically polymerizable vinyl monomers containing ~SO_3Na groups, or ~SO_3H groups, can be used in graft copolymerization with porous polymers containing polymerizable double bonds. These monomers can be selected from 4-styrene sulfonic acid sodium salt, vinyl sulfonic acid sodium salt, 2-acrylamido-2-methyl-1-propanesulfonic acid, 2-acrylamido-2-methyl-1-propanesulfonic sodium salt, 3-sulfopropyl acrylate sodium salt, 3-sulfopropyl methacrylate sodium salt, [2-(methacryloyloxy)ethyl] dimethyl-(3-sulfopropyl)ammonium hydroxide, N-(3-sulfopropyl)-N-(methacryloxyethyl)-N,N-dimethylammonium betaine, para-styrene sulfonyl chloride, or any combinations thereof. Furthermore, para-styrene sulfonyl chloride can be polymerized in the presence of divinylbenzene and hydrolyzed with sodium hydroxide solution to directly yield poly(styrene-*co*-divinylbenzene) porous material with ~SO_3Na groups.

[0065] In another embodiment, the present invention relates to a sulfonated polymer comprised of at least one crosslinking agent for making the polymer and at least one dispersing agent whereby the dispersing agent forms a biocompatible surface on the polymer.

[0066] In one embodiment the porous polymers of this invention are made by suspension polymerization in a formulated aqueous phase with free radical initiation in the presence of aqueous phase dispersants that are selected to provide a biocompatible and a hemocompatible exterior surface to the formed polymer beads. The sulfonation of the resultant beads yields an ion exchange resin coated with a hemocompatible hydrogel. The beads are made porous by the macroreticular synthesis with an appropriately selected porogen (pore forming agent) and an appropriate time-temperature profile for the polymerization in order to develop the proper pore structure. The subsequent introduction of the sulfonic acid groups in the already formed network forms a sulfonic acid salt inner core (ion exchange resin) and a hemocompatible outer hydrogel

exterior. Suitable choice of the reaction conditions for the sulfonation allows preservation or expression (via a protecting group) of the hemocompatible nature of the exterior hydrogel.

[0067] In another embodiment polymers made by suspension polymerization can be made biocompatible and hemocompatible by further grafting of biocompatible and hemocompatible monomers or low molecular weight oligomers. It has been shown that the radical polymerization procedure does not consume all the vinyl groups of DVB introduced into copolymerization. On average, about 30% of DVB species fail to serve as crosslinking bridges and remain involved in the network by only one of two vinyl groups. The presence of a relatively high amount of pendant vinyl groups is therefore a characteristic feature of the macroporous adsorbents. It can be expected that these pendant vinyl groups are preferably exposed to the surface of the polymer beads and their macropores should be readily available to chemical modification. The chemical modification of the surface of macroporous DVB-copolymers relies on chemical reactions of the surface-exposed pendant vinyl groups and aims at converting these groups into more hydrophilic functional groups. This conversion via free radical grafting of monomers and/or cross-linkers or low molecular weight oligomers provides the initial hydrophobic adsorbing material with the property of hemocompatibility. The subsequent introduction of the sulfonic acid groups into the already formed network forms a sulfonic acid salt inner core (ion exchange resin) and a hemocompatible outer hydrogel exterior. Suitable choice of the reaction conditions for the sulfonation allows preservation or expression (via a protecting group) of the hemocompatible nature of the exterior hydrogel.

[0068] Still another embodiment consists of binding long hydrophilic polymer chains onto the beads' surfaces, which should preclude contact between blood cells and the sulfonated polystyrene surface. This can be accomplished via free radical or S_N2 type chemistry. The chemical modification of the surface of sorbent beads, which is the case in the above modification, is facilitated by the remarkable peculiarity of the hypercrosslinked polystyrene; namely, that the reactive functional groups of the polymer are predominantly located on its surface. The hypercrosslinked polystyrene is generally prepared by crosslinking polystyrene chains with large amounts of bifunctional compounds, in particular, those bearing two reactive chloromethyl groups. The latter alkylate, in a two-step reaction, two phenyl groups of neighboring polystyrene chains according to Friedel-Crafts reaction, with evolution of two molecules of HCl and formation of a cross bridge. During the crosslinking reaction, the three-

dimensional network formed acquires rigidity. This property gradually reduces the rate of the second step of the crosslinking reaction, since the reduced mobility of the second pendant functional group of the initial crosslinking reagent makes it more and more difficult to add an appropriate second partner for the alkylation reaction. This is especially characteristic of the second functional groups that happen to be exposed to the surface of the bead. Therefore, of the pendant unreacted chloromethyl groups in the final hypercrosslinked polymer, the largest portion, if not the majority of the groups, are located on the surface of the bead (or on the surface of large pores). This circumstance makes it possible to predominantly modify the surface of the polymer beads by involving the above chloromethyl groups into various chemical reactions that allow attachment of biocompatible and hemocompatible monomers, and/or cross-linkers or low molecular weight oligomers. The subsequent introduction of the sulfonic acid groups in the already formed network forms a sulfonic acid salt inner core (ion exchange resin) and a hemocompatible outer hydrogel exterior. Suitable choice of the reaction conditions for the sulfonation allows preservation or expression (via a protecting group) of the hemocompatible nature of the exterior hydrogel.

[0069] In yet another embodiment, the radical polymerization initiator is initially added to the dispersed organic phase, not the aqueous dispersion medium as is typical in suspension polymerization. During polymerization, many growing polymer chains with their chain-end radicals show up at the phase interface and can initiate the polymerization in the dispersion medium. Moreover, the radical initiator, like benzoyl peroxide, generates radicals relatively slowly. This initiator is only partially consumed during the formation of beads even after several hours of polymerization. This initiator easily moves toward the surface of the bead and activates the surface exposed pendant vinyl groups of the divinylbenzene moiety of the bead, thus initiating the graft: polymerization of other monomers added after the reaction has proceeded for a period of time. Therefore, free-radical grafting can occur during the transformation of the monomer droplets into polymer beads thereby incorporating monomers and/or cross-linkers or low molecular weight oligomers that impart biocompatibility or hemocompatibility as a surface coating. The subsequent introduction of the sulfonic acid groups in the already formed network forms a sulfonic acid salt inner core (ion exchange resin) and a hemocompatible outer hydrogel exterior. Suitable choice of the reaction conditions for the sulfonation allows preservation or expression (via a protecting group) of the hemocompatible nature of the exterior hydrogel.

[0070] In still yet another embodiment, hypercrosslinked or macroreticular porous polymer beads (including commercial versions) that have been sulfonated under mild conditions that retain residual functionality such as unreacted double bonds or chloromethyl groups can be modified via free radical or S_N2 type chemistry which would allow attachment of biocompatible and a hemocompatible monomers, and/or cross-linkers or low molecular weight oligomers. Among various "mild" sulfonating agents, Acetyl Sulfate (prepared from 98% conc. Sulfuric acid and acetic anhydride at low temperatures) is known to be very efficient for DVB or Styrene based polymeric materials. Sulfonation is usually done at 50°C for several hours using equimolar amounts of acetyl sulfate and DVB or styrene based polymers. Sulfonation occurs mainly at the benzene ring and unreacted double bonds (in DVB based cross-linked polymeric porous beads) would be preserved for further functionalization. Usually after sulfonation with acetyl sulfate, the polymer is converted into $-SO_3Na$ form and can be graft copolymerized with N-vinyl pyrrolidone or other hemocompatible monomers and/or cross-linkers or low molecular weight oligomers (in bulk with benzoyl peroxide as initiator) or in water solutions (using sodium persulfate initiator). Resulting sulfonated polymer is "coated" with poly(N-vinylpyrrolidone), as an example, to create a hemocompatible material capable of removing K^+ cations from physiological fluids.

[0071] Some embodiments of the invention involve direct synthesis of porous polymeric beads containing $–SO_3Na$ groups. Any polymerizable vinyl monomer containing $–SO_3Na$ (or $–SO_3H$) groups can be polymerized in the presence of cross-linker monomer (like DVB, bis-acrylamide, bis-(meth)acrylates, etc.) and suitable porogen to yield porous polymeric beads containing above mentioned functionalities ($-SO_3Na$ or SO_3H). Vinyl monomers containing SO_3Na or SO_3H groups can also be copolymerized with hemocompatible monomer (NVP. 2-HEMA, etc.) in presence of porogen to yield hemocompatible porous beads containing $-SO_3Na$ groups.

[0072] Another embodiment of the invention involves making porous polymer beads containing SO_3Na groups via graft copolymerization of premade porous polymers (containing double bonds unreacted) with polymerizable vinyl monomers containing $–SO_3Na$ or $–SO_3H$ groups (with the mixture of suitable hemocompatible vinyl monomers). Such monomers can be vinyl sulfonic acid Na salt, 4-styrene sulfonic acid Na salt, etc.

[0073] The hemoperfusion and perfusion devices consist of a packed bead bed of the porous polymer beads in a flow-through container fitted with either a retainer screen at both the

exit end and the entrance end to maintain the bead bed inside the container or with a subsequent retainer screen to collect the beads after mixing. The hemoperfusion and perfusion operations are performed by passing the whole blood, blood plasma or physiologic fluid through the packed bead bed. During the perfusion through the bead bed, the toxic molecules are retained by sorption, torturous path, and/or ion exchange mechanism the while the remainder of the fluid and intact cell components pass through essentially unchanged in concentration.

[0074] In some other embodiments, an in-line filter is comprised of a packed bead bed of the porous polymer beads in a flow-through container, fitted with a retainer screen at both the exit end and the entrance end to maintain the bead bed inside the container. pRBCs are passed from a storage bag once-through the packed bead bed via gravity, during which the toxic molecules are retained by sorption, torturous path, and/or ion exchange mechanisms, while the remainder of the fluid and intact cell components pass through essentially unchanged in concentration.

[0075] Certain polymers useful in the invention (as is or after further modification) 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): macroporous polymeric sorbents 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 sorbents 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, Diaion™ SP 207SS. Purolite Company: Purosorb™ AP 250 and Purosorb™ AP 400, and Kaneka Corp. Lixelle beads.

[0076] Various proteins may be adsorbed by the composition of the instant disclosure. Some of these proteins and their molecular weights are shown in the table below.

Protein	**Molecular Weight (Da)**	**Protein**	**Molecular Weight (Da)**
PAF (Platelet Activating Factor)	524	Enterotoxin A, S. aureus	27,800
bilirubin	548.6	alpha toxin A&B, S. aureus	28,000
heme b	616.5	PCNA, proliferating cell nuclear antigen	29,000
MIP-1alpha	8,000	Arginse I	35,000
Complement C5a	8,200	Carboxypeptidase A	35,000
Complement C3a	9,089	Thrombin	36,700
IL-8	9,000	alpha-1 antitrypsin	44,324
S100B (dimerizes)	10,000	TNF-alpha	52,000
β-2 microglobulin	11,800	Activated Protein C	56,200
Procalcitonin	13,000	Amylase	57,000
Phospholipase A2, secretory PLA2 type I pancreatic	14,000	hemopexin	57,000
PLA2G2A	16,083	alpha-1 antichymotrypsin	55,000-68,000
IL-7	17,400	Diptheria toxoid	62,000
Myoglobin	17,699	hemoglobin, oxy	64,000
Trypsin-human pancreas	23,300	Pseudomonas Exotoxin A	66, 000
IL-6	23,718	ShigaToxin (A 32 kDa, 5xB 7.7 kDa)	69,000
Toxic shock syndrome toxin 1 (TSST-1	24,000	Calpain-1 (human erythrocytes)	112,00
Enterotoxin B, S aureus	24,500	C reactive Protein (5x25 kDa)	115,000
HMGB1	24,894	Myeloperoxidase (neutrophils)	150,000
Interferon gamma	25,000	Immunoglobulin G IgG	150,000
Chymotrypsin	25,000	NOS synthase	150,000
Elastase (neutrophil)	25,000	Immunoglobulin A IgA	162,000
Trypsin	*26,488*	Immunoglobulin E (IgE)	190,000
PF4	27,100	Immunoglobulin M IgM	950,000

[0077] The following examples are intended to be exemplary and non-limiting.

Example 1: Base Sorbent Synthesis CY12004, CY15042, CY15044, CY15045, and CY15077

[0078] The general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as defined in the appended claims. Other aspects of the present invention will be apparent to those skilled in the art in view of the detailed description of the invention as provided herein.

[0079] Reactor Setup; a 4-neck glass lid was affixed to a 3000mL jacketed cylindrical glass reaction vessel using a stainless steel flange clamp and PFTE gasket. The lid was fitted with a PFTE stirrer bearing, RTD probe adapter, and water-cooled reflux condenser. A stainless steel stirring shaft having five 45° agitators was fit through the stirrer bearing and inserted into a digital overhead stirrer. An RTD probe was fit through the corresponding adapter, and connected to a PolyStat circulating heating and chilling unit. Compatible tubing was used to connect the inlet and outlet of the reaction vessel jacket to the appropriate ports on the PolyStat. The unused port in the lid was used for charging the reactor and was plugged at all other times.

[0080] Polymerization; Aqueous phase and organic phase compositions are shown below, in Table I and Table II, respectively. Ultrapure water was split into approximately equal parts in two separate Erlenmeyer flasks each containing a PFTE coated magnetic stir bar. Poly(vinyl alcohol) (PVA), having a degree of hydrolysis of 85.0 to 89.0 mol percent and a viscosity of 23.0 to 27.0 cP in a 4% aqueous solution at 20°C, was dispersed into the water in the first flask and heated to 80°C on a hot plate with agitation. Salts (see Table 1, MSP, DSP, TSP and Sodium nitrite) were dispersed into the water in the second flask and heated to 80°C on a hot plate with agitation. Circulation of heat transfer fluid from the PolyStat through the reaction vessel jacket was started, and fluid temperature heated to 60°C. Once PVA and salts dissolved, both solutions were charged to the reactor, one at a time, using a glass funnel. The digital overhead stirrer was powered on and the rpm set to a value to form appropriate droplet sizes upon organic phase addition. Temperature of the aqueous phase in the kettle was set to 70°C. The organic phase was prepared by adding benzoyl peroxide (BPO) to the divinylbenzene (DVB) and styrene in a 2L Erlenmeyer flask and swirling until completely dissolved. 2,2,4-trimethylpentane and toluene were added to the flask, which was swirled to mix well. Once the temperature of the aqueous phase in the reactor reached 70°C, the organic phase was charged into the reactor using a narrow-necked glass funnel. Temperature of the reaction volume

dropped upon the organic addition. A temperature program for the PolyStat was started, heating the reaction volume from 60 to 77°C over 30 minutes, 77 to 80°C over 30 minutes, holding the temperature at 80°C for 960 minutes, and cooling to 20°C over 60 minutes. 1-Vinyl-2-pyrrolidinone (VP) was added dropwise via glass separatory funnel once the reaction reached identity point, approximately one hour after the reaction temperature reached 80°C. Note: the temperature program for preparation of polymer CY15042 was different, proceeding as follows; reaction volume heated from 55 to 62°C over 30 minutes, 62 to 65°C over 30 minutes, held at 65°C for 1320 minutes, heated from 65 to 82°C over 30 minutes, 82 to 85°C over 30 minutes, held at 85°C for 60 minutes, then cooled to 20°C over 60 minutes.

Table I: Aqueous Phase Composition

Reagent	Mass (g)
Ultrapure water	1500.000
Poly(vinyl alcohol) (PVA)	4.448
Monosodium phosphate (MSP)	4.602
Disodium phosphate (DSP)	15.339
Trisodium phosphate (TSP)	9.510
Sodium nitrite	0.046
Total	1533.899

Table II: Organic Phase Compositions

	CY12004	CY15042	CY15044	CY15045	CY15077
Reagent	Mass (g)	Mass (g)	Mass (g)	Mass (g)	Mass (g)
Divinylbenzene, 63% (DVB)	508.751	451.591	386.284	386.284	498.383
Styrene	0.000	0.00	374.118	374.118	0.000
2,2,4-trimethylpentane (Isooctane)	384.815	125.800	271.210	271.210	482.745
Toluene	335.004	712.869	235.725	235.725	222.404
Benzoyl peroxide, 98% (BPO)	3.816	18.432	5.703	5.703	3.738
1-Vinyl-2-pyrrolidinone (VP)	151.578	0.000	0.000	167.288	0.000
Total (excluding BPO and VP)	1228.571	1290.260	1267.337	1267.337	1203.532

[0081] The general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as defined in the appended claims. Other aspects of the present invention will be apparent to those skilled in the art in view of the detailed description of the invention as provided herein.

[0082] Work-up; reaction volume level in the reactor was marked. Overhead stirrer agitation was stopped, residual liquid siphoned out of the reactor, and the reactor filled to the mark with ultrapure water at room temperature. Overhead stirrer agitation was restarted and the slurry heated to 70°C as quickly as possible. After 30 minutes, agitation was stopped and residual liquid siphoned out. Polymer beads were washed five times in this manner. During the final wash, the slurry temperature was cooled to room temperature. After the final water wash, polymer beads were washed with 99% isopropyl alcohol (IPA) in the same manner. 99% IPA was siphoned out and replaced with 70% IPA before transferring the slurry into a clean 4L glass container. Unless noted otherwise, on an as-needed basis the polymer was steam stripped in a stainless steel tube for 8 hours, rewet in 70% IPA, transferred into DI water, sieved to obtain only the portion of beads having diameters between 300 and 600 μm, and dried at 100°C until no further weight loss on drying was observed.

[0083] Cumulative pore volume data, measured by nitrogen desorption isotherm, for polymers CY12004, CY15042, CY15044, and CY15045, are presented below, in Tables III, IV, V, and VI, respectively. Cumulative pore volume data, measured by mercury intrusion porosimetry, for polymer CY15077 is presented in Table VII, below.

Table III: Nitrogen Desorption Data for CY12004

Pore Diameter Range (Å)	Average Diameter (Å)	Cumulative Pore Volume (cm^3/g)	Pore Diameter Range (Å)	Average Diameter (Å)	Cumulative Pore Volume (cm^3/g)
1221.6 - 868.1	985.2149834	0.009113091	273.9 - 256.6	264.6494358	0.777049805
868.1 - 751.9	801.4105771	0.019081821	256.6 - 237.0	245.9517985	0.830089884
751.9 - 661.5	700.749642	0.032021618	237.0 - 225.7	231.0229263	0.857298007
661.5 - 613.5	635.6650389	0.048206769	225.7 - 215.6	220.375968	0.88145223
613.5 - 568.5	589.2088599	0.067981224	215.6 - 145.5	166.3375231	1.066971104
568.5 - 509.8	535.8385194	0.114704165	145.5 - 104.6	117.8539174	1.181204175
509.8 - 456.1	479.8625277	0.214714265	104.6 - 84.4	92.0541661	1.241569291
456.1 - 418.7	435.7117054	0.311269356	84.4 - 71.4	76.67121175	1.285618005

418.7 - 374.6	394.0534583	0.455991378	71.4 - 60.9	65.20679768	1.326059561
374.6 - 330.2	349.456374	0.579735461	60.9 - 52.7	56.07123392	1.360787093
330.2 - 319.6	324.7147611	0.612988132	52.7 - 46.5	49.12518253	1.389258246
319.6 - 281.8	298.1620033	0.708072633	46.5 - 41.3	43.53851295	1.416541075
281.8 - 273.9	277.7142728	0.73291244	41.3 - 37.1	38.91936166	1.445235862

Table IV: Nitrogen Desorption Data for CY15042

Pore Diameter Range (Å)	Average Diameter (Å)	Cumulative Pore Volume (cm^3/g)	Pore Diameter Range (Å)	Average Diameter (Å)	Cumulative Pore Volume (cm^3/g)
2011.0 - 633.1	751.380276	0.003621266	81.8 - 67.3	72.96250925	0.911182647
633.1 - 424.8	488.0919378	0.006317461	67.3 - 57.7	61.63744463	0.954008444
424.8 - 418.5	421.593936	0.006912678	57.7 - 50.3	53.43111186	0.983515641
418.5 - 353.5	380.29179	0.008267096	50.3 - 44.4	46.93705679	1.010486042
353.5 - 280.4	308.2300243	0.011094129	44.4 - 38.6	41.02620024	1.037817277
280.4 - 275.4	277.8814342	0.01168737	38.6 - 34.5	36.30857144	1.058861412
275.4 - 249.5	261.1230419	0.012721633	34.5 - 30.9	32.48566551	1.08400665
249.5 - 209.1	225.543664	0.015611261	30.9 - 27.3	28.85395017	1.10131894
209.1 - 206.8	207.9070897	0.016388077	27.3 - 24.3	25.59611525	1.12576046
206.8 - 137.5	157.790999	0.442556595	24.3 - 22.3	23.18199338	1.143118464
137.5 - 98.1	110.7933773	0.765560391	22.3 - 19.6	20.72009386	1.167009752
98.1 - 81.8	88.28728758	0.845836735	19.6 - 17.4	18.32182238	1.190109864

Table V: Nitrogen Desorption Data for CY15044

Pore Diameter Range (Å)	Average Diameter (Å)	Cumulative Pore Volume (cm^3/g)	Pore Diameter Range (Å)	Average Diameter (Å)	Cumulative Pore Volume (cm^3/g)
2529.6 - 789.0	936.1742201	1.75877E-06	52.8 - 46.8	49.32751384	0.373710394
789.0 - 446.0	526.203721	0.000135623	46.8 - 41.4	43.66300585	0.378313283
446.0 - 219.6	260.7379647	0.002068559	41.4 - 37.2	39.02724789	0.38481289
219.6 - 213.4	216.3756282	0.004663144	37.2 - 33.2	34.8920748	0.391803441
213.4 - 205.7	209.3598959	0.0088853	33.2 - 30.0	31.34913535	0.393761301
205.7 - 144.7	164.0510277	0.131650053	30.0 - 27.3	28.49102813	0.394422444
144.7 - 99.6	113.2793455	0.294709491	27.3 - 24.7	25.83440471	0.396180539
99.6 - 82.1	88.98089675	0.331539838	24.7 - 22.3	23.34690716	0.401510134
82.1 - 71.4	75.89033961	0.34527909	22.3 - 19.8	20.83368622	0.40782788
71.4 - 60.0	64.52630192	0.360216738	19.8 - 17.5	18.45917969	0.416568116
60.0 - 52.8	55.83732662	0.367929549			

Table VI: Nitrogen Desorption Data for CY15045

Pore Diameter Range (Å)	Average Diameter (Å)	Cumulative Pore Volume (cm^3/g)	Pore Diameter Range (Å)	Average Diameter (Å)	Cumulative Pore Volume (cm^3/g)
1277.7 - 542.6	649.560333	0.000489722	48.0 - 42.5	44.81172299	0.421626585
542.6 - 213.2	252.9981774	0.000667721	42.5 - 38.3	40.08447096	0.428067208
213.2 - 206.9	209.9696024	0.001419558	38.3 - 34.4	36.07215077	0.431303175
206.9 - 141.9	161.6476715	0.261729457	34.4 - 31.5	32.76081107	0.433543649
141.9 - 106.3	118.498425	0.346563251	31.5 - 26.3	27.29321095	0.440720595
106.3 - 84.0	92.17838423	0.37856771	26.3 - 23.8	24.89263623	0.44207166
84.0 - 71.8	76.76600632	0.393497452	23.8 - 21.3	22.31849785	0.443967237
71.8 - 62.4	66.31374327	0.404409264	21.3 - 19.1	19.99937462	0.45436982
62.4 - 53.6	57.17863111	0.411077722	19.1 - 16.1	17.16801839	0.47745598
53.6 - 48.0	50.38372676	0.416000386			

Table VII: Mercury Intrusion Data for CY15077

Pore size Diameter (A)	Cumulative Intrusion (mL/g)	Pore size Diameter (A)	Cumulative Intrusion (mL/g)	Pore size Diameter (A)	Cumulative Intrusion (mL/g)
226299.0625	3.40136E-30	672.187561	1.581117511	111.9475937	2.162935257
213166.0781	0.001678752	636.7885742	1.60271585	108.8830032	2.167646885
201295.1563	0.002518128	604.7248535	1.621845484	106.6480179	2.174062729
172635.8125	0.004364755	558.1287231	1.651492	104.5217743	2.179908991
139538.0625	0.007554384	518.2624512	1.678913713	102.4295197	2.179908991
113120.7813	0.011919139	483.5536499	1.708594561	100.1580353	2.182951927
90542.36719	0.01645177	453.5110779	1.735918999	98.29322052	2.184018135
78733.25781	0.0203129	426.9998474	1.755934	96.44822693	2.191127539
72446.375	0.022327403	403.1251526	1.783603072	94.42159271	2.198545218
60340.40234	0.027867284	382.7776794	1.793849826	91.52587891	2.209161043
48343.83984	0.035327822	362.7162476	1.817784309	89.25807953	2.209312439
39009.13672	0.040918175	342.3734436	1.838774562	87.0777359	2.215425491
32136.4082	0.04899035	330.1105042	1.851493955	85.42358398	2.221472025
25330.65625	0.063195683	315.5238037	1.869742155	83.62612915	2.232139587
20981.51563	0.079529688	302.2973938	1.885128617	82.11174011	2.237514496
16219.86426	0.108860672	290.2946777	1.895119786	79.91614532	2.239231586
13252.41211	0.141730919	279.1246643	1.912378907	78.01462555	2.239560127
10501.53613	0.193969816	268.7442627	1.924305081	76.19993591	2.239560127
8359.911133	0.262399256	259.1106873	1.936048627	75.09249115	2.239560127
6786.30127	0.345866203	241.8737793	1.955100656	73.41201019	2.239560127

5538.122559	0.438174427	226.7678223	1.972970247	72.23709869	2.240245819
4337.931152	0.563276172	213.3626251	1.988123298	71.09960175	2.242422104
3501.674805	0.681870878	201.4908142	2.007521152	69.86301422	2.243849993
2838.742188	0.804727197	194.9888611	2.022114754	68.40761566	2.257676363
2593.016846	0.865813017	188.9506989	2.033871174	67.13697815	2.259181261
2266.688965	0.938610673	180.582901	2.035052776	66.03359222	2.266284466
1831.041748	1.056586146	172.8530121	2.050720692	65.08189392	2.270181179
1509.850708	1.163395643	164.9621735	2.062945843	64.04368591	2.272682428
1394.006104	1.21002543	157.8110657	2.071056128	62.38490295	2.280714512
1294.780151	1.257248282	151.1540375	2.082133055	61.32764053	2.280714512
1207.692627	1.293158531	143.9185333	2.096480608	60.30379868	2.287917852
1131.860962	1.326992273	138.4670563	2.106938839	59.41370392	2.287917852
1065.099976	1.35812819	132.8492737	2.119287968	58.54679489	2.293802738
953.1816406	1.405935764	129.5760345	2.126605988	57.79866409	2.297607183
884.0358887	1.445426106	126.5438614	2.126605988	56.88977814	2.299046278
823.5491333	1.478719592	124.2635574	2.132267475	55.9213295	2.302111387
770.9108276	1.510579824	120.8976135	2.141504765	54.98665237	2.303381443
722.4724731	1.537048101	117.3792267	2.150759459		
684.6119995	1.564400196	114.791893	2.154810667		

Example 2: Polymer Modification CY15087

[0084] The general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as defined in the appended claims. Other aspects of the present invention will be apparent to those skilled in the art in view of the detailed description of the invention as provided herein.

[0085] N-vinylpyrrolidone functionalization; base polymer, CY15077, was not steam stripped or sieved prior to functionalization. Two 99% IPA washes at 50°C were completed during workup for the base polymer, as opposed to one wash at RT. Following IPA washes, the polymer was washed three times with an excess of DI water. Wetted CY15077 polymer beads were added to a 1L jacketed glass reaction kettle, fitted with a Teflon coated agitator, containing 450 mL DI water, 50.0g N-vinylpyrrolidone monomer, and 1.5g sodium persulfate. The reaction was allowed to proceed for 24 hours at 75°C, with agitation speed set to 100RPM. Upon completion the polymer beads were washed five times with 500mL DI water at 70°C, steam stripped in a stainless steel tube for 8 hours, rewet in 70% IPA, transferred into DI water, sieved

to obtain only the portion of beads having diameters between 300 and 600 μm, and dried at 100°C until no further weight loss on drying was observed. The yield was 95.5g of polymer CY15087. Atomic concentrations measured by XPS, and cumulative pore volume data measured by mercury intrusion porosimetry, are shown in Tables VIII and IX, respectively.

Table VIII: Atomic Concentrations (in %) for CY15077 and CY15087

Polymer	Condition	C	N	O
CY15077	Bead	96.2	0.0	3.8
CY15077	Ground	98.6	0.0	1.4
CY15087	Bead	95.5	0.4	4.2
CY15087	Ground	98.3	0.2	1.5

Table IX: Mercury Intrusion Data for CY15087

Pore size Diameter (A)	Cumulative Intrusion (mL/g)	Pore size Diameter (A)	Cumulative Intrusion (mL/g)	Pore size Diameter (A)	Cumulative Intrusion (mL/g)
226275.6875	3.003E-30	671.8579712	1.033001781	111.9504318	1.56092155
213126.625	0.001333927	636.456604	1.044957519	108.9145203	1.564850807
201250.5938	0.002964283	604.6593018	1.05753231	106.6669846	1.571887255
172601.8438	0.005928566	557.9059448	1.079107881	104.5330276	1.574593782
139532.5469	0.009189277	518.4785156	1.102458835	102.4421844	1.584572434
113124.3359	0.012449989	483.8456726	1.127018452	100.1668015	1.591516852
90545.25	0.015710698	453.9489746	1.151340365	98.28172302	1.594149351
78739.35156	0.017489269	426.8711243	1.174746156	96.44982147	1.595042825
72432.5625	0.01897141	402.8918152	1.194709539	94.43471527	1.595328212
60333.77734	0.021935694	382.4490967	1.213674426	91.55084229	1.595610261
46762.60547	0.026795639	360.680481	1.231868267	89.27562714	1.604250789
39173.96094	0.03074207	342.5672302	1.252067924	87.08631134	1.61047101
31808.34375	0.034442116	329.8339539	1.267953753	85.43348694	1.616541862
25357.64648	0.040027067	315.4637756	1.28668797	83.63105011	1.620805621
20929.94141	0.046409778	302.4020996	1.299176812	82.10086823	1.627643347
16182.15234	0.056623131	290.331665	1.314114213	79.91345978	1.629765868
13255.21973	0.065796889	279.2361145	1.322446585	78.01348877	1.631207824
10561.28809	0.080750667	268.7993164	1.34148562	76.20350647	1.63190341

8353.926758	0.105692402	259.2027283	1.349915743	75.09172821	1.634262919
6778.929199	0.138670683	241.8540192	1.363333344	73.41147614	1.638391137
5543.002441	0.177410021	226.7354431	1.38415575	72.23751831	1.642881751
4342.263672	0.24024339	213.408844	1.386666298	71.10028076	1.646320224
3502.678711	0.308058321	201.5056763	1.411639214	69.861763	1.648736954
2839.226807	0.388105094	194.9947357	1.426415801	68.40744019	1.655003667
2591.51416	0.428066701	188.935318	1.428328514	67.13788605	1.662294388
2267.699951	0.48154822	180.6179199	1.441128492	66.03204346	1.667405605
1831.208252	0.570007741	172.8575745	1.453100324	65.08184814	1.670548201
1510.12561	0.655585647	164.9869385	1.464205742	64.04498291	1.671463728
1394.226563	0.696180701	157.740097	1.473819733	62.38602829	1.673002481
1294.746582	0.729135811	151.1829987	1.486423731	61.32709885	1.673002481
1208.07251	0.76245892	143.9502716	1.499343991	60.30479813	1.673002481
1132.023804	0.795990944	138.4791107	1.509965897	59.41309738	1.673002481
1065.684937	0.815372229	132.8890839	1.522242427	58.54596329	1.673002481
953.989502	0.855566621	129.5950317	1.529255748	57.799366	1.673613429
883.8703613	0.871785223	126.493248	1.529255748	56.88968277	1.673613429
823.4996338	0.921781898	124.2660522	1.53686142	55.92052078	1.677541733
771.3513794	0.949763238	120.8921432	1.543375134	54.98633194	1.677541733
722.1901245	1.018806458	117.3944702	1.549948096		
684.8914185	1.027466536	114.7864304	1.558065772		

Example 3: Polymer Modification CY15100 and CY15102

[0086] The general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as defined in the appended claims. Other aspects of the present invention will be apparent to those skilled in the art in view of the detailed description of the invention as provided herein.

[0087] Sulfonation procedure; dried base polymer was added to a 1L jacketed glass reactor, which was equipped with a Teflon coated agitator. A mixture of concentrated sulfuric acid (98%) and fuming sulfuric acid (20% SO_3 in sulfuric acid) was added to the reactor containing base polymer. The reaction was carried out at 90°C for 24 hours, with constant agitation at 100RPM.

[0088] Work-up; the reaction volume was allowed to cool to room temperature (RT), and was slowly added into a chemical glass beaker with an excess of at least 1L ice cold DI water.

Sulfonated polymer was washed with excess DI water at RT until the supernatant reached a neutral pH. The resulting polymer was then treated with 100mL 1M $NaOH_{(aq)}$ for 1 hour at RT to convert polymer bound ~SO_3H into ~SO_3Na groups. Polymer was washed again with an excess of DI water at RT until the supernatant reached a neutral pH, then dried in an oven at 100°C until no further loss on drying was observed. The dried ~SO_3Na functional polymer yield was measured. Reaction compositions for CY15100 and CY15102 are provided in Table X. Table XI displays atomic concentrations for polymers CY15100, CY15102, and CY15087, as measured by XPS. Log differential pore volume plots are presented in Figures 1, 2, and 3, and cumulative pore volume data are presented in Tables XII, XIII, and XIV. When interpreting pore structure data obtained from nitrogen desorption isotherm or mercury intrusion porosimetry using dried polymer as the sample, it is important to consider that pore size may change upon swelling of sulfonated poly(styrene-*co*-divinylbenzene) porous beads once wetted in solution. In addition to potential changes in pore structure, the bead size may also change upon transition from dry to swollen state. This phenomenon was evaluated in "Preparation and Evaluation of Differently Sulfonated Styrene-Divinylbenzene Cross-Linked Copolymer Cationic Exchange Resins as Novel Carriers for Drug Delivery", published in AAPS PharmSciTech June 2009; 10(2): 641-648.

[0089] Thrombogenicity was measured by the uPTT assay in which materials were compared to the negative control (plasma alone), positive control (glass beads) and reference beads to determine the degree of contact activation activity. In the uPTT assay, the % change in clot formation over time as compared to the reference materials was determined, then grouped according to: <25% activators, 25-49% moderate activators, 50-74% mild activators, 75-100% minimal and >100% non-activators of the intrinsic coagulation pathway. Polymer CY15100, 82%, was a minimal activator.

Table X: Modification Compositions for CY15100 and CY15102

	CY15100	CY15102
Base Polymer	CY15045	CY15087
Mass Base Polymer (g)	220.0	80.0
Mass Concentrated Sulfuric Acid (g)	950.0	550.0

Mass Fuming Sulfuric Acid (g)	50.0	30.0
Yield Dry Modified Polymer (g)	355.5	204.6

Table XI: Atomic Concentrations (in %) for CY15100, CY15102, and CY15087

Polymer	Condition	C	N	O	Na	S
CY15100	Bead	65.7	0.2	20.5	8.0	5.7
CY15102	Bead	71.6	0.5	17.2	6.6	4.1
CY15087	Bead	95.5	0.4	4.2	0.0	0.0
CY15087	Ground	98.3	0.2	1.5	0.0	0.0

Table XII: Nitrogen Desorption Data for CY15100

Pore Diameter Range (Å)	Average Diameter (Å)	Cumulative Pore Volume (cm^3/g)	Pore Diameter Range (Å)	Average Diameter (Å)	Cumulative Pore Volume (cm^3/g)
2072.6 - 552.5	648.562383	0.000416099	131.6 - 99.3	110.8101833	0.170472908
552.5 - 354.3	410.9223564	0.000905416	99.3 - 72.3	81.43320551	0.20555251
354.3 - 337.5	345.4980521	0.001122701	72.3 - 62.2	66.46726774	0.212857437
337.5 - 311.7	323.5292132	0.001561729	62.2 - 52.1	56.21812708	0.218554756
311.7 - 288.8	299.3515093	0.001919004	52.1 - 45.7	48.42881742	0.221509707
288.8 - 272.0	279.8911375	0.002345465	45.7 - 39.4	42.03869424	0.223879096
272.0 - 252.4	261.4265539	0.002783018	39.4 - 34.5	36.58507436	0.225521077
252.4 - 239.0	245.303922	0.003244227	34.5 - 29.1	31.32500867	0.230015257
239.0 - 225.7	231.9701343	0.004052829	29.1 - 25.1	26.83485239	0.230195589
225.7 - 212.7	218.7962082	0.005280802	25.1 - 22.0	23.36857621	0.230286279
212.7 - 204.5	208.4059706	0.007418375	22.0 - 19.4	20.51213112	0.232863812
204.5 - 131.6	152.2941936	0.087124099			

Table XIII: Nitrogen Desorption Data for CY15102

Pore Diameter Range (Å)	Average Diameter (Å)	Cumulative Pore Volume (cm^3/g)	Pore Diameter Range (Å)	Average Diameter (Å)	Cumulative Pore Volume (cm^3/g)
1598.8 - 1238.8	1372.941344	0.026272341	206.8 - 140.7	160.5985991	0.863794835
1238.8 - 946.4	1053.220361	0.092081573	140.7 - 106.0	118.0466801	0.922556622
946.4 - 758.1	831.0482586	0.194131921	106.0 - 82.8	91.24150017	0.968039661
758.1 - 677.1	712.8857859	0.258283006	82.8 - 68.2	73.90381313	1.001829887

677.1 - 529.4	584.7345957	0.38744334	68.2 - 60.9	64.05281388	1.020920023
529.4 - 485.2	505.2928332	0.431560876	60.9 - 52.5	55.98109194	1.044868856
485.2 - 443.2	462.211297	0.481712669	52.5 - 46.3	48.94597942	1.065247397
443.2 - 396.6	417.205311	0.529431372	46.3 - 41.2	43.35983259	1.084233305
396.6 - 361.7	377.5005059	0.571368548	41.2 - 37.0	38.81504369	1.106456908
361.7 - 324.6	341.0804153	0.616836751	37.0 - 33.1	34.78421912	1.129603729
324.6 - 296.1	308.9881056	0.653318693	33.1 - 30.0	31.33519542	1.146218801
296.1 - 271.6	282.7268533	0.684779469	30.0 - 27.3	28.4688972	1.162517069
271.6 - 256.8	263.7792955	0.704908544	27.3 - 24.6	25.75215358	1.182048628
256.8 - 239.4	247.4475287	0.727833901	24.6 - 22.4	23.33791231	1.201310022
239.4 - 230.2	234.5702219	0.739926683	22.4 - 19.8	20.89212489	1.229148706
230.2 - 217.1	223.2037828	0.756372211	19.8 - 17.6	18.54892595	1.260822457
217.1 - 206.8	211.680438	0.769442061			

Table XIV: Mercury Intrusion Data for CY15102

Pore size Diameter (A)	Cumulative Intrusion (mL/g)	Pore size Diameter (A)	Cumulative Intrusion (mL/g)	Pore size Diameter (A)	Cumulative Intrusion (mL/g)
226247.25	3.02E-30	672.791748	0.283745468	111.9444351	0.981295645
213156.0625	0.000893837	636.3512573	0.295114249	108.8816452	0.981295645
201297.1875	0.002383566	605.4035034	0.309263676	106.6592331	0.986702561
172619.2656	0.004320214	558.758606	0.326112717	104.5428238	0.996097863
139526.7344	0.006107889	518.5050049	0.352752388	102.4358368	1.000003457
113150.6484	0.007448644	483.7310181	0.367008656	100.1722946	1.003374338
90544.85156	0.009236319	453.6919861	0.390547335	98.26839447	1.006461024
78737.24219	0.010130156	426.9628296	0.407471895	96.44637299	1.008966684
72447.07031	0.011172966	403.0959778	0.4232741	94.41146851	1.012030125
60339.52344	0.012066803	382.8546753	0.444355428	91.54938507	1.015347958
49074.61719	0.012066803	362.905426	0.463873088	89.25726318	1.018440247
38783.65625	0.012066803	342.0473328	0.487040371	87.0788269	1.021567345
32031.35742	0.012456137	329.7276001	0.504495382	85.42123413	1.024644852
25154.1582	0.01550037	315.7310791	0.522837102	83.62944031	1.028239489
20919.94336	0.01550037	302.3917236	0.545027971	82.1011734	1.02980864
16226.36035	0.016433783	290.2372131	0.567096949	79.91355133	1.032312155
13231.0293	0.018065026	279.1113586	0.588691056	78.00926208	1.034948707
10569.24219	0.020413134	268.6489563	0.608853817	76.20082092	1.037501097
8346.358398	0.023545867	259.2150879	0.635331511	75.09120178	1.039880157
6777.795898	0.027556093	241.9123993	0.710671127	73.4092865	1.042042732

5545.635742	0.032167129	226.7029877	0.774290979	72.23842621	1.043176413
4347.45166	0.039555997	213.3559113	0.867704988	71.09993744	1.047091961
3496.898926	0.049277436	201.5307922	0.867704988	69.86208344	1.047258615
2839.973145	0.057190847	195.0246887	0.867704988	68.40840912	1.049208641
2592.47998	0.06178461	188.9438019	0.867704988	67.1362381	1.05278945
2267.395264	0.071647309	180.6033783	0.867704988	66.0329895	1.05278945
1831.758789	0.089788206	172.8410034	0.869671643	65.08166504	1.053350925
1510.39563	0.112907536	164.969101	0.869671643	64.04417419	1.054639339
1394.068237	0.125744253	157.8126526	0.87475878	62.38519287	1.055902362
1294.699707	0.136810422	151.1803131	0.905465066	61.32834625	1.060090899
1207.551147	0.147966579	143.936264	0.909094393	60.30381012	1.062460899
1132.260498	0.159586608	138.4554596	0.931292474	59.41312408	1.063420892
1065.672974	0.171025708	132.8584442	0.938616037	58.54793549	1.064275384
954.0095215	0.191800222	129.575531	0.938616037	57.79902267	1.066532493
884.2581177	0.20811981	126.4766693	0.971493781	56.88972473	1.068112493
823.8370972	0.228217274	124.2657852	0.971493781	55.92105865	1.072528958
771.1380615	0.239915013	120.9015427	0.972762465	54.9865036	1.072528958
721.8734131	0.275565475	117.374855	0.977469385		
684.4716797	0.281177133	114.7828751	0.981295645		

Example 4: Polymer Modification CY14144 and CY15101

[0090] The general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as defined in the appended claims. Other aspects of the present invention will be apparent to those skilled in the art in view of the detailed description of the invention as provided herein.

[0091] Sulfonation procedure; dried base polymer was mixed with glacial acetic acid in a 500mL glass reactor equipped with a Teflon coated mechanical agitator, and heated to 50°C with agitation set to 100RPM. A mild sulfonating agent was prepared by adding acetic anhydride (99%) to a 100mL chemical glass beaker, cooled in an ice bath, and slowly adding concentrated sulfuric acid (98%) over 30 minutes. Temperature of the mixture was monitored and maintained between 15-40°C by replenishing the ice bath. After completion of the sulfuric acid addition, the reddish-brown viscous liquid was kept at RT for 1 hour, and then slowly added to the reactor. The reaction was allowed to proceed for a specified amount of time.

[0092] Work-up; the reaction volume was allowed to cool to room temperature (RT), and was slowly added into a chemical glass beaker with an excess of at least 1L ice cold DI water. Sulfonated polymer was washed with excess DI water at RT until the supernatant reached a neutral pH. The resulting polymer was then treated with 100mL 1M $NaOH_{(aq)}$ for 1 hour at RT to convert polymer bound ~SO_3H into ~SO_3Na groups. Polymer was washed again with an excess of DI water at RT until the supernatant reached a neutral pH, then dried in an oven at 100°C until no further loss on drying was observed. The dried ~SO_3Na functional polymer yield was measured. Reaction compositions for polymers CY14144 and CY15101 are shown in Table XV, below. Atomic concentrations determined by XPS for polymers CY14144, CY12004, CY15101, and CY15087 are presented below, in Table XVI. Figures 4, 5, and 6 show plots of log differential pore volume for each of the modified polymers described above. Cumulative pore volume data are shown below in Tables XVII, XVIII, and XIX.

[0093] Thrombogenicity was measured by the uPTT assay in which materials were compared to the negative control (plasma alone), positive control (glass beads) and reference beads to determine the degree of contact activation activity. In the uPTT assay, the % change in clot formation over time as compared to the reference materials was determined, then grouped according to: <25% activators, 25-49% moderate activators, 50-74% mild activators, 75-100% minimal and >100% non-activators of the intrinsic coagulation pathway. Polymer CY15101, 88%, was a minimal activator.

[0094]

Table XV: Modification Compositions for CY14144 and CY15101

	CY14144	CY15101
Base Polymer	CY12004	CY15087
Mass Base Polymer (g)	11.7	80.5
Volume Glacial Acetic Acid (mL)	75	400
Mass Acetic Anhydride (g)	15.5	125.0
Mass Concentrated Sulfuric Acid (g)	10.0	80.0
Reaction Time (hr)	1	2
Yield Dry Modified Polymer (g)	15.2	103.4

Table XVI: Atomic Concentrations (in %) for CY14144, CY12004, CY15101 and CY15087

Polymer	Condition	C	N	O	Na	S
CY14144	Ground	87.0	0.0	8.7	2.5	1.8
CY12004	Bead	88.7	3.4	7.9	0.0	0.0
CY12004	Ground	95.0	0.4	4.7	0.0	0.0
CY15101	Bead	93.3	0.7	5.5	0.4	0.1
CY15087	Bead	95.5	0.4	4.2	0.0	0.0
CY15087	Ground	98.3	0.2	1.5	0.0	0.0

Table XVII: Nitrogen Desorption Data for CY14144

Pore Diameter Range (Å)	Average Diameter (Å)	Cumulative Pore Volume (cm^3/g)	Pore Diameter Range (Å)	Average Diameter (Å)	Cumulative Pore Volume (cm^3/g)
1316.7 - 872.8	1006.357045	0.00765904	218.4 - 143.9	165.3652577	1.129471233
872.8 - 760.0	808.4322272	0.01624896	143.9 - 105.5	118.3403917	1.219663568
760.0 - 683.5	717.5974884	0.028034508	105.5 - 85.5	93.18473659	1.269908393
683.5 - 625.7	651.9899544	0.04390322	85.5 - 70.2	76.1345754	1.313809596
625.7 - 580.4	601.3250683	0.063539075	70.2 - 59.9	64.12468772	1.346563035
580.4 - 506.1	537.9818896	0.171853178	59.9 - 51.8	55.16793458	1.375536168
506.1 - 449.5	474.3191955	0.315569993	51.8 - 45.4	48.0976978	1.401122481
449.5 - 395.6	418.9973346	0.494055963	45.4 - 40.2	42.43389408	1.424635177
395.6 - 367.4	380.4061561	0.562885137	40.2 - 36.1	37.88651456	1.449718809
367.4 - 336.7	350.6379611	0.677258819	36.1 - 32.1	33.79019728	1.477483715
336.7 - 297.9	314.7821036	0.775586161	32.1 - 28.9	30.28159181	1.497726602
297.9 - 293.1	295.4222209	0.799779319	28.9 - 26.3	27.45536434	1.516706872
293.1 - 271.2	281.2260787	0.844974101	26.3 - 23.6	24.73777781	1.540207545
271.2 - 254.9	262.5094171	0.885670627	23.6 - 21.1	22.17739744	1.565080566
254.9 - 241.5	247.8251105	0.914384164	21.1 - 19.0	19.93703511	1.59109954
241.5 - 229.9	235.3841146	0.939107638	19.0 - 16.5	17.51596978	1.630846881
229.9 - 218.4	223.8303393	0.963836661			

Table XVIII: Nitrogen Desorption Data for CY15101

Pore Diameter Range (Å)	Average Diameter (Å)	Cumulative Pore Volume (cm^3/g)	Pore Diameter Range (Å)	Average Diameter (Å)	Cumulative Pore Volume (cm^3/g)
1633.5 - 1308.6	1434.817706	0.015869195	207.3 - 144.0	163.6239028	0.618758477

1308.6 - 938.9	1063.085479	0.076011287	144.0 - 103.4	116.4570854	0.668697015
938.9 - 822.1	872.5400938	0.113427572	103.4 - 85.6	92.59846579	0.694263778
822.1 - 664.4	726.153686	0.190492729	85.6 - 72.1	77.55016135	0.716487235
664.4 - 541.2	589.8410779	0.271968628	72.1 - 60.7	65.25664927	0.73733967
541.2 - 495.4	516.2061221	0.306797766	60.7 - 53.0	56.18831893	0.752958019
495.4 - 452.4	471.8824199	0.342922234	53.0 - 46.6	49.26725758	0.767344784
452.4 - 411.9	430.1606805	0.374728484	46.6 - 41.5	43.64795708	0.78015016
411.9 - 373.7	390.8559715	0.406903208	41.5 - 37.3	39.09541737	0.794981989
373.7 - 338.1	354.0440222	0.436879429	37.3 - 33.3	35.01993833	0.810085989
338.1 - 306.8	320.8627294	0.464287882	33.3 - 30.2	31.57107231	0.8201347
306.8 - 282.0	293.2737773	0.487609004	30.2 - 27.5	28.71043051	0.829560837
282.0 - 258.7	269.2384186	0.507679709	27.5 - 24.8	25.99331273	0.839975544
258.7 - 244.7	251.276503	0.519925622	24.8 - 22.6	23.59379328	0.8493402
244.7 - 229.0	236.3042502	0.53405423	22.6 - 20.0	21.1163566	0.861908143
229.0 - 216.9	222.6261956	0.545016489	20.0 - 17.8	18.73336683	0.874402144
216.9 - 207.3	211.8651212	0.55492914			

Table XIX: Mercury Intrusion Data for CY15101

Pore size Diameter (A)	Cumulative Intrusion (mL/g)	Pore size Diameter (A)	Cumulative Intrusion (mL/g)	Pore size Diameter (A)	Cumulative Intrusion (mL/g)
226247.25	3.367E-30	672.2320557	0.703246117	111.937149	1.237899184
213156.0625	0.001661795	636.7992554	0.713504672	108.9081039	1.239180923
201297.1875	0.002658872	604.4926758	0.726847529	106.6535568	1.245096564
172619.2656	0.005317744	558.8725586	0.746505737	104.5474396	1.24916625
139526.7344	0.007976616	517.9966431	0.774387836	102.455368	1.25267899
113150.6484	0.009638411	483.9524536	0.799027622	100.1680145	1.261325955
90544.85156	0.012297283	453.7037354	0.824069798	98.2784729	1.261325955
78737.24219	0.014125257	426.9303894	0.846621335	96.45231628	1.267885208
72447.07031	0.015620873	403.1401672	0.898474514	94.40316772	1.274962544
60339.52344	0.017947385	382.6773987	0.91877532	91.53180695	1.279593945
49556.56641	0.01949878	362.9386292	0.946397841	89.26702118	1.285915971
38738.37109	0.021929506	342.2199707	0.946397841	87.08314514	1.285915971
31002.00586	0.023903539	330.153656	0.953894079	85.42582703	1.287682652
25333.7832	0.02616792	315.6123962	0.954481184	83.6335144	1.29400897
20724.62109	0.029177248	302.6812439	0.954481184	82.10058594	1.300267935
16168.99121	0.033409968	290.4436646	0.967425823	79.91345978	1.30387032
13230.375	0.037765641	279.009491	0.974567354	78.01080322	1.308264375

10563.43555	0.044586275	268.8323975	0.974567354	76.19985962	1.313777924
8346.731445	0.054462213	259.2565308	0.974567354	75.09228516	1.318249345
6776.340332	0.0666546	241.9353333	1.028741002	73.41210175	1.321508646
5536.147949	0.083998173	226.8330078	1.048289418	72.23653412	1.323805094
4342.036621	0.107802272	213.444046	1.065926313	71.09803772	1.32500124
3501.501953	0.137485042	201.5080414	1.074228048	69.86273193	1.334167719
2837.420654	0.177576199	195.0001221	1.095143437	68.40810394	1.336985707
2594.672363	0.200087309	188.9437103	1.106776357	67.13769531	1.340026617
2269.617432	0.233489379	180.6530914	1.11556828	66.03487396	1.340026617
1831.204224	0.295208424	172.9412994	1.127364159	65.0819931	1.340224981
1510.503906	0.360582143	164.9789429	1.139592171	64.04338074	1.340224981
1395.643555	0.392902017	157.7405396	1.150992036	62.38589478	1.346690297
1293.973755	0.421268374	151.1612091	1.161784291	61.32817841	1.358168244
1207.494141	0.447410613	143.9489746	1.172875285	60.30670166	1.358168244
1131.894531	0.47241658	138.4779053	1.185242534	59.41316605	1.358532906
1065.193237	0.49649471	132.8603821	1.194525123	58.54763031	1.358532906
953.9039307	0.535679519	129.5736542	1.200321555	57.79816818	1.358532906
884.3017578	0.568524599	126.4793472	1.207967401	56.88824844	1.358532906
823.786377	0.597846568	124.2483292	1.213427901	55.92269516	1.366921306
771.5706177	0.616960466	120.9080048	1.221876502	54.98662186	1.373521209
722.1925049	0.691450536	117.3827286	1.223723292		
684.2458496	0.697761118	114.771225	1.23161757		

Example 5: Mild sulfonation of poly(divinylbenzene) based uncoated porous polymeric beads with acetyl sulfate, followed by functionalization with poly(N-vinylpyrrolidone) as a hemocompatible coating, used to prepare modified polymer CY15048

[0095] The general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as defined in the appended claims. Other aspects of the present invention will be apparent to those skilled in the art in view of the detailed description of the invention as provided herein.

[0096] Among various "mild" sulfonating agents acetyl sulfate (prepared from 98% conc. Sulfuric acid and acetic anhydride at low temperatures) is known to be very efficient for DVB or styrene based polymeric materials. Sulfonation is usually done at 50 ^{0}C for several hours

using equimolar amounts of acetyl sulfate and DVB or styrene based polymers. Sulfonation occurs mainly at benzene ring and unreacted double bonds (in DVB based cross-linked polymeric porous beads) could be preserved for further functionalization. Usually after sulfonation with acetyl sulfate, the polymer is converted into ~SO_3Na form and can be graft copolymerized with N-vinyl pyrrolidone (in bulk with benzoyl peroxide as initiator) or in water solutions (using sodium persulfate initiator). Resulting sulfonated polymer is "coated" with poly(N-vinylpyrrolidone) to make hemocompatible material capable of removing K^+ cations from physiological fluids.

[0097] The base polymer selected for this modification was polymer CY15044. The sulfonation and workup were carried out as described in Example 4, using 45.0g dry CY15044 polymer, 150mL glacial acetic acid, 62.0g acetic anhydride, and 40.0g concentrated sulfuric acid. The resulting sulfonated polymer, in ~SO_3Na form, was rewet in DI water in a 1L jacketed reaction vessel fitted with a Teflon coated agitator. DI water was removed from the vessel, and a solution composed of 75mL NVP monomer, 1.7g sodium persulfate, and 25mL DI water was added. The reaction was allowed to proceed for 72 hours at 70°C with agitation speed set to 100RPM. Resulting poly(NVP) coated polymer was washed five times using 200mL DI water, and dried in a vacuum oven until no further loss on drying was observed. Cumulative pore volume data for polymer CY15048 is shown below, in Table XX. A log differential pore volume plot is shown in Figure 7.

[0098] Thrombogenicity was measured by the uPTT assay in which materials were compared to the negative control (plasma alone), positive control (glass beads) and reference beads to determine the degree of contact activation activity. In the uPTT assay, the % change in clot formation over time as compared to the reference materials was determined, then grouped according to: <25% activators, 25-49% moderate activators, 50-74% mild activators, 75-100% minimal and >100% non-activators of the intrinsic coagulation pathway. Polymer CY15048, 94%, was a minimal activator.

Table XX: Nitrogen Desorption Data for CY15048

Pore Diameter Range (Å)	Average Diameter (Å)	Cumulative Pore Volume (cm^3/g)	Pore Diameter Range (Å)	Average Diameter (Å)	Cumulative Pore Volume (cm^3/g)
4355.2 - 828.4	944.3942734	0.0001057	60.2 - 52.6	55.8248996	0.329250736
828.4 - 474.0	558.6159743	0.000283797	52.6 - 46.6	49.1740518	0.335209946
474.0 - 303.3	351.2170892	0.000357942	46.6 - 41.3	43.5462226	0.339923553
303.3 - 224.3	251.4508466	0.000719278	41.3 - 37.4	39.07691383	0.349323983

224.3 - 216.6	220.2880162	0.001144201	37.4 - 32.5	34.52204235	0.351977397
216.6 - 208.1	212.161881	0.001932015	32.5 - 29.4	30.76412188	0.352966945
208.1 - 143.6	163.4823625	0.075370749	29.4 - 27.3	28.24001433	0.353787455
143.6 - 108.1	120.3913517	0.239861146	27.3 - 24.6	25.76447932	0.355166927
108.1 - 81.7	90.85045572	0.292261423	24.6 - 22.3	23.26898468	0.357207636
81.7 - 71.8	76.00202402	0.305608258	22.3 - 19.9	20.87422635	0.360962494
71.8 - 60.2	64.83123041	0.320783836	19.9 - 17.5	18.46778237	0.367188172

Example 6: Mild sulfonation of poly(styrene-*co*-divinylbenzene) uncoated porous polymeric beads, followed by functionalization with poly(N-vinylpyrrolidone) as a hemocompatible coating, used to prepare modified polymer CY15049

[0099] The general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as defined in the appended claims. Other aspects of the present invention will be apparent to those skilled in the art in view of the detailed description of the invention as provided herein.

[0100] The base polymer selected for this modification was polymer CY15042. The sulfonation and workup were carried out as described in Example 4, using 45.0g dry CY15042 polymer, 200mL glacial acetic acid, 62.0g acetic anhydride, and 40.0g concentrated sulfuric acid. The reaction was allowed to proceed for 2 hours. The resulting dried sulfonated polymer, in ~SO_3Na form, was added to a 1L jacketed reaction vessel fitted with a Teflon coated agitator. 140.0g N-vinylpyrrolidone monomer and 2.0g benzoyl peroxide were added to the reactor. The reaction was allowed to proceed for 24 hours at 70°C with agitation speed set to 100RPM. Resulting poly(N-vinylpyrrolidone) coated polymer was washed five times using 200mL DI water, and dried in a vacuum oven until no further loss on drying was observed. Table XXI, below, displays cumulative pore volume data for polymer CY15049. Figure 8 presents a log differential pore volume plot.

Table XXI: Nitrogen Desorption Data for CY15049

Pore Diameter Range (Å)	Average Diameter (Å)	Cumulative Pore Volume (cm^3/g)	Pore Diameter Range (Å)	Average Diameter (Å)	Cumulative Pore Volume (cm^3/g)
6798.1 - 997.4	1113.294549	0.002499046	99.0 - 82.5	89.05063735	0.848450234
997.4 - 529.0	628.6356118	0.005782394	82.5 - 69.8	74.92200629	0.902458565
529.0 - 503.0	515.3445059	0.00652485	69.8 - 59.0	63.37885992	0.947842682

503.0 - 431.3	461.4274588	0.007796961	59.0 - 51.2	54.4553105	0.981969695
431.3 - 320.8	359.3702778	0.010896953	51.2 - 44.8	47.47101253	1.011973922
320.8 - 317.4	319.0643487	0.011833304	44.8 - 39.4	41.69146063	1.039279282
317.4 - 274.0	292.3669097	0.013396248	39.4 - 35.3	37.10279099	1.066468142
274.0 - 230.2	248.1049882	0.016483381	35.3 - 31.3	33.03019211	1.096075821
230.2 - 225.4	227.7447013	0.017366617	31.3 - 28.2	29.57468036	1.118921801
225.4 - 211.6	218.0383103	0.018833905	28.2 - 25.5	26.70738162	1.143080339
211.6 - 195.5	202.8978228	0.029306436	25.5 - 22.8	23.944141	1.17115692
195.5 - 143.0	160.6741284	0.494786051	22.8 - 20.4	21.43590284	1.201324419
143.0 - 99.0	112.5005572	0.779812896	20.4 - 18.2	19.13416412	1.23163662

Example 7: Single-pass filtration for hemoglobin and potassium removal

[0101] The general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as defined in the appended claims. Other aspects of the present invention will be apparent to those skilled in the art in view of the detailed description of the invention as provided herein.

[0102] Units of human pRBC were allowed to equilibrate to room temperature for 30 minutes, where the units were gently mixed for 15 minutes. A blood spike was inserted into the unit and samples for the initial hemoglobin (Hb) and potassium concentrations were taken. The blood spike line was attached to the top port of the polymer containing filtration device, and a sample collection line attached to the bottom port. A pinch clamp was fitted on the sample collection line for flow control. Approximately one bed volume, 30mL, was flushed through the device into a waste container to purge the device of normal saline solution. The sample collection tube was placed over 15mL conical tubes where 12mL fractions of pRBCs were collected at a flow rate of about 3-3.5mL/min until the unit was completely filtered. Sample tubes were centrifuged for 15 minutes at 4600RPM at 4°C. Plasma supernatant from each sample tube was collected and the plasma free hemoglobin level was determined by an absorbance read at 450nm and potassium levels were measured with a potassium ion-selective electrode. The percentage of initial free hemoglobin removed during single-pass filtration, averaged from three trials, is presented in Figure 9. Figure 10 displays pre- and post- filtration potassium ion concentration in blood, averaged from three trials. Polymers CY15101 and CY15102 are able to remove significant quantities of both potassium and hemoglobin, while polymer CY15100 only removes the potassium and does not remove hemoglobin.

Example 8: Dynamic recirculation filtration

[0103] The general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as defined in the appended claims. Other aspects of the present invention will be apparent to those skilled in the art in view of the detailed description of the invention as provided herein.

[0104] Polymer CY14144 has been tested in a dynamic competitive system evaluating albumin (30 mg/mL) and myoglobin (100 mg/L) removal from a PBS solution with 8mEq/L potassium. This model has been designed to reflect clinical albumin and myoglobin (rhabdomyolysis) values. The dynamic system allows for the continuous measurement of protein adsorption by the polymer beads at two UV wavelengths. As long as the surrogate proteins, such as albumin and myoglobin, have different UV absorption profiles, the two protein surrogates can be measured simultaneously, providing competitive adsorption conditions. This allows a rapid assessment of polymer performance for the simultaneous adsorption of target and non-target factors under flow conditions; a key parameter to assess studies that balance sorption with hemocompatibility. The dynamic system has been fully calibrated (absorbance and flow conditions) and was used to measure binding with a 6 mL polymer filled device at a flow rate of 6 mL/min for five hours at room temperature. CY14144 has a robust myoglobin adsorption, potassium removal and demonstrated good selectivity with minimal albumin removal. Dynamic recirculation data for CY14144, averaged from 7 trials, is shown below in Figure 11. The average potassium removal, measured as the percent reduction from initial quantity, was found to be 25.3% with a standard deviation of 1.42.

[0105] Thrombogenicity was measured by the uPTT assay in which materials were compared to the negative control (plasma alone), positive control (glass beads) and reference beads to determine the degree of contact activation activity. In the uPTT assay, the % change in clot formation over time as compared to the reference materials was determined, then grouped according to: <25% activators, 25-49% moderate activators, 50-74% mild activators, 75-100% minimal and >100% non-activators of the intrinsic coagulation pathway. Shown below, in Table XXII, is a comparison of thrombogenicity for two different potassium removing polymers. Polymer CY14144 exhibits minimal thrombogenic activity while still removing potassium and myoglobin simultaneously in a dynamic recirculation model in phosphate buffered saline (PBS).

In comparison, potassium sorbent CY14022 is a moderate activator of the intrinsic coagulation pathway by the uPTT assay and is ineffective in myoglobin removal.

Table XXII: Myoglobin and Potassium Removal from PBS in a Dynamic Recirculation Model

Polymer	uPTT	Myoglobin Removal	Potassium Removal
CY14144	87%	71.63%	25.3%
CY14022	59%	5.94%	66.07%

The general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as defined in the appended claims. Other aspects of the present invention will be apparent to those skilled in the art in view of the detailed description of the invention as provided herein.

[0106] Additionally, polymer CY14144 is able to remove significant levels of potassium from blood plasma in a dynamic recirculation model. The normal range for blood potassium is 3.5-5 mEq/L while a patient suffering from hyperkalemia might have blood potassium levels up to 7-7.5 mEq/L. Reperfusion of plasma with a starting concentration of potassium 7.45 mEq/L through a device filled with polymer CY14144 under recirculation conditions that mimic the clinical application reduced the potassium concentration to 4.52 mEq/L (a 2.93 mEq/L reduction) in 5 hours.

[0107] The general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as defined in the appended claims. Other aspects of the present invention will be apparent to those skilled in the art in view of the detailed description of the invention as provided herein.

What is claimed is:

1. A biocompatible polymer system comprising at least one polymer, said polymer comprising (i) a plurality of pores and (ii) a sulfonic acid salt functionality;

said polymer system capable of adsorbing (i) a broad range of protein based toxins and inflammatory mediators and (ii) positively charged ions.

2. The biocompatible polymer system of claim 1 wherein the said toxins and inflammatory mediators have a molecular weight of from less than about 0.5 kDa to about 1,000 kDa.

3. The biocompatible polymer system of claim 1 wherein the said toxins and inflammatory mediators have a molecular weight of from less than about 1 kDa to about 1,000 kDa.

4. The biocompatible polymer system of claim 1 wherein the polymer's pore structure has a total volume of pore sizes in the range of from 10 Å to 40,000 Å greater than 0.1 cc/g and less than 5.0 cc/g dry polymer.

5. The biocompatible polymer system of claim 1 wherein the polymer is hemocompatible.

6. The biocompatible polymer system of claim 1 wherein the agent used to imbue biocompatibility is either (i) heparin or (ii) a heparin mimicking polymer.

7. The biocompatible polymer system of claim 1 wherein the polymer is formed and subsequently made to be biocompatible.

8. The biocompatibility imbuing modification of claim 7 wherein the agent used to imbue biocompatibility is either (i) heparin or (ii) a heparin mimicking polymer.

9. The biocompatible polymer system of claim 1 wherein the polymer system has the form of a solid support, which may include but is not limited to a bead, fiber, monolithic column, film, membrane, or semi-permeable membrane.

10. The biocompatible polymer system of claim 1 wherein, the toxins and inflammatory mediators comprise of one or more of cytokines, superantigens, monokines, chemokines, interferons, proteases, enzymes, peptides including bradykinin, soluble CD40 ligand, bioactive lipids, oxidized lipids, cell-free hemoglobin, cell-free myoglobin, DAMPS, growth factors, glycoproteins, prions, toxins, bacterial and viral toxins, PAMPS, endotoxins, drugs, vasoactive substances, foreign antigens, antibodies, and positively charged ions.

11. The biocompatible polymer system of claim 1, wherein the positively charged ion is potassium.

12. The biocompatible polymer system of claim 1 wherein said polymer is made using suspension polymerization, emulsion polymerization, bulk polymerization, or precipitation polymerization.

13. The biocompatible polymer system of claim 1 wherein said polymer is a hypercrosslinked polymer.

14. The biocompatible polymer system of claim 9 wherein the solid support has a biocompatible hydrogel coating.

15. The biocompatible polymer system of claim 1 wherein the polymer is in the form of hypercrosslinked or a macroreticular porous polymer that has been sulfonated under mild conditions that retain residual functionality of any unreacted double bonds and chloromethyl groups.

16. The biocompatible polymer system of claim 15, wherein the unreacted double bonds or chloromethyl groups can be modified via free radical or S_N2 type chemistry to attach one or more of biocompatible and hemocompatible monomers, cross-linkers or low molecular weight oligomers.

17. The biocompatible polymer system of claim 1 wherein porous polymer comprises sulfonic acid groups or a salt thereof, sulfonyl chloride, or sulfonate ester groups.

18. The biocompatible polymer system of claim 17, wherein the polymer comprising sulfonic acid groups or a salt thereof, sulfonyl chloride, or sulfonate ester groups is produced by graft copolymerization of (i) premade porous polymer that contains unreacted double bonds with (ii) polymerizable vinyl monomers containing sulfonic acid groups or a salt thereof to form a mixture comprising hemocompatible vinyl monomers.

19. The biocompatible polymer system of claim 1 constructed from polymerizable vinyl monomers containing sulfonic acid groups or a salt thereof which are copolymerized in the presence of cross-linker, hemocompatible monomer, monomer and suitable porogen to yield porous polymeric polymer containing a sulfonic acid salt functionality.

20. The biocompatible polymer system of claim 1, wherein said polymer system is capable of adsorbing (i) a broad range of protein based toxins having a molecular weight of from about 0.5 kDa to about 1,000 kDa and (ii) positively charged ions.

21. The biocompatible polymer system of claim 1, wherein said polymer system is capable of adsorbing (i) a broad range of protein based toxins having a molecular weight of from about 1 kDa to about 1,000 kDa and (ii) positively charged ions.

22. A method of perfusion comprising passing a physiologic fluid once through or by way of a suitable extracorporeal circuit through a device comprising the biocompatible polymer system of any one of claims 1-21.

23. A device for removing (i) a broad range of protein based toxins and inflammatory mediators and (ii) positively charged ions from physiologic fluid comprising the biocompatible polymer system of any one of claims 1-21.

24. The device of claim 23 wherein the said toxins and inflammatory mediators have a molecular weight of from less than about 0.5 kDa to about 1,000 kDa.

25. The device of claim 23 wherein the said toxins and inflammatory mediators have a molecular weight of from less than about 1 kDa to about 1,000 kDa.

26. The biocompatible polymer system of claim 1, wherein the polymer is housed in a container suitable to retain the polymer and for transfusion of whole blood, packed red blood cells, platelets, albumin, plasma or any combination thereof.

27. The biocompatible polymer system of claim 1, wherein the polymer is in a device suitable to retain the polymer and be incorporated into an extracorporeal circuit.

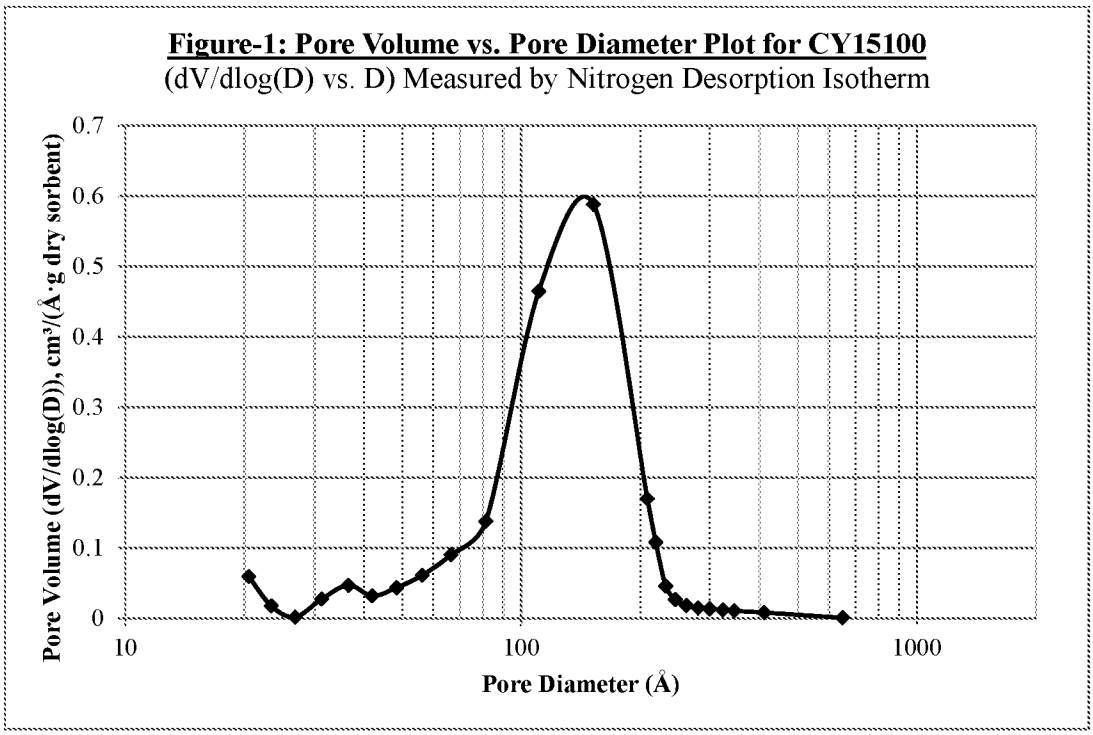
Figure-1: Pore Volume vs. Pore Diameter Plot for CY15100
(dV/dlog(D) vs. D) Measured by Nitrogen Desorption Isotherm
Pore Volume (dV/dlog(D)), cm³/(Å·g dry sorbent)
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
10
100
1000
Pore Diameter (Å)

Figure 1

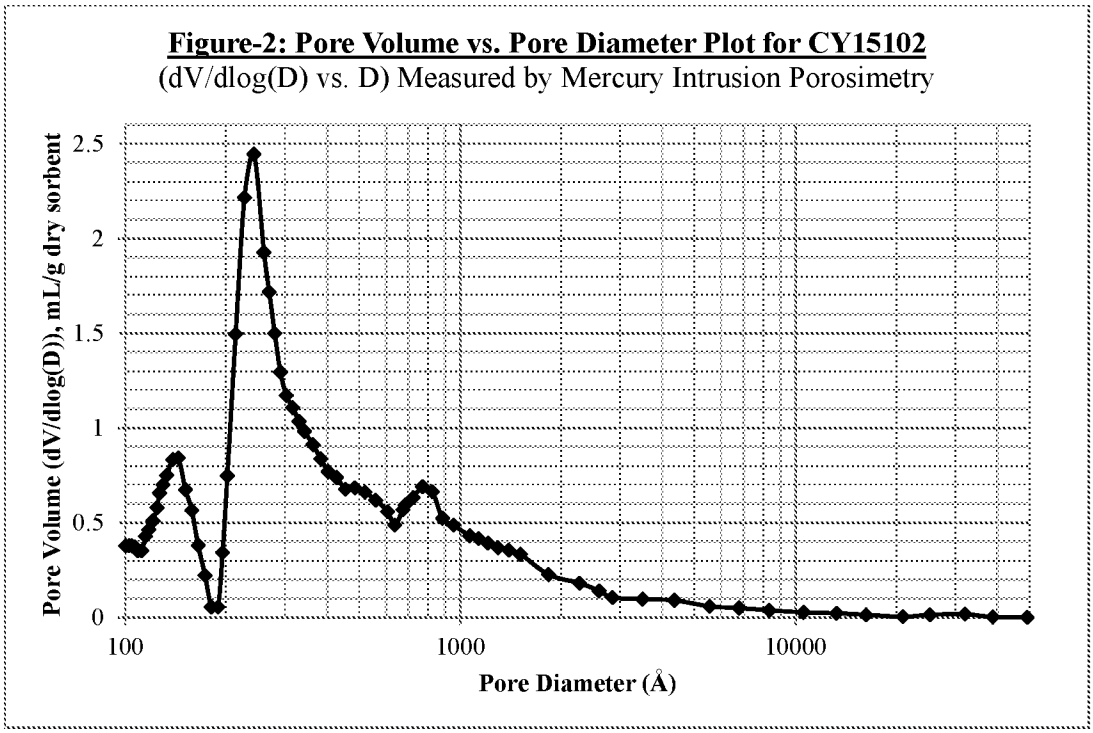
Figure-2: Pore Volume vs. Pore Diameter Plot for CY15102
(dV/dlog(D) vs. D) Measured by Mercury Intrusion Porosimetry
Pore Volume (dV/dlog(D)), mL/g dry sorbent
2.5
2
1.5
1
0.5
0
100
1000
10000
Pore Diameter (Å)

Figure 2

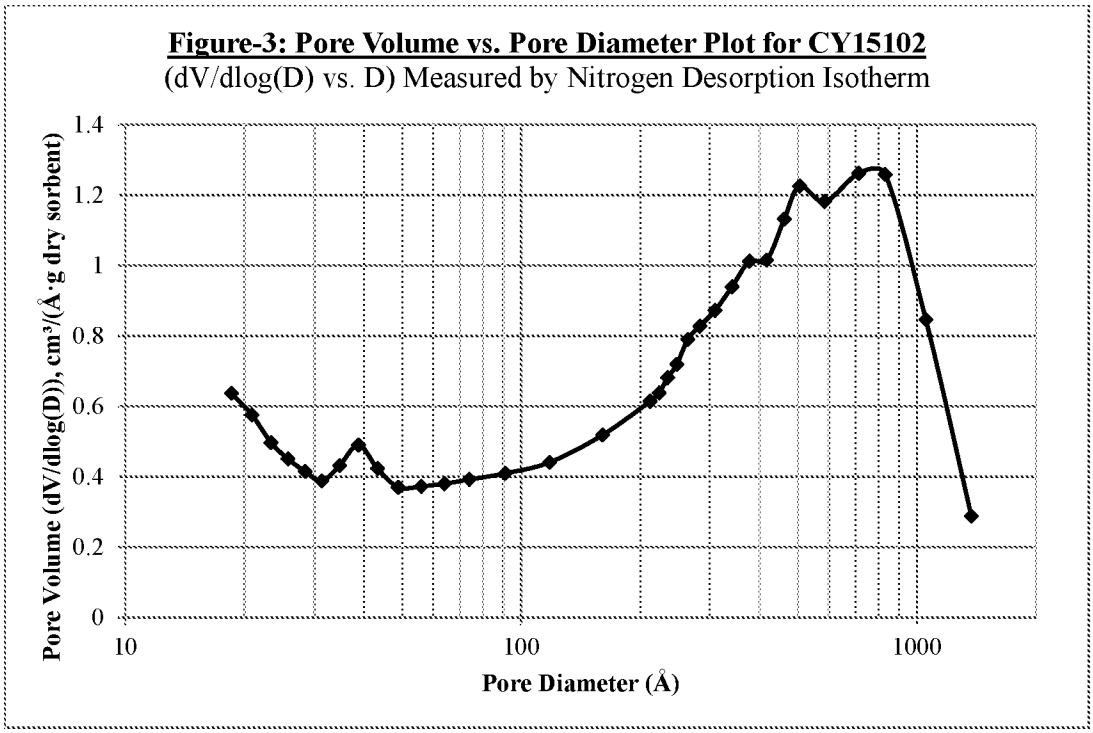
Figure-3: Pore Volume vs. Pore Diameter Plot for CY15102
(dV/dlog(D) vs. D) Measured by Nitrogen Desorption Isotherm
Pore Volume (dV/dlog(D)), cm³/(Å·g dry sorbent)
1.4
1.2
1
0.8
0.6
0.4
0.2
0
10
100
1000
Pore Diameter (Å)

Figure 3

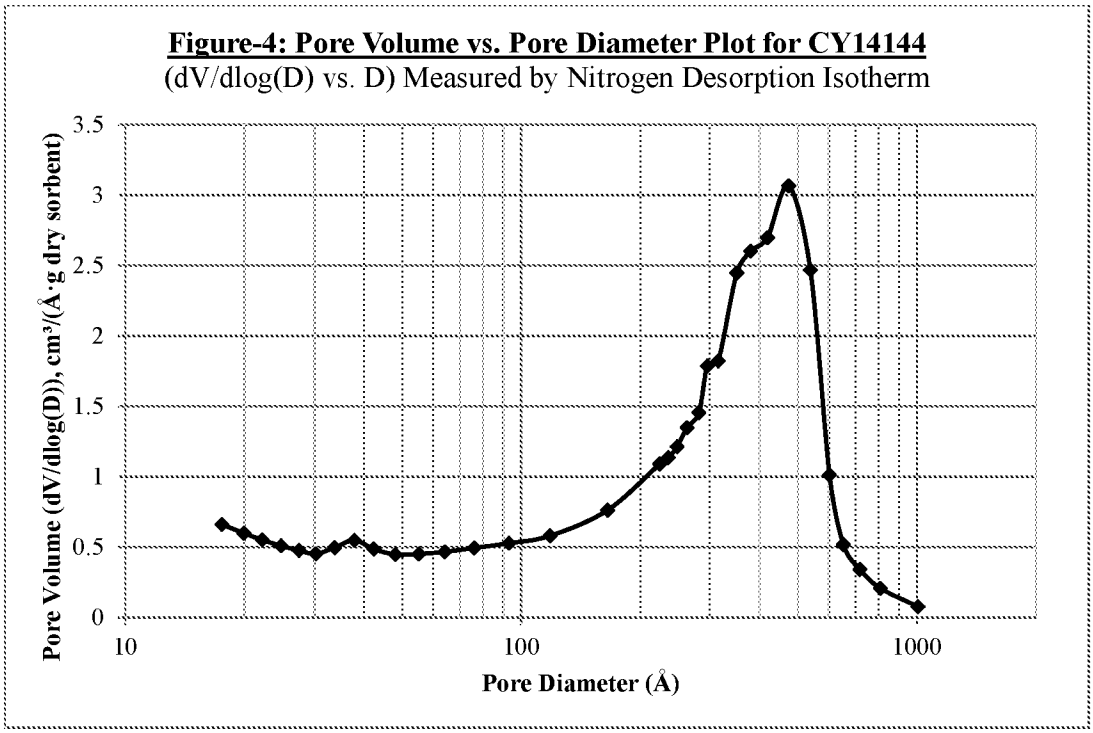
Figure-4: Pore Volume vs. Pore Diameter Plot for CY14144
(dV/dlog(D) vs. D) Measured by Nitrogen Desorption Isotherm
Pore Volume (dV/dlog(D)), cm³/(Å·g dry sorbent)
3.5
3
2.5
2
1.5
1
0.5
0
10
100
1000
Pore Diameter (Å)

Figure 4

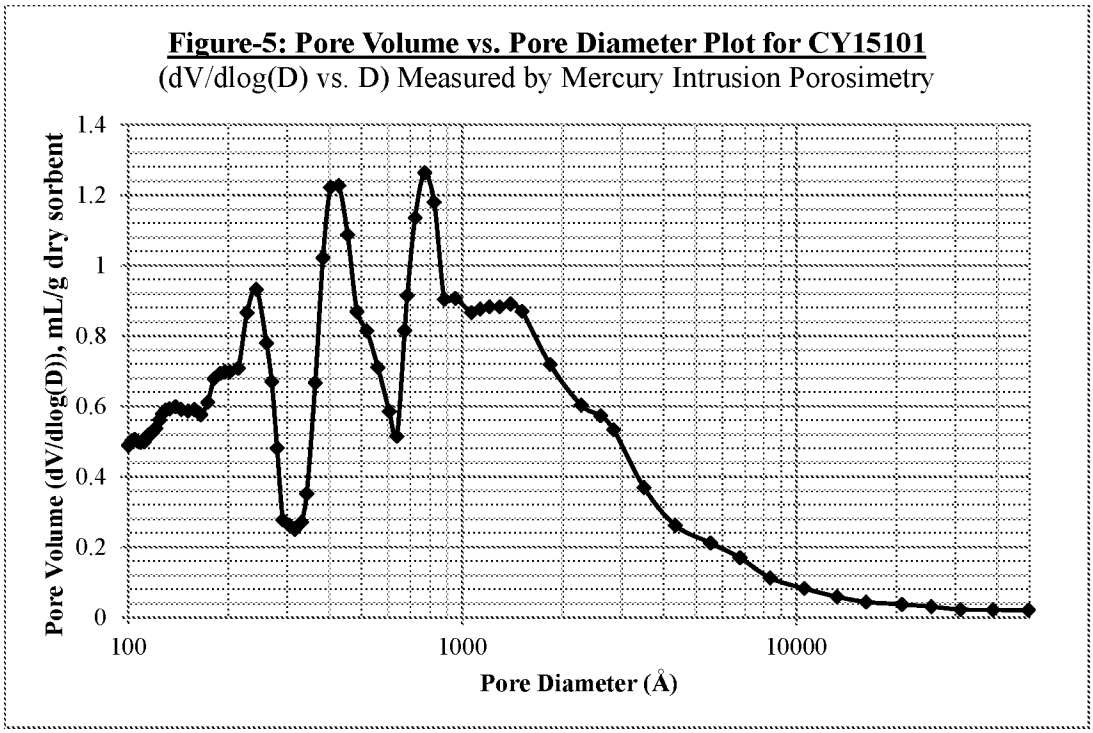
Figure-5: Pore Volume vs. Pore Diameter Plot for CY15101
(dV/dlog(D) vs. D) Measured by Mercury Intrusion Porosimetry
Pore Volume (dV/dlog(D)), mL/g dry sorbent
1.4
1.2
1
0.8
0.6
0.4
0.2
0
100
1000
10000
Pore Diameter (Å)

Figure 5

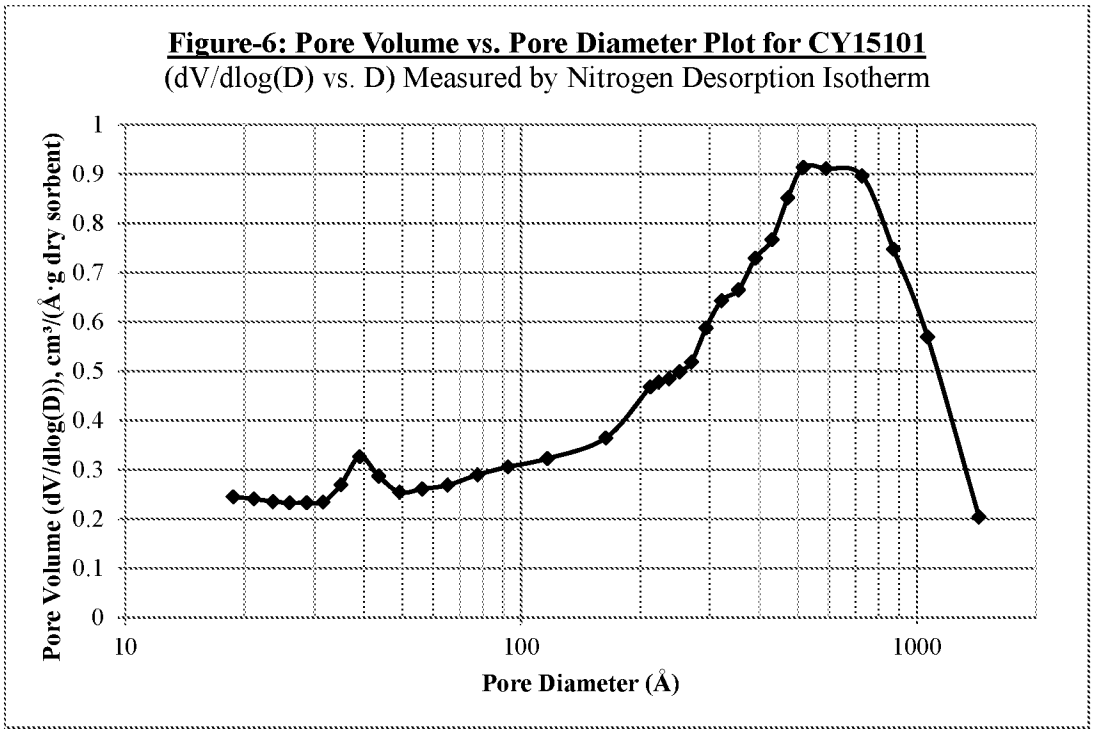
Figure-6: Pore Volume vs. Pore Diameter Plot for CY15101
(dV/dlog(D) vs. D) Measured by Nitrogen Desorption Isotherm
Pore Volume (dV/dlog(D)), cm³/(Å·g dry sorbent)
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
10
100
1000
Pore Diameter (Å)

Figure 6

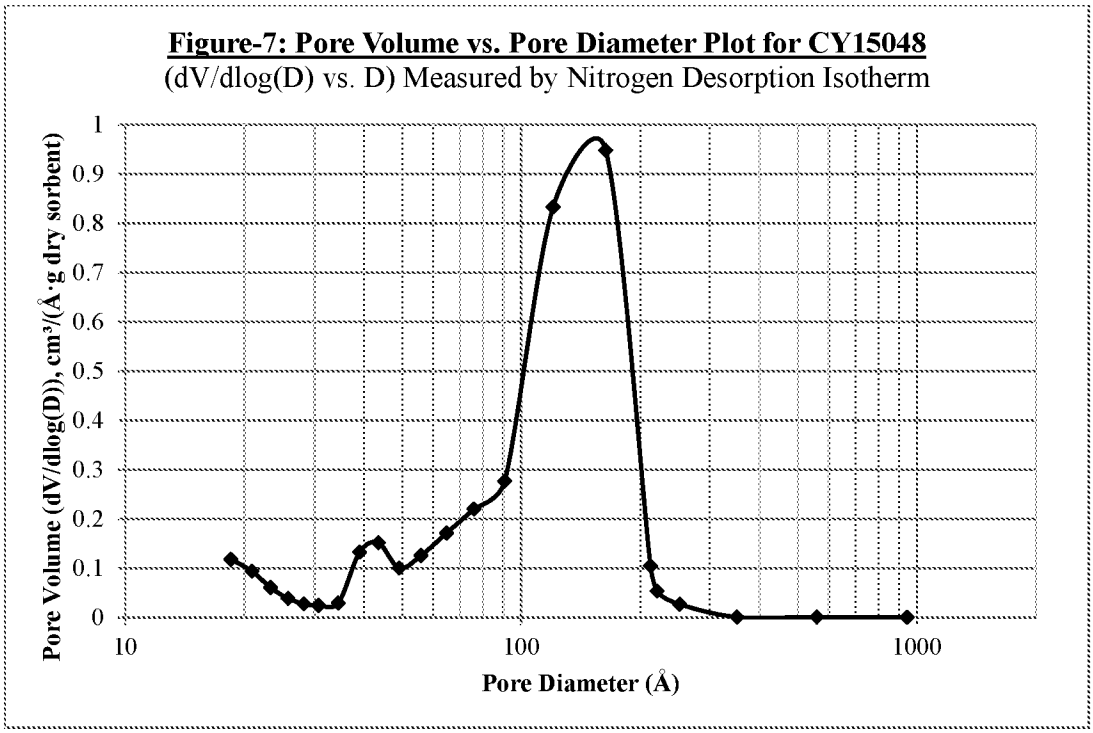
Figure-7: Pore Volume vs. Pore Diameter Plot for CY15048
(dV/dlog(D) vs. D) Measured by Nitrogen Desorption Isotherm
Pore Volume (dV/dlog(D)), cm³/(Å·g dry sorbent)
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
10
100
1000
Pore Diameter (Å)

Figure 7

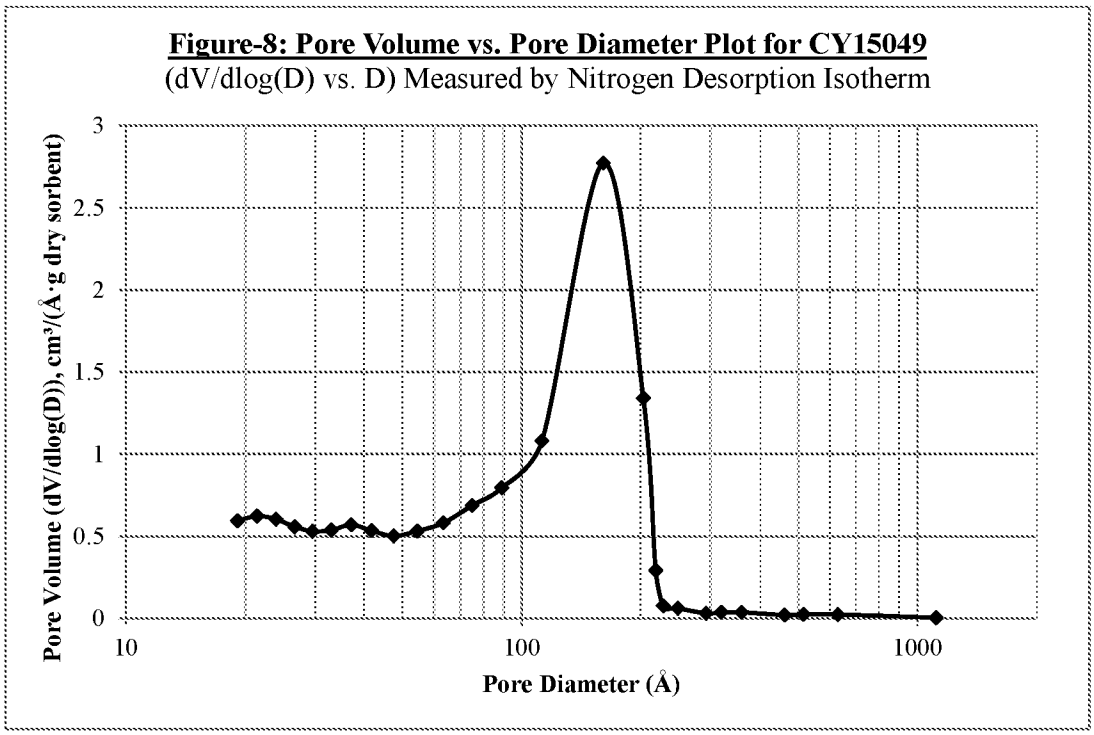
Figure-8: Pore Volume vs. Pore Diameter Plot for CY15049
(dV/dlog(D) vs. D) Measured by Nitrogen Desorption Isotherm
Pore Volume (dV/dlog(D)), cm³/(Å·g dry sorbent)
3
2.5
2
1.5
1
0.5
0
10
100
1000
Pore Diameter (Å)

Figure 8

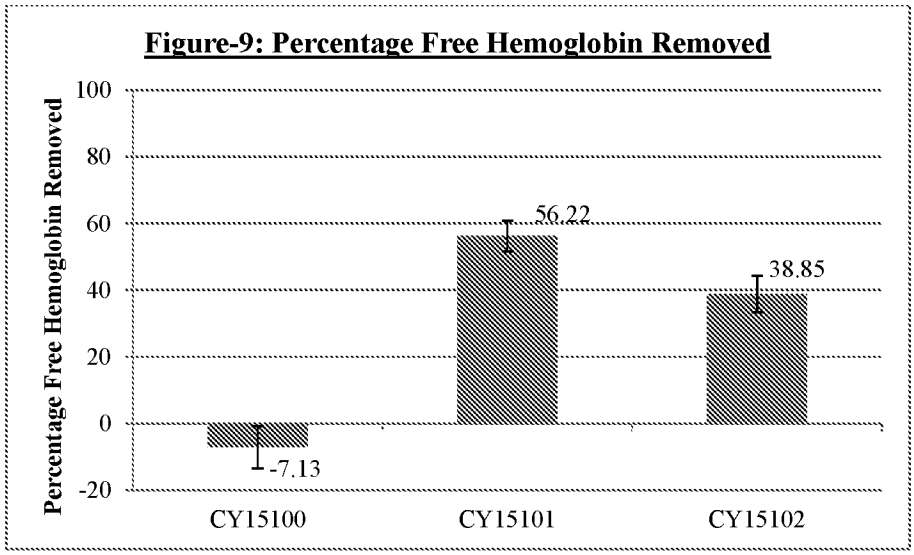
Figure-9: Percentage Free Hemoglobin Removed
Percentage Free Hemoglobin Removed
100
80
60
40
20
0
-20
56.22
38.85
-7.13
CY15100
CY15101
CY15102

Figure 9

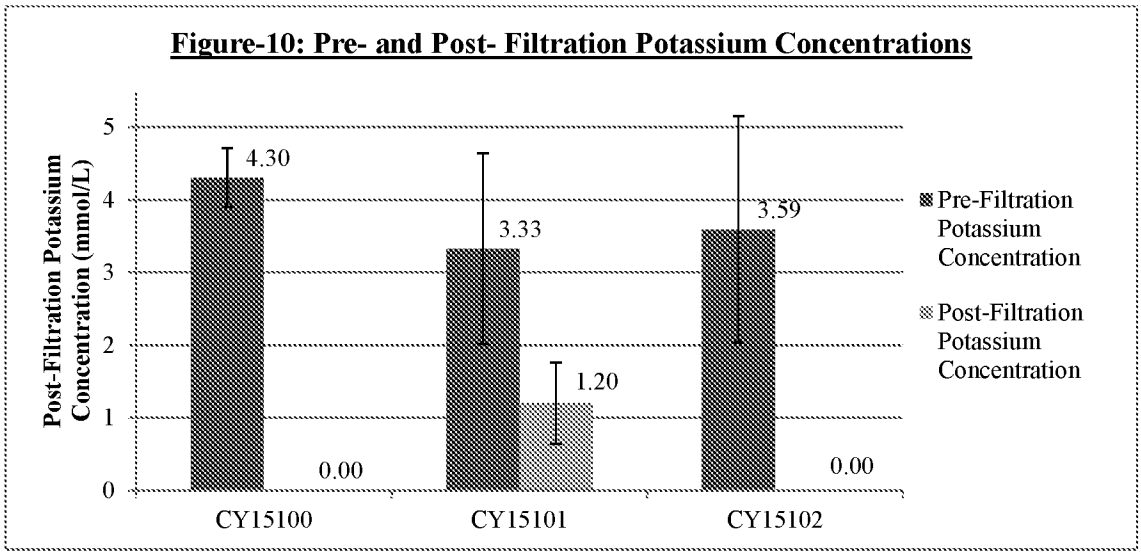
Figure-10: Pre- and Post- Filtration Potassium Concentrations
Post-Filtration Potassium Concentration (mmol/L)
5
4
3
2
1
0
4.30
0.00
3.33
1.20
3.59
0.00
CY15100
CY15101
CY15102
Pre-Filtration Potassium Concentration
Post-Filtration Potassium Concentration

Figure 10

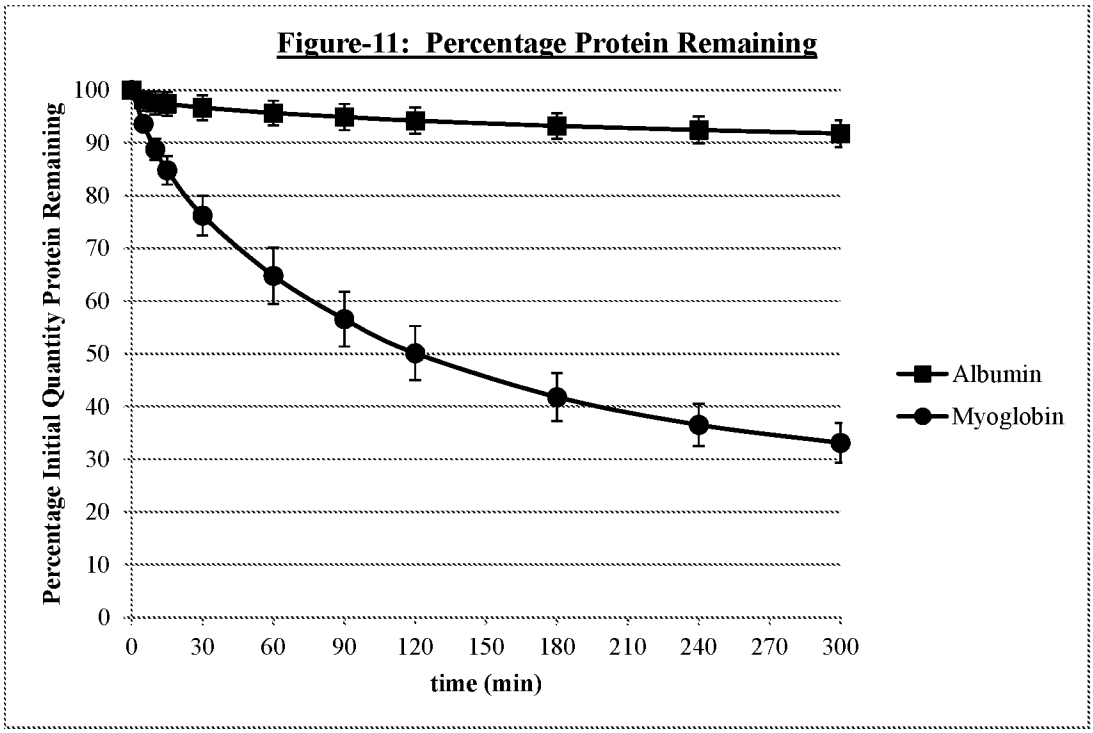
Figure-11: Percentage Protein Remaining
Percentage Initial Quantity Protein Remaining
100
90
80
70
60
50
40
30
20
10
0
0
30
60
90
120
150
180
210
240
270
300
time (min)
Albumin
Myoglobin

Figure 11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/58019

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61M 5/165, 1/34; A61K 47/20, 31/795 (2016.01)
CPC - A61M 5/165, 1/34; A61K 47/20, 31/795; B01J 20/3208, 49/0008
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) Classifications: A61M 5/165, 1/34; A61K 47/20, 31/795 (2016.01)
CPC Classifications: A61M 5/165, 1/34; A61K 47/20, 31/795; B01J 20/3208, 49/0008

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); Google Scholar; EBSCO; Pubmed
polymer, sulfonic acid, potassium adsorption, biocompatible, heparin, coating, cytokines

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2014/005039 A2 (CYTOSORBENTS CORPORATION) 3 January 2014; paragraphs [0030], [0055], [0063]-[0064], [0068]-[0069], [0074], [0081]; claims 1, 3, 5, 28-29, 41, 52, 54, 77	1-21, 22/1-21, 23/1-21, 24/23/1-21, 25/23/1-21, 26-27
Y	US 4837015 A (OLSEN, JL) 6 June 1989; abstract; column 3, lines 19-15, 50-53; claims 1, 9	1-21, 22/1-21, 23/1-21, 24/23/1-21, 25/23/1-21, 26-27
Y	US 6833153 B1 (ROORDA, WE et al.) 21 December 2004; column 2, lines 29-32; claims 1, 7, 9	6, 8, 22/6, 22/8, 23/6, 23/8, 24/23/6, 24/23/8, 25/23/6, 25/23/8
Y	US 5628730 A (SHAPLAND, JE et al.) 13 May 1997; column 10, lines 31-32; claims 1-3	14, 22/14, 23/14, 24/23/14, 25/23/14
Y	US 2008/0176966 A1 (TAKAGI, S et al.) 24 July 2008; claim 3	18-19, 22/18-19, 23/18-19, 24/23/18-19, 25/23/18-19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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

Date of the actual completion of the international search	Date of mailing of the international search report
5 December 2016 (05.12.2016)	12 JAN 2017
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)