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(54) **ENGINEERED HEPARIN BIOACTIVE MATRIX FOR CLINICAL APPLICATION OF BLOOD CONTACTING SURFACE AND METHOD OF MANUFACTURING THE SAME**

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(57) **ABSTRACT**

A manufacturing method fora pipeline flow diverter or stent includes activating a blood-contacting metal surface of the medical device via i) propene plasma treatment or ii) contacting the surface with an organic solution comprising a silane functional compound having an ethylenically unsaturated functional group, wherein the organic solution follows a blood flow path through the medical device; grafting a polymeric hydrogel to the activated surface; bonding a positively charged spacer molecule to the polymeric hydrogel by contacting the polymeric hydrogel with a first wet chemistry treatment composition comprising an aqueous solution containing a cationic polymer, wherein the first wet chemistry treatment follows a blood flow path through the medical device; and covalently bonding heparin to the spacer molecule by contacting the spacer molecule with a second wet chemistry treatment composition comprising heparin, wherein the second wet chemistry treatment follows a blood flow path through the medical device.

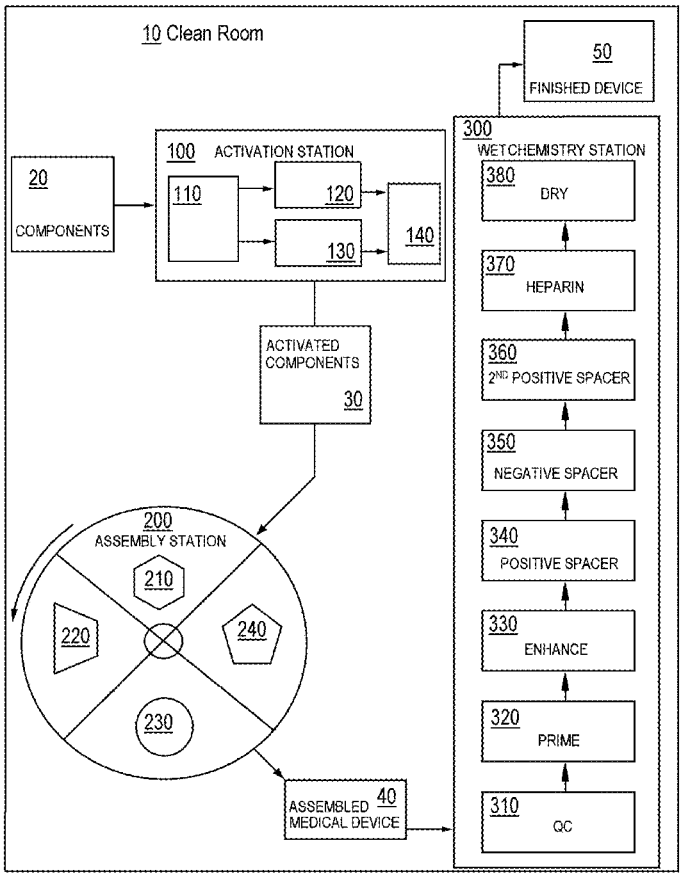
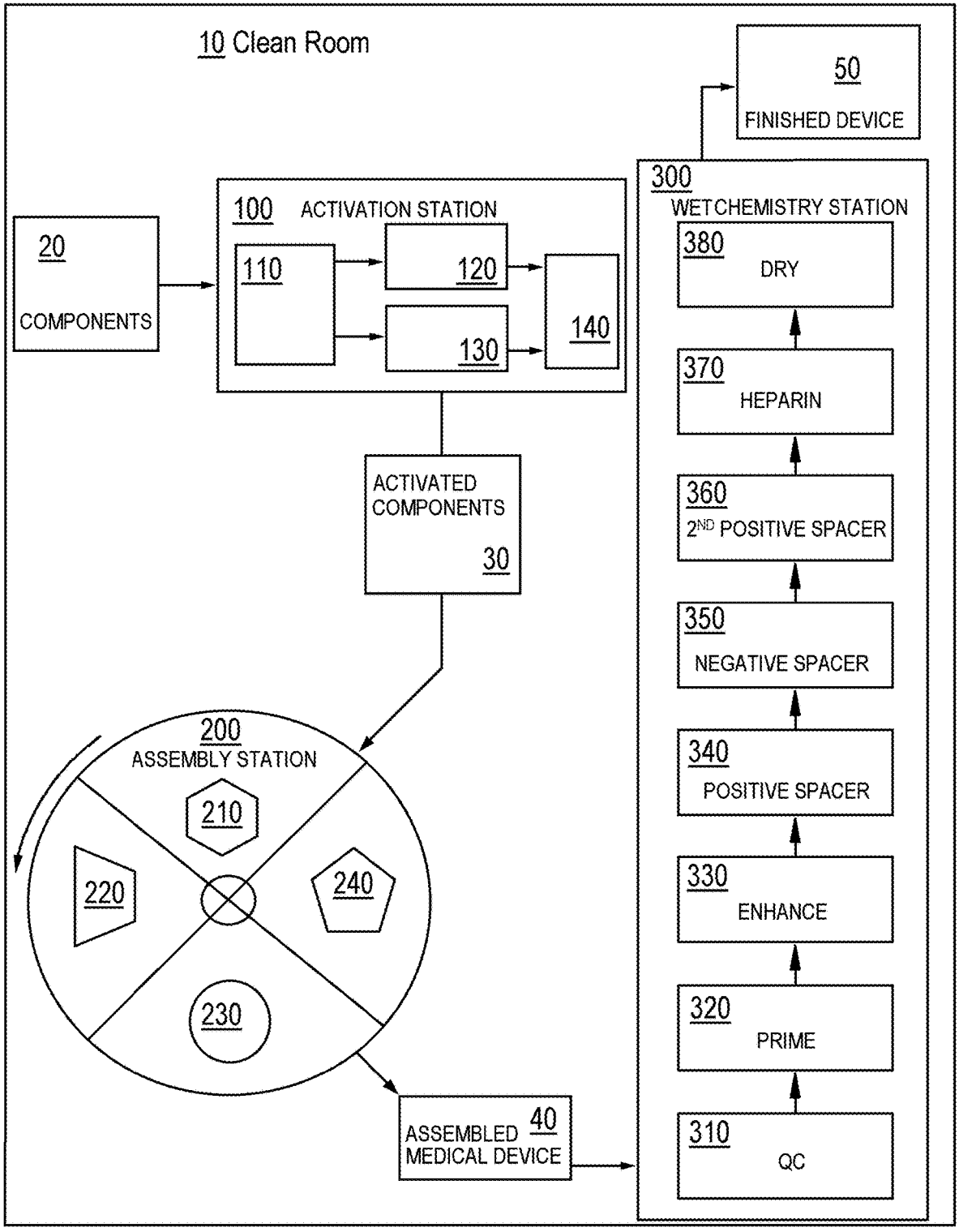


FIG. 1


10 Clean Room
50
FINISHED DEVICE
300
WETCHEMISTRY STATION
380
DRY
370
HEPARIN
360
2ND POSITIVE SPACER
350
NEGATIVE SPACER
340
POSITIVE SPACER
330
ENHANCE
320
PRIME
310
QC
100
ACTIVATION STATION
110
120
130
140
20
COMPONENTS
ACTIVATED
COMPONENTS
30
200
ASSEMBLY STATION
210
220
230
240
ASSEMBLED
MEDICAL DEVICE
40

ENGINEERED HEPARIN BIOACTIVE MATRIX FOR CLINICAL APPLICATION OF BLOOD CONTACTING SURFACE AND METHOD OF MANUFACTURING THE SAME

RELATED APPLICATIONS

[0001] The present application claims the benefit of U.S. Provisional Application Ser. No. 63/458,692 filed Apr. 12, 2023 and titled "Engineered Heparin Bioactive Matrix for Clinical Application of Blood Contacting Surface and Method of Manufacturing the Same" which is incorporated herein by reference.

[0002] The present application is a continuation in part of application Ser. No. 17/074,888 filed Oct. 20, 2020 and which published as U.S. Patent 2021/0100935 Apr. 8, 2021 which application and publication are incorporated herein by reference. application Ser. No. 17/074,888 is a continuation of international patent application serial number PCT/US2018/061993 filed Nov. 20, 2018 and published Oct. 24, 2019 as WO 2019/203898, which application and publication are incorporated herein by reference. International patent application serial number PCT/US2018/061993 claims the benefit of U.S. Provisional Application Ser. No. 62/660,804 filed Apr. 20, 2018 and titled "Engineered Heparin Bioactive Matrix for Clinical Application of Blood Contacting Surface and Method of Manufacturing the Same" which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

Field of the Invention

[0003] The present invention relates to surface treated blood contacting medical devices such as blood oxygenators and to surface treated blood contacting medical devices such as extracorporeal circulation devices including blood oxygenators and cardio pulmonary bypass (CPB) equipment, catheters including Renal Dialysis catheters, Cardiovascular Catheters, Neurovascular Catheters Balloon Catheters, Pipeline flow diverters and drug delivery catheters.

Background Information

[0004] Devices used in the medical field must be manufactured using materials having biocompatibility, also called biomaterials, having particular surface properties so that the device functions without causing adverse effects to the patient. Technically, according to Black's Medical Dictionary, 2010, biocompatibility is defined as the ability of a biomaterial to perform its desired function with respect to a medical therapy, without eliciting any undesirable or systemic effects in the recipient or beneficiary of that therapy, but generating the most appropriate beneficial cellular or tissue response in that specific situation, and optimizing the clinically relevant performance of the therapy. The definition is somewhat looser in practice in that the strict application of the definition of "generating the most appropriate beneficial cellular or tissue response" is not always achieved with materials that are classified as biomaterials and sometimes a material is deemed biocompatible if there is no immediate catastrophic adverse tissue response or immediately observable increased patient mortality.

[0005] Biomaterials are typically made of inert metals, polymers, or ceramics to ensure durability and to try to have the materials not adversely react with the physiological environment with which they come into contact, such as with blood or tissues. More particularly, many biomedical devices may or may not require blood compatible, infection resistant, and/or tissue compatible surfaces. For example, it is often desirable to manufacture medical devices, such as catheters, that have properties that discourage adherence of blood or tissue elements to the device. Adverse reactions between materials and blood components are predominant factors limiting the use of synthetic materials that come into contact with physiological fluids.

[0006] A number of approaches have been suggested to improve the biocompatibility and blood compatibility of medical devices. One approach has been to modify the surface of the material to prevent undesirable protein adhesion by providing the material with a low polarity surface, a negatively charged surface, or a surface coated with biological materials, such as enzymes, endothelial cells, and proteins. Another approach has been to bind anticoagulants to the surface of biologically inert materials to impart anti- or non-thrombogenic characteristics to the materials. Still another approach used in the art has been the copolymerization of various phospholipids which are used as coating materials for various substrates. Partial polymeric backbone coatings have also been used in a similar fashion. However, many of these methods can result in a leaching or "stripping off" of the coating.

[0007] In devices requiring the transfer of gases, for example, in blood oxygenators requiring the exchange of oxygen and carbon dioxide through a membrane or porous fiber, there are additional drawbacks. Often surfaces that have been rendered biocompatible by the coating of biomolecules attract phospholipids. Phospholipids that adhere to the surface coat the pores and wet the surface of the device, making it hydrophilic. Water adversely affects gas transfer, making the oxygenator significantly less effective. There remains a need in the art to develop processes for preparing substrates coated biomolecules that demonstrate biocompatibility and blood compatibility, while maintaining gas permeability.

[0008] The patent literature details general oxygenator operation and construction. U.S. Patent Application Publication Numbers 2017-0312416, 2017-0007755, 2016-0136347, 2015-0182681, 2014-0037500, 2013-0343954, 2013-0296633, 2013-0094997, 2010-0272602, 2008-0199357, 2007-0249888, 2005-0042141 and 2002-0057989 are representative examples which are incorporated herein by reference. Many of the above systems relate to an integrated centrifugal blood pump-oxygenator having a rotational body being rotatable in a rotor-housing, often located on the bottom.

[0009] Lung diseases are the third largest cause of death in the United States of America, accounting for approximately 1 out of every 7 adult deaths. It has been estimated that 30 million Americans are living with chronic lung disease. Adult respiratory distress syndrome (ARDS) has been reported to afflict approximately 150,000 patients annually in the U.S, and despite advances in critical care, mortality remains around 40-50%. Currently available therapies for patients with chronic respiratory failure include, for example, ventilation and extracorporeal membrane oxygenation (ECMO). In intensive care medicine, extracorporeal membrane oxygenation (ECMO) is an extracorporeal technique of providing both cardiac and respiratory support

oxygen to patients whose heart and lungs are so severely diseased or damaged that they can no longer serve their function.

[0010] ECMO systems attempt to closely simulate physiological gas exchange. Attempts have been made to integrate multiple components of cardiopulmonary, ECMO-systems into single structures so as to eliminate or minimize the need for the extension of lengthy, blood-filled tubes. Various integrated pump-oxygenators have been described as discussed in U.S. Pat. Nos. 5,217,689; 5,266,265; 5,270,005; 5,770,149; 4,975,247; 5,395,468; 5,429,486; 6,963,222; and 6,730,267. U.S. Pat. No. 4,639,353 discloses the use of an arrangement of bundles of hollow fibers perpendicular to the direction of blood flow via a series of flow guide structures. U.S. Pat. No. 5,263,924 discloses the use of an integrated centrifugal pump and membrane oxygenator comprising hollow fibers, which are displaced circumferentially in a ring around an impeller of the centrifugal pump and through which blood is pumped for oxygenation. See also U.S. Pat. Nos. 3,998,593 and 4,490,331 which are incorporated herein by reference. Other efforts to decrease the effect of the boundary layer include actively rotating hollow fiber membranes or moving fiber membranes in the path of blood flow, examples of which are described in U.S. Pat. Nos. 5,830,370; 6,217,826; 6,503,450; 6,723,284; and 7,122,155. Additional patents and publications giving a general overview of conventional blood pump-oxygenators include U.S. Pat. Nos. 4,239,729, 6,929,777, and 7,927,544, and U.S. Publication Nos. 2004-0219059, 2008-0190870, 2009-0175762, 2010-0101657, 2010-0288703, 2016-0296685 and 2017-0021081 which are incorporated herein by reference.

[0011] U.S. Publication 2015/0352265, which is incorporated herein by reference, discloses hemo-compatible, anti- and non-thrombogenic, heparin-based bioactive coatings for a surface to be contacted with blood, such as a surface of an oxygenator device (also called a Hollow Fiber Membrane (HFM) surface) or an artificial lung, which coatings include a quaternary ammonium salt and heparin complex (QUAT). According to representative embodiments, the surface is treated with polyvinylpyrolidone (PVP), followed by a coating layer of said quaternary ammonium salts and heparin complex (QUAT) to form a PVP-QUAT coating. According to an alternative embodiment, anionic functional groups are created on the one or more surfaces of the HFM by modifying the surface of the HFM using ionic complexes dissolved in a solvent mixture that includes major quantity of alcohol along with a minor quantity of organic dissolving agents. None of the approaches presented yield optimized Physiologically Significant Bioactivity and Stability.

[0012] A surface treatment approach for treating medical devices is described in U.S. Pat. No. 8,114,465 and U.S. Patent Application Publication Numbers 2008-0241349 in which a typical process comprises: a) providing a substrate, such as fibers for an oxygenator; b) coating the substrate with a polysiloxane or acrylamide; c) rendering the polysiloxane and/or acrylamide surface amino functional; and d) contacting the amino-functional polysiloxane surface with a biomolecule, such as heparin under conditions effective to attach the biomolecule to the substrate. This surface modification or treatment approach has distinct advantages over typical coating approaches, but can be further optimized for increased stability and bioactivity and scalability.

[0013] U.S. Patent Publication 2012-0231043 and U.S. Patent Publication 2003-0163198 may also be considered as relevant to the state of the art and are incorporated herein by reference.

[0014] The remains a need for an engineered bioactive heparin matrix with optimized physiologically significant bioactivity and increased stability suitable for clinical applications and universally applicable methods of manufacturing the same

SUMMARY OF THE INVENTION

[0015] One aspect of this invention is directed to a method of manufacturing a medical product having an engineered heparin bioactive matrix for clinical application on a blood contacting surface comprising the steps of: a) activating a blood contacting surface of at least one component of a medical device via one of plasma treatment or gas activation; b) assembling the medical product; c) setting up medical device for wet chemistry in which wet chemistry treatments follows a blood flow path through device; d) enhancing at least the blood contacting surface with a wet chemistry treatment including an aqueous solution having a strong oxidizing agent, such as ammonium persulfate; e) adding a positively charged spacer molecule to at least the blood contacting surface with a wet chemistry treatment including an aqueous solution having a cationic polymer, such as PEI; and f) covalently immobilizing heparin to at least the blood contacting surface with a wet chemistry treatment including heparin, preferably deaminated heparin.

[0016] The present invention is further directed to method of manufacturing a medical device such as a medical pipeline flow diverter or stent, having an engineered heparin bioactive matrix on a blood-contacting metal surface, comprising: a) activating a blood-contacting metal surface of at least one component of the medical device to form an activated surface via i) propene plasma treatment or ii) contacting the surface with an organic solution comprising a silane functional compound having at least one ethylenically unsaturated functional group, wherein the organic solution is introduced to and follows a blood flow path through the medical device; b) grafting a polymeric hydrogel to the activated surface; c) optionally hydrolyzing the polymeric hydrogel to form carboxyl functional groups on the polymeric hydrogel; d) bonding a positively charged spacer molecule to the polymeric hydrogel by contacting the polymeric hydrogel with a first wet chemistry treatment composition comprising an aqueous solution containing a cationic polymer, wherein the first wet chemistry treatment follows a blood flow path through the medical device; and e) covalently bonding heparin to the spacer molecule by contacting the spacer molecule with a second wet chemistry treatment composition comprising heparin, wherein the second wet chemistry treatment follows a blood flow path through the medical device.

[0017] The present invention is further directed to a method of manufacturing a medical catheter having an engineered heparin bioactive matrix on a blood-contacting polymeric surface. The method comprises: a) activating a blood-contacting polymeric surface of at least one component of the medical catheter to form an activated surface via i) propene or sodium naphthalate plasma treatment, ii) corona activation, iii) radiation activation or iv) ozone gas activation, wherein the blood-contacting polymeric surface comprises a fluoropolymer, (vanillyl alcohol-containing

copolyoxalate) copolymer (PVAX), or a block copolymer of ethylene oxide and tetramethylene glycol; b) grafting a polymeric hydrogel to the activated surface; c) optionally hydrolyzing the polymeric hydrogel to form carboxyl functional groups on the polymeric hydrogel; d) bonding a positively charged spacer molecule to the polymeric hydrogel by contacting the polymeric hydrogel with a first wet chemistry treatment composition comprising an aqueous solution containing a cationic polymer, wherein the first wet chemistry treatment follows a blood flow path through the medical catheter; and e) covalently bonding heparin to the spacer molecule by contacting the spacer molecule with a second wet chemistry treatment composition comprising heparin, wherein the second wet chemistry treatment follows a blood flow path through the medical device.

[0018] These and other advantages are described in the brief description of the preferred embodiments in which like reference numeral represent like elements throughout.

BRIEF DESCRIPTION OF THE FIGURES

[0019] FIG. **1** is a schematic view of a manufacturing facility for forming a medical device for clinical application having an engineered heparin bioactive matrix of blood contacting surface in accordance with one aspect of the present invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0020] It is noted that, as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless expressly and unequivocally limited to one referent.

[0021] For the purposes of this specification, unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and other parameters used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are approximations that may vary depending upon the desired properties to be obtained by the present invention. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

[0022] All numerical ranges herein include all numerical values and ranges of all numerical values within the recited numerical ranges. Notwithstanding that the numerical ranges and parameters setting forth the broad scope of the invention are approximations, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical value, however, inherently contain certain errors necessarily resulting from the standard deviation found in their respective testing measurements.

[0023] The various embodiments and examples of the present invention as presented herein are each understood to be non-limiting with respect to the scope of the invention.

[0024] As used in the following description and claims, the following terms have the indicated meanings:

[0025] The terms "on", "appended to", "affixed to", "bonded to", "adhered to", or terms of like import means that the designated item, e.g., a coating, film or layer, is either directly connected to (superimposed on) the object surface, or indirectly connected to the object surface, e.g., through one or more other coatings, films or layers (superposed on).

[0026] The terms "attach", "couple", and "link" refer to securing a material or biomolecule to a substrate, for example, by chemical covalent or ionic bonding, such that the coating or biomolecule is immobilized with respect to the substrate.

[0027] The term "medical device" is a device that has at least one surface that contacts tissue, blood, or other bodily fluids in the course of its operation, which fluids are present within or subsequently introduced into patients and which has an internal blood/fluid flow path through the device. This definition can include, for example, extracorporeal circulation devices for use in surgery such as blood oxygenators, blood pumps, blood sensors, cardio pulmonary bypass (CPB) equipment, tubing used to carry blood and the like which contact blood which is then returned to the patient. This can also include endo-prostheses implanted in blood contact in a human or animal body such as vascular grafts, stents, heart valves, and the like that are implanted in blood vessels or in the heart. Pipeline flow diverters are also included in this listing. This can also include devices for temporary intravascular use such as catheters, dialysis machine, and the like which are placed into the blood vessels or the heart for purposes of monitoring or repair. Catheters include, but are not limited to, Renal Dialysis catheters, Cardiovascular Catheters, Neurovascular Catheters Balloon Catheters, and drug delivery catheters.

[0028] The term "biomolecule" refers to a biologically active molecule.

[0029] A "biocompatible" material does not generally cause significant adverse reactions (e.g., toxic or antigenic responses) in the body, whether it degrades within the body, remains for extended periods of time, or is excreted whole (see ISO 10993). Ideally, a biocompatible material will not induce undesirable reactions in the body as a result of contact with bodily fluids or tissue, such as infection, coagulation, tissue death, tumor formation, allergic reaction, foreign body reaction (rejection) or inflammatory reaction.

[0030] A "blood compatible" material is one that will not induce undesirable reactions in the body as a result of contact with blood, such as blood clotting or infection. A blood compatible material is understood to be biocompatible.

[0031] The present invention also is particularly applicable to blood gas exchange devices, e.g., oxygenators which, in general are extremely well known in the art, as fully described in the above cited patents and published patent applications that are incorporated herein by reference. The present invention is particularly well suited for both well-known sheet and tubular forms of membrane oxygenators. In a membrane oxygenator, the blood is separated from direct contact with the oxygenating gas by a membrane, which is disposed within a hollow housing. This membrane is microporous or semipermeable, that is, capable of permitting carbon dioxide and oxygen to permeate through it while at the same time preventing the blood itself from passing there through.

[0032] The tubular oxygenators are also known or referred to as hollow fiber oxygenators, and the general format is illustrated in U.S. Pat. No. 4,239,729. A hollow fiber oxygenator employs a large plurality (typically thousands) of

microporous or semipermeable hollow fibers disposed within a housing. These hollow fibers are sealed in the end walls of the housing; the end walls are then fitted with skirted end caps. One end cap is fitted with an inlet, and the other is fitted with an outlet. In the '729 patent oxygenator, the hollow fibers are aligned in the housing so that their longitudinal axes are generally parallel to the longitudinal axis of the housing. In this device, blood enters through the inlet of one end cap, passes through the lumens of the hollow fibers, and exits through the outlet of the other end cap. Oxygenated gas enters the device through the inlet in the peripheral wall near one end of the device, passes over the outer surfaces of the hollow fibers, and exits the device through the outlet in the peripheral wall near the other end of the device. It will be understood that carbon dioxide diffuses from the blood flowing inside the hollow fibers through the fiber walls into the stream of oxygenating gas. At the same time, oxygen from the oxygenating gas flowing over the outer surfaces of the hollow fibers diffuses through the walls of the hollow fibers into the lumens thereof to oxygenate the blood flowing there through. Other oxygenators comprising hollow fibers have been developed. These oxygenators typically comprise a plurality of hollow fibers disposed within a hollow housing and arranged so that blood typically flows over the hollow fibers and gases typically flow through the hollow fibers. Many configurations are possible as to the direction of fluid flow and the arrangement of fibers. The fibers may be in a linear, circular, or spiral arrangement, for example, or may be wrapped or wound around a core in various configurations. Hollow fiber membrane oxygenators are described, for example, in U.S. Pat. Nos. 4,975,247 and 5,395,468, which are incorporated herein by reference.

[0033] A second type of membrane oxygenator, called the flat plate membrane oxygenator, employs one or more thin, flat sheets of microporous membrane. In its most basic form, the flat plate oxygenator has a single sheet of microporous membrane sealed into a housing so as to provide in the housing a first compartment (the "blood compartment") for the flow of blood, and a second compartment (the "gas compartment") for the flow of an oxygenating gas. Each of the compartments is fitted with an inlet and an outlet. Blood flows into and out of the blood compartment and the oxygenating gas flows into and out of the gas compartment. Oxygen passes from the oxygenating gas across the membrane into the blood flowing through the blood compartment. Carbon dioxide passes from the entering blood across the membrane to be entrained in the oxygenating gas. The exiting blood, now reduced in carbon dioxide and enriched in oxygen, is returned to the patient.

[0034] FIG. **1** is a schematic view of a manufacturing facility for forming a medical device **50** for clinical application having an engineered heparin bioactive matrix of blood contacting surface in accordance with the present invention. The medical device **50** is preferably one of an extracorporeal circulation device such as blood oxygenator or cardio pulmonary bypass (CPB) equipment, a vascular graft, stent, heart valve, pipeline flow diverter, or catheters such as a renal dialysis catheter, cardiovascular catheter, neurovascular catheter, balloon catheter, and drug delivery catheter. Preferably the medical device **50** is a tubular blood oxygenator as generically described above. The present invention is related to an engineered heparin bioactive matrix on a blood contacting surface of the medical device **50** as described below, but the present method and manufacturing system may be used for other biomolecules. An engineered heparin bioactive matrix, or any engineered bioactive matrix within the meaning of this application refers to a substrate which has undergone surface treatment in accordance with engineering principles of maintaining homeostasis (See ISO 10993-4), and specific to blood contacting surfaces, maintaining hemostasis, namely maintaining the ability of the blood to maintain normal function as determined or verified by measuring the molecular and cellular elements of the blood maintaining within accepted clinical parameters. The engineered heparin bioactive matrix of blood contacting surface in accordance with present invention yields clinically relevant Physiological biofunctionality (bioactivity) which is stable over a long period of time.

[0035] In summary, the present invention provides a method of manufacturing a medical product **50** for clinical application having an engineered heparin bioactive matrix on a blood contacting surface in which components **20** have surface activation of select surfaces at an activation station **100**; the activated components **30** of the device **50** are forwarded to an assembly station **200**, and the assembled medical device **40** is forwarded to a wet chemistry station **300** for application of having an engineered heparin bioactive matrix on a blood contacting surface to form the finished medical device **50**. The essential steps include a) activating a blood contacting surface of at least one component of a medical device **50** via one of plasma treatment **120** or gas activation **130**; b) assembling the medical product at station **200**; c) setting up the assembled medical device for wet chemistry (**310**, **320**) in which wet chemistry treatments follows a blood or fluid flow path through device **50**; d) enhancing at step **330** at least the blood contacting surface with a wet chemistry treatment including an aqueous solution having a strong oxidizing agent; e) adding a positively charged spacer molecule at step **340** to at least the blood contacting surface with a wet chemistry treatment including an aqueous solution having a cationic polymer; and f) covalently immobilizing heparin at step **370** to at least the blood contacting surface with a wet chemistry treatment including heparin.

[0036] The manufacturing process of the present invention is configured for being performed within a single clean room **10**. Cleanroom **10** is an enclosed and environmentally-controlled space in which temperature, humidity, pressure and contaminant levels are kept within defined limits. The controlled environment provided by the clean room **10** helps to ensure that products **50** remain under controlled contamination levels throughout the production process, thereby reducing potential risks to patients. The single clean room **10** for the process of the present invention is beneficial for the production of safe devices **50**. Details for the construction and operation of the clean room **10** are set forth in ISO 14644.

[0037] The components **20** forming the medical device **50** are brought into the clean room **10** and to an inspection station **110** at the activation station **100**. Following the inspection the individual components **20** typically goes onto the activation via plasma treatment **120** or gas activation **130**, or may go to a cleaning step if the inspection identifies an issue, or the component is discarded if a cleaning cannot remedy the problem with the component **20**. Any component **20** of the device **50** must pass its own inspection according

to the associated product **50** protocol. It is possible that some components **20** will undergo a pre-cleaning before the clean room to assure that the component **20** is beginning from a desired state, and such pre-cleaning may be useful if there is variability from manufacturing or multiple vendors.

[0038] The components **20** passing inspection at step **110**, which may be cleaned and inspected again, move onto activating a blood contacting surface of at least one component **20** of the medical device **50** via one of plasma treatment **120** or gas activation **130**.

[0039] Plasma treatment **120** take place within a plasma chamber containing electrodes, across which a voltage is applied. The chamber may be partially evacuated. The plasma treatment of the present invention may be with propene, oxygen, siloxane (hexamethyldisiloxane-HMDSO and/or tetramethyldisiloxane-TMDSO) or acrylic acid, in which a stream of the relevant gas is fed into the chamber. When a high frequency voltage is applied between the electrodes, current flows into the chamber, forming a plasma, which is a glowing electrical discharge within the gas. Reactive chemical species are formed in this electrical discharge. Plasma treatment **120** has certain advantages over gas treatment **130** and may be preferable for polycarbonate substrates.

[0040] Gas activation **130** within the meaning of this application is ozone activation or ozone treatment also known as UV ozone treatment. Gas activation **130** may be done at ambient pressures. Gas activation **130** may be preferable for polypropylene (PP), polyurethane (PU) polyethylene (PE) and silicone substrates.

[0041] Following surface activation via one of plasma treatment **120** or gas activation **130**, the component is moved to performance testing **140** in which representative components **20** are inspected and tested using conventional testing such as one of FTIR, SEM Contact angle and XPS. Following passing of the performance testing **140** the activated components **30** are forwarded to the assembly station **200**. The record of the performance testing **140** is maintained to establish a quality review record of the production of the finished device **50**, or for a batch of the finished devices **50**.

[0042] The activated components **30** are assembled into the medical product **40** at station **200**, specifically at assembly station **240**. The present invention is particularly well suited to application where the medical device **50** is one of an extracorporeal circulation device such as blood oxygenator or cardio pulmonary bypass (CPB) equipment, a vascular graft, stent, heart valve, pipeline flow diverter, or catheters such as a renal dialysis catheter, cardiovascular catheter, neurovascular catheter, balloon catheter, and drug delivery catheter.

[0043] Regarding blood oxygenators the present invention is well suited for forming tubular blood oxygenators. In the formation of a tubular blood oxygenator as the medical device **50**, the first step of the assembly station **200** is a winding apparatus or station **210** forming a tubular fiber bundle for the tubular blood oxygenator. The winding station may also be referred to as fiber bundling which is the winding of the hollow (often polypropylene although Polymethylpentene PMP is commonly used as oxygenation membranes) fibers into the fiber bundle that forms the central core of a membrane oxygenator. The details of the winding device and the formed bundle will depend on the particulars of the oxygenator housing and operational parameters and desired surface area and other specifications, however for some general background see "Fiber manufacturing, membrane classification, and winding technologies associated with membrane oxygenators" by Schaadt J. J Extra Corpor Technol. 1998 March; 30(1):30-4.

[0044] Following the winding station **210** is a potting station **220** for the tubular fiber bundle in which the tubular fiber bundle is placed in a centrifugal potting apparatus for proper distribution of the potting material (adhesive or resin). Following the potting station **210** is a toming station or trimming station in which the potted fiber bundle is finished for assembly. The finished fiber bundle is moved, with the remaining components of the tubular blood oxygenator to the assembly station **240** for assembling of the trimmed potted fiber bundle and other components of the tubular blood oxygenator. Components are assembled at the station **240** to form the assembled medical device which can be moved to the wet chemistry station **300**. The assembly station **200** may be efficiently formed in a compact arrangement as an index able turntable, or a stationary platform with a central pick and place robot. The process of the invention remains substantially unchanged if workers manually advance the components along through the station **200**.

[0045] The assembly station **200** will be constructed significantly different for different medical products, as non-tubular oxygenators, or catheters will not have the winding **210**, potting **220** or toming **230** stations as will be evident. Other sub-assembly steps can be incorporated into the station **200** as appropriate for the specific medical device **50** such as a vascular graft, stent, heart valve, pipeline flow diverter, or catheters such as a renal dialysis catheter, cardiovascular catheter, neurovascular catheter, balloon catheter, and drug delivery catheter.

[0046] The assembled medical device **40** with some activated surfaces is moved to the wet chemistry station **300** for wet chemistry treatments which will follow a blood or fluid flow path through device **50**. The first step is setting up the assembled device **40** for wet chemistry with in-line quality control at step **310**. The present invention contemplates a batch process for manufacturing multiple devices **50** simultaneously. The devices **40** must be set up such that all devices **40** receive uniform treatment to assure uniform finished devices **50**. In this context parallel set ups rather than serial alignment of devices **40** is preferred, as serial alignment of devices **40** can yield lower treatment yields/levels for downstream devices and unacceptable lack of uniformity between devices. The set up includes coupling the devices to source of wet chemistry treatments. Additionally the present invention provides for in-line quality control through the visual staining of sacrificial inline tubing section, as desired. In other words the present method includes additional inline sacrificial tubing for processing device **50** (or set of devices **50**). The tubing will be selectively removed and stained to determine treatment effectiveness and provide a verifiable record of quality control. The initial sacrificial tubing section of step **310** represents the baseline before wet chemistry treatments have started on the connected device **40** for creating a quality review record of the process for the device **50** (as the quality review is determined to be needed).

[0047] The next step **320** is a water priming step which is also used for checking for leaks or undesired blockage in the set up to verify the set up arrangement. The water priming is accomplished at ambient or room temperature and is also

utilized for calculating priming volume for the coupled devices **40** and treatment apparatus.

[0048] Following the priming step of **320** is the enhancing step **330** for enhancing at least the blood contacting surface with a wet chemistry treatment including an aqueous solution having a strong oxidizing agent, preferably Ammonium persulfate $(NH_4)_2S_20_8$. Specifically, [1-15%] $(NH_4)_2S_20_8$ in (deionized) DI H_2O. The ammonium persulfate will enhance the activated and non-activated component surfaces of the medical device **40** as Ammonium persulfate assists in activation of PVC and polycarbonate which may represent other components of a tubular oxygenator other than the fiber bundle that is treated as described above. The Enhancing wet chemistry treatment of step **330** is preferably at an elevated temperature of at least 50° C., preferably 60° C.-65° C., and is recirculated through the device(s) **40** for a circulation time of 5-45 minutes, preferably 15-30 minutes. The enhancing step **330** then includes a non-recirculating rinse of about 3× priming volume of DI water at room temperature.

[0049] Following the enhancing step **330** is a step **340** of coupling a positive spacer, namely adding a positively charged spacer molecule to at least the blood contacting surface with a wet chemistry treatment including an aqueous solution having a cationic polymer. Preferably this cationic polymer solution is a 0.001 to 0.1% w aqueous solution of positively charged spacer polyethylenimine (PEI) molecule with cross-linker, preferably crotonaldehyde ($CH_3CH{=}CHCHO$) in buffer at a pH of about PH9. The cross linker crotonaldehyde may be present in concentrations of about 100-500μ/liter solution. The positive spacer wet chemistry treatment of step **340** is preferably ambient or room temperature and is recirculated through the device(s) **40** for a circulation time of 5-45 minutes, preferably 15-30 minutes. The positive spacer wet chemistry treatment of step **340** then includes a non-recirculating rinse of about 3× priming volume of DI water at room temperature.

[0050] The positive spacer wet chemistry treatment of step **340** then may include a quality control check of taking an in-line sacrificial tube section and stain the section and maintaining the results as a record of the wet chemistry process. This section of step **340** can be objectively compared to the baseline section taken in step **310**. The quality review steps discussed here can be accomplished with every process for every device **50**, but in typical practice it may be accomplished on selected devices **50** (often a given total number of quality reviews, say 10-30, at random intervals for every 1000 units produced). The main advantage of the quality review of the present invention is that it provides objective analysis without sacrificing production units of devices **50**. The final medical devices **50** formed in manufacturing may have a certain number sacrificed for other regulatory requirements which this quality control paradigm might not satisfy and the present quality review paradigm allows the present methodology to go beyond the minimum reviews required without sacrificing additional units **50**.

[0051] Following the positive spacer wet chemistry treatment of step **340** is a step **350** of coupling a positive spacer, namely adding a negatively charged spacer molecule to at least the blood contacting surface with a wet chemistry treatment including an aqueous solution having an anionic polymer. Preferably this anionic polymer solution is a, namely 0.001 to 0.1% w of negatively charged spacer such as Dextran sulfate in saline solution pH 3. The negative spacer wet chemistry treatment of step **350** is preferably at an elevated temperature of at least 50° C., preferably 60° C.-65° C., and is recirculated through the device(s) **40** for a circulation time of 5-45 minutes, preferably 15-30 minutes. The negative spacer wet chemistry treatment of step **350** then includes a non-recirculating rinse of about 3× priming volume of DI water at room temperature. The negative spacer wet chemistry treatment of step **350** then may, if desired, include a quality control check of taking an in-line sacrificial tube section and stain the section and maintaining the results as a record of the wet chemistry process.

[0052] Following the negative spacer wet chemistry treatment of step **350** is a step **360** of coupling a 2^{nd} positive spacer, namely adding a positively charged spacer molecule to at least the blood contacting surface with a wet chemistry treatment including an aqueous solution having a cationic polymer. Preferably this cationic polymer solution is a 0.001 to 0.1% w aqueous solution of positively charged spacer (PEI) molecule (with no cross-linker) in DI water at a pH of about PH9. The 2^{nd} positive spacer wet chemistry treatment of step **360** is preferably ambient or room temperature and is recirculated through the device(s) **40** for a circulation time of 5-45 minutes, preferably 15-30 minutes. The 2^{nd} positive spacer wet chemistry treatment of step **360** then includes a non-recirculating rinse of about 3× priming volume of DI water at room temperature. The 2^{nd} positive spacer wet chemistry treatment of step **360** then may include a quality control check, if desired, of taking an in-line sacrificial tube section and stain the section and maintaining the results as a record of the wet chemistry process.

[0053] Following the 2^{nd} positive spacer wet chemistry treatment of step **360** is a step **370** of covalently immobilizing heparin to at least the blood contacting surface with a wet chemistry treatment including heparin. Preferably the Heparin covalent immobilization wet chemistry treatment is 0.1 to 2 mg/ml, and preferred 0.4 to 1.4 mg/ml, deaminated heparin, in Sodium chloride solution at pH 3.5-4.5. Additionally sodium cyanoborohydride may be added in amounts of 0.01 to 0.1% w to the heparin solution for the wet chemistry around 5 to 15 minutes prior to circulation of the heparin solution wet chemistry treatment of step **370**. The heparin wet chemistry treatment of step **370** is preferably at an elevated temperature of at least 50° C., preferably 60° C.-65° C., and is recirculated through the device(s) **40** for a circulation time of 60-180 minutes, preferably 90-150 minutes. The heparin wet chemistry treatment of step **370** then includes a non-recirculating 1^{st} rinse of about 3× priming volume of DI water at room temperature. Following the initial water rinse the heparin wet chemistry treatment of step **370** may include a sodium chloride solution (0.2-0.8M Sodium Chloride) rinse which is recirculated at ambient conditions for 5-20 minutes, and then this is followed by non-recirculating 2^{nd} water rinse of about 3× priming volume of DI water at room temperature. The heparin wet chemistry treatment of step **370** then may, if desired, include a quality control check of taking an in-line sacrificial tube section and stain the section and maintaining the results as a record of the wet chemistry process.

[0054] Following the heparin wet chemistry treatment of step **370** is a drying step **380** that may include a pressured gas flush of the devices **40** with an inert gas such as argon or nitrogen or air for 5 to 10 minutes, followed by clean filtered dry air a period of 8 to 24 hours to complete dehydration. The drying of step **380** then may, if desired, include a quality control check of taking an in-line sacrificial

tube section and stain the section and maintaining the results as a record of the wet chemistry process, and this may be followed by testing or measuring of heparin bioactivity in the devices **50**.

[0055] An alternative to the above process is not utilizing the negative spacer of step **350** and the 2nd positive spacer of step **360**. In this engineered heparin matrix only a single PEI spacer is present. The process may be described as the same as above but not including the cross linker in step **340** and thereafter proceeding directly to the heparin wet chemistry treatment of step **370** while skipping steps **350** and **360**, an alternative explanation is that the process skips from the enhancing step **330** to the second positive spacer step **360** Skipping steps **340-350**. Both descriptions of this alternative arrangement are accurate and simply define a single positive spacer.

[0056] The method of the present invention is universally applicable in that it defines a method of manufacturing medical products **50** with the ability to meet standard physiologically significant bioactivity with increased stability for clinical applications on a collection of substrates. As a comparison, extracorporeal circulation devices such as those sold by Medtronic have been treated with an electrostatically deposited multi-layer heparin bioactive coating under the CORTIVA BIOACTIVE SURFACE brand. These bioactive coated devices marketed by Medtronic has clinical and scientific evidence in peer-reviewed cardiovascular surgery, perfusion, and scientific literature of yielding: Less blood product use than untreated devices; Less perioperative blood loss in patients than untreated devices; Shorter ventilator time than untreated devices; Shorter hospital length of stay than untreated devices; Less postoperative body temperature rise than untreated devices; Significantly greater urine output during CPB than untreated devices; Lower costs, as related to improved clinical outcomes than untreated devices; Less negative impact on the body's defense systems than untreated devices, including the: contact system, coagulation system, fibrinolytic system, complement system, and cytokine proteins; and Reduced impact on the blood's formed elements than untreated devices, including: platelets, red blood cells and leukocytes.

[0057] The extracorporeal circuit device **50** of the present invention yields a treatment with improved bioactivity, greater adhesion and more durable than the same extracorporeal circuit device treated with the electrostatically deposited multi-layer heparin bioactive coating under the CORTIVA BIOACTIVE SURFACE brand. The extracorporeal circuit device **50** of the present invention will consequently yield further improved results in each of the above categories

[0058] In a separate embodiment of the present invention, a method (process) of manufacturing a medical device having an engineered heparin bioactive matrix on a blood-contacting metal surface is provided. In this embodiment, the medical device may comprise, for example, a stent or a pipeline embolism device or flow diverter used to treat intracranial aneurysms, which has a blood-contacting metal surface. Such flow diverters are increasingly used in the endovascular treatment of intracranial aneurysms as such treatments have been associated with the lowest complication rates when used to treat small ICA aneurysms. See Kallmes D F, Hanel R, Lopes D, Boccardi E, Bonafé A, Cekirge S, Fiorella D, Jabbour P, Levy E, McDougall C, Siddiqui A, Szikora I, Woo H, Albuquerque F, Bozorgchami H, Dashti S R, Delgado Almandoz J E, Kelly M E, Turner R 4th, Woodward B K, Brinjikji W, Lanzino G, Lylyk P. *International retrospective study of the pipeline embolization device: a multicenter aneurysm treatment study*. AJNR Am J Neuroradiol. 2015 January; 36(1):108-15. doi: 10.3174/ajnr.A4111. Epub 2014 Oct. 29. Erratum in: AJNR Am J Neuroradiol. 2015 May; 36(5): E39-40. PMID: 25355814; PMCID: PMC7965920.

[0059] Typically, the device is assembled prior to beginning the method steps, but individual blood-contacting components of the device may be separately treated by the method prior to assembly, or assembly of the device may occur at any point during the method.

[0060] One such commercial flow diverter is sold by Medtronic under the PIPELINE™ Flex brand which supports a safe and highly effective procedure. This representative device is a 48-strand braided mesh design and a soft low profile distal tip for flexible conformability. The device is 75% cobalt chromium/25% platinum tungsten for radial force and uniform radiopacity. The method of the present invention for blood-contacting metal surface usually comprises cobalt-chromium alloy, platinumtungsten alloy, titanium, a titanium alloy, tantalum, a tantalum alloy, nickel-titanium alloy (Nitinol), aluminum oxide, platinum, and/or stainless steel. As detailed above, an exemplary pipeline flow diverter has a blood-contacting metal surface comprising a combination of cobalt-chromium alloy and platinum-tungsten alloy.

[0061] The device may be pre-cleaned as noted above prior to beginning the process. Ultrasonic cleaning is frequently used. The first process step comprises a) activating a blood-contacting metal surface of at least one component of the medical device to form an activated surface. Such activation may be achieved via propene plasma treatment, as described above. Alternatively, the surface activation may be done by contacting the surface with an organic solution comprising a silane functional compound having at least one ethylenically unsaturated functional group. In this scenario, the organic solution is introduced into (such as by pumping), and follows, a blood flow path through the medical device (i. e., the path through which blood flows when the device is in use), as opposed to immersing the component into the organic solution. Usually, the silane functional compound comprises one or more of trimethoxyvinylsilane, triethoxyvinylsilane, and trichlorovinylsilane, present in the organic solution in low concentrations, such as less than 5 percent by weight or less than 3 percent by weight, in an organic solvent such as xylene. The organic solution may be pumped through the device for several minutes to ensure maximum coverage of the metal surfaces that will contact blood during subsequent use of the device. After activation, the surfaces may be rinsed with one or more aqueous or organic solvents such as methanol, ethanol, n-propanol, isopropanol, water, and acetone, and allowed to air-dry.

[0062] In the second process step, a polymeric hydrogel is grafted to the activated surface. The grafting includes polymerizing a reaction mixture via free radical addition polymerization on the activated surface. An exemplary reaction mixture is aqueous and comprises (meth)acrylamide, (meth)acrylic acid, methoxyethyl acrylate, and/or a phosphorylcholine having an ethylenically unsaturated functional group. The reaction mixture may further include a polymerization initiator. The reaction mixture is introduced

into a blood flow path of the medical device and follows the blood flow path through the medical device.

[0063] Following grafting of the polymeric hydrogel, the hydrogel may be hydrolyzed to form carboxyl functional groups on the polymeric hydrogel, particularly when none are introduced through the use of an acid functional monomer. Hydrolysis is necessary when no acid functional monomers are used to form the graft polymer. Hydrolysis may be performed using art-recognized techniques.

[0064] Next, a positively charged spacer molecule is bonded to the polymeric hydrogel by contacting the polymeric hydrogel with a first wet chemistry treatment composition comprising an aqueous solution containing a cationic polymer. The cationic polymer may be any of those disclosed above; it typically comprises polyethyleneimine (PEI). The first wet chemistry treatment composition follows a blood flow path through the medical device.

[0065] In certain examples of the present invention, after bonding the positively charged spacer molecule to the polymeric hydrogel, a negatively charged spacer molecule such as any of those disclosed above (typically dextran sulfate) may be bonded to the positively charged spacer molecule as described above by contacting the positively charged spacer molecule with an aqueous solution containing the negatively charged spacer molecule. In this step, the aqueous solution containing the negatively charged spacer molecule follows a blood flow path through the medical device. After bonding the negatively charged spacer molecule to the positively charged spacer molecule, a second positively charged spacer molecule is bonded to the negatively charged spacer molecule by contacting the negatively charged spacer molecule with an aqueous solution containing the second positively charged spacer molecule. The second positively charged spacer molecule may be the same as or different from the first positively charged spacer molecule, but usually at least one of the positively charged spacer molecules comprises polyethyleneimine (PEI). Additionally, the aqueous solution containing the second positively charged spacer molecule follows a blood flow path through the medical device to contact the negatively charged spacer molecule. These process steps may be performed as described above.

[0066] After bonding one or more spacer molecules to the hydrogel as described above, heparin is covalently bonded to the terminal spacer molecule by contacting the spacer molecule with a second wet chemistry treatment composition comprising heparin. The second wet chemistry treatment composition follows a blood flow path through the medical device. As in the process above, preferably the second wet chemistry treatment composition comprising heparin is 0.1 to 2 mg/ml, more often 0.4 to 1.4 mg/ml, deaminated heparin, in sodium chloride solution at pH 3.5-4.5. Additionally, sodium cyanoborohydride may be added in amounts of 0.01 to 0.1% w to the second wet chemistry treatment composition around 5 to 15 minutes prior to circulation of the second wet chemistry treatment composition. The second wet chemistry treatment composition is preferably at an elevated temperature of at least 50° C., preferably 60° C.-65° C., and is recirculated through the device(s) **40** for a circulation time of 60-180 minutes, preferably 90-150 minutes. The step of bonding the heparin may be followed by a non-recirculating 1st rinse of about 3× priming volume of DI water at room temperature. Following the initial water rinse a sodium chloride solution (0.2-0.8M Sodium Chloride) rinse may follow, which is recirculated at ambient conditions for 5-20 minutes, and then this is followed by non-recirculating 2nd water rinse of about 3× priming volume of DI water at room temperature. A quality control check of taking an inline sacrificial tube section and stain the section and maintaining the results as a record of the wet chemistry process, may be included.

[0067] The resulting medical device formed by the process may be a nitinol self-expanding stent used for symptomatic venous outflow obstruction such as sold under the ABRE brand. Other examples include a coronary stent, such as a bare-wire stent, and a drug eluting stent. In a drug eluting stent, the above process precedes attachment of the drug to be administered.

[0068] In another embodiment of the present invention, a method (process) of manufacturing a medical catheter having an engineered heparin bioactive matrix on a blood-contacting polymeric surface is provided, comprising: a) activating a blood-contacting polymeric surface of at least one component of the medical catheter to form an activated surface via i) propene or sodium naphthalate plasma treatment, ii) corona activation, iii) radiation activation or iv) ozone gas activation, wherein the blood-contacting polymeric surface comprises a fluoropolymer, (vanillyl alcohol-containing copolyoxalate) copolymer (PVAX), or a block copolymer of ethylene oxide and tetramethylene glycol; b) grafting a polymeric hydrogel to the activated surface; c) optionally hydrolyzing the polymeric hydrogel to form carboxyl functional groups on the polymeric hydrogel; d) bonding a positively charged spacer molecule to the polymeric hydrogel by contacting the polymeric hydrogel with a first wet chemistry treatment composition comprising an aqueous solution containing a cationic polymer, wherein the first wet chemistry treatment follows a blood flow path through the medical catheter; and e) covalently bonding heparin to the spacer molecule by contacting the spacer molecule with a second wet chemistry treatment composition comprising heparin, wherein the second wet chemistry treatment follows a blood flow path through the medical device.

[0069] Typically, the device is assembled prior to beginning the method steps, but individual blood-contacting components of the device may be separately treated by the method prior to assembly, or assembly of the device may occur at any point during the method.

[0070] The blood-contacting polymeric surface usually comprises a fluoropolymer, (vanillyl alcohol-containing copolyoxalate) copolymer (PVAX), or a block copolymer of ethylene oxide and tetramethylene glycol.

[0071] The catheter may be pre-cleaned as noted above prior to beginning the process. Ultrasonic cleaning is frequently used. The first process step comprises a) activating a blood-contacting polymeric surface of at least one component of the catheter to form an activated surface. Such activation may be achieved via propene or sodium naphthalate plasma treatment, as described above; corona activation; radiation activation such as x-ray, beta, and/or gamma radiation activation; or ozone gas activation as described above.

[0072] Often, when the blood-contacting polymeric surface comprises a fluoropolymer such as polytetrafluoroethylene (PTFE) and/or fluorinated ethylene propylene (FEP), the blood-contacting polymeric surface is most effectively activated via propene or sodium naphthalate plasma treatment. When the blood-contacting polymeric surface com-

prises a (vanillyl alcohol-containing copolyoxalate) copolymer (PVAX), or a block copolymer of ethylene oxide and tetramethylene glycol, the surface may be activated by any of the above-mentioned techniques, most preferably propene plasma treatment, corona activation, or ozone gas activation.

[0073] Steps b) through e) may be performed in a manner similar to those described above.

[0074] In formation of a drug eluting step the above process may be followed with coupling of the drug to be eluted as the process yields an improved substrate for coupling the treating drug upon.

[0075] The preferred embodiments described above are illustrative of the present invention and not restrictive hereof. It will be obvious that various changes may be made to the present invention without departing from the spirit and scope of the invention. The precise scope of the present invention is defined by the appended claims and equivalents thereto.

What is claimed is:

1. A method of manufacturing a medical device having an engineered heparin bioactive matrix on a blood-contacting metal surface, comprising:

a) activating a blood-contacting metal surface of at least one component of the medical device to form an activated surface via i) propene plasma treatment or ii) contacting the surface with an organic solution comprising a silane functional compound having at least one ethylenically unsaturated functional group, wherein the medical device comprises a pipeline flow diverter or a stent and wherein the organic solution is introduced into and follows a blood flow path through the medical device;

b) grafting a polymeric hydrogel to the activated surface;

c) optionally hydrolyzing the polymeric hydrogel to form carboxyl functional groups on the polymeric hydrogel;

d) bonding a positively charged spacer molecule to the polymeric hydrogel by contacting the polymeric hydrogel with a first wet chemistry treatment composition comprising an aqueous solution containing a cationic polymer, wherein the first wet chemistry treatment follows a blood flow path through the medical device; and

e) covalently bonding heparin to the spacer molecule by contacting the spacer molecule with a second wet chemistry treatment composition comprising heparin, wherein the second wet chemistry treatment follows a blood flow path through the medical device.

2. The method of claim **1** wherein the medical device comprises a pipeline flow diverter, which in turn comprises an endovascular prosthesis used to treat intracranial aneurysms.

3. The method of claim **1** wherein the blood-contacting metal surface comprises cobaltchromium alloy, platinum-tungsten alloy, titanium, a titanium alloy, tantalum, a tantalum alloy, nickel-titanium alloy (Nitinol), aluminum oxide, platinum, and/or stainless steel.

4. The method of claim **1** wherein the blood-contacting metal surface is activated via i) propene plasma treatment.

5. The method of claim **1** wherein the blood-contacting metal surface is activated via ii) contacting the surface with the organic solution comprising a silane functional compound having at least one ethylenically unsaturated functional group, wherein the organic solution is introduced to and follows a blood flow path through the medical device.

6. The method of claim **5** wherein the silane functional compound comprises trichlorovinyl silane.

7. The method of claim **1** wherein the grafting of the polymeric hydrogel to the activated surface comprises polymerizing a reaction mixture via free radical addition polymerization on the activated surface, wherein the reaction mixture comprises (meth)acrylamide, (meth)acrylic acid, methoxyethyl acrylate, and/or a phosphorylcholine having an ethylenically unsaturated functional group, and wherein the reaction mixture is introduced to a blood flow path and follows the blood flow path through the medical device.

8. The method of claim **1** wherein the cationic polymer comprises polyethyleneimine (PEI).

9. The method of claim **1** wherein after bonding the positively charged spacer molecule to the polymeric hydrogel, a negatively charged spacer molecule is bonded to the positively charged spacer molecule by contacting the positively charged spacer molecule with an aqueous solution containing the negatively charged spacer molecule, wherein the aqueous solution containing the negatively charged spacer molecule follows a blood flow path through the medical device; followed by a step of bonding a second positively charged spacer molecule to the negatively charged spacer molecule by contacting the negatively charged spacer molecule with an aqueous solution containing the second positively charged spacer molecule, wherein the aqueous solution containing the second positively charged spacer molecule follows a blood flow path through the medical device.

10. The method of claim **9** wherein at least one of the positively charged spacer molecules comprises polyethyleneimine (PEI).

11. The method of claim **9** wherein the negatively charged spacer molecule comprises dextran sulfate.

12. A medical pipeline flow diverter manufactured according to the method of claim **1**.

13. A method of manufacturing a medical catheter having an engineered heparin bioactive matrix on a blood-contacting polymeric surface, comprising:

a) activating a blood-contacting polymeric surface of at least one component of the medical catheter to form an activated surface via i) propene or sodium naphthalate plasma treatment, ii) corona activation, iii) radiation activation or iv) ozone gas activation, wherein the blood-contacting polymeric surface comprises a fluoropolymer, (vanillyl alcohol-containing copolyoxalate) copolymer (PVAX), or a block copolymer of ethylene oxide and tetramethylene glycol;

b) grafting a polymeric hydrogel to the activated surface;

c) optionally hydrolyzing the polymeric hydrogel to form carboxyl functional groups on the polymeric hydrogel;

d) bonding a positively charged spacer molecule to the polymeric hydrogel by contacting the polymeric hydrogel with a first wet chemistry treatment composition comprising an aqueous solution containing a cationic polymer, wherein the first wet chemistry treatment follows a blood flow path through the medical catheter; and

e) covalently bonding heparin to the spacer molecule by contacting the spacer molecule with a second wet chemistry treatment composition comprising heparin, wherein the second wet chemistry treatment follows a blood flow path through the medical device.

14. The method of claim **13** wherein the blood-contacting polymeric surface comprises a fluoropolymer and wherein the blood-contacting polymeric surface is activated via i) propene or sodium naphthalate plasma treatment.

15. The method of claim **14** wherein the fluoropolymer comprises polytetrafluoroethylene (PTFE), and/or fluorinated ethylene propylene (FEP).

16. The method of claim **13** wherein the blood-contacting polymeric surface comprises a (vanillyl alcohol-containing copolyoxalate) copolymer (PVAX), or a block copolymer of ethylene oxide and tetramethylene glycol.

17. The method of claim **13** wherein the grafting of the polymeric hydrogel to the activated surface comprises polymerizing a reaction mixture via free radical addition polymerization on the activated surface, wherein the reaction mixture comprises (meth)acrylamide, (meth)acrylic acid, methoxyethyl acrylate, and/or a phosphorylcholine having an ethylenically unsaturated functional group, and wherein the reaction mixture is introduced to a blood flow path and follows the blood flow path through the medical catheter.

18. The method of claim **13** wherein the cationic polymer comprises polyethyleneimine (PEI).

19. The method of claim **13** wherein after bonding the positively charged spacer molecule to the polymeric hydrogel, a negatively charged spacer molecule is bonded to the positively charged spacer molecule by contacting the positively charged spacer molecule with an aqueous solution containing the negatively charged spacer molecule, wherein the aqueous solution containing the negatively charged spacer molecule follows a blood flow path through the medical device; followed by a step of bonding a second positively charged spacer molecule to the negatively charged spacer molecule by contacting the negatively charged spacer molecule with an aqueous solution containing the second positively charged spacer molecule, wherein the aqueous solution containing the second positively charged spacer molecule follows a blood flow path through the medical catheter.

20. A medical catheter manufactured according to the method of claim **13**.

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