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Review

Recent Developments and Current Challenges of Heparin-Grafted Hemodialysis Membranes

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Abstract: Hemodialysis (HD) is a life-sustaining extracorporeal blood purifying treatment for end-stage renal disease (ESRD) patients. However, this membrane-based therapy is associated with acute side effects, life-threatening chronic conditions, and unacceptably high morbidity and mortality rates. Numerous surface coatings have been developed to improve the blood compatibility of biomaterials. Heparin is a widely used anticoagulant substance that increases the clotting time and increases the membrane hemocompatibility in terms of platelet adhesion and protein adsorption and anti-clotting activity. However, using heparin is challenging due to its severe or life-threatening side effects such as heparin-induced thrombocytopenia (HIT), in addition to heparin induced thrombocytopenia and thrombosis (HITT). In addition, heparin is strongly electronegative and exhibits a binding affinity for the positive active sites of human serum proteins, which is an additional challenge. Consequently, covalently immobilized heparin would create a more charged surface to induce more blood–membrane interactions, and consequently more adsorbed human serum proteins and biochemical pathway activations, which can negatively affect dialysis patients. Therefore, the current critical review has thoroughly focused on different heparin HD membrane systems, the challenges of heparin-coated dialysis membranes, and the factors affecting its hemocompatibility, in addition to the methods that can be used to enhance its hemocompatibility. Furthermore, this review summarizes the advantages and disadvantages of heparin-grafted methods. Furthermore, the influence of the heparin-immobilization method on the hemocompatibility and performance of the HD membrane was comprehensively analyzed. Finally, we conclude with the future perspectives for the strategies toward the heparinization and heparin-like/mimicking modification of membrane surfaces.

Keywords: hemodialysis membrane; heparin; hemocompatibility; anticoagulant; immobilization

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1. Introduction

Hemodialysis (HD) is a life-sustaining extracorporeal blood purifying treatment for end-stage renal disease (ESRD) patients. However, blood–membrane interactions activate blood cells and trigger fibrinogen (FB) conformation, which promotes inflammation cascades. Complement activation results in inflammatory mediator products that cause allergic reactions during HD and can also lead to acute intradialytic pulmonary hypertension, chronic low-grade systemic inflammation, and leukocyte dysfunction [1–3]. Bio-incompatibility is also the major reason for albumin adsorption, platelet adhesion, and the production of bradykinin (white blood cells (WBCs) due to inflammation), blood clots, and thrombosis. Coagulation can be prevented with heparin, as the most efficient anticoagulant [4,5].

Several research efforts for hemodialysis membrane coatings have been developed to improve the blood compatibility of biomaterials [6–9]. Heparin is a widely used anticoagulant substance that increases the clotting time and increases the membrane hemocompatibility in terms of platelet adhesion and protein adsorption and anti-clotting activity. A heparin-coated membrane might unexpectedly reduce the concentration of pro-inflammatory cytokines [10]. Nineteen stable HD patients were first dialyzed with conventional membranes and enoxaparin as an anticoagulant, and then with the heparin-coated membrane without systemic anticoagulation. After the HD session with an Evodial dialyzer (heparin-grafted membrane), the plasma levels of the monocyte chemoattractant protein, endostatin, and activin A were 2–3-fold lower than with standard dialysis. Nevertheless, covalently immobilized heparin would create a more charged surface to induce more blood–membrane interactions, and consequently more adsorbed human serum proteins and biochemical pathway activations, which can negatively affect dialysis patients. Therefore, optimal anticoagulation remains a controversial issue for clinical practice, and use of anticoagulants may increase the uremic bleeding tendency.

Therefore, the current critical review has thoroughly focused on different heparin HD membrane systems, the challenges of heparin-coated dialysis membranes, factors affecting its hemocompatibility, in addition to the methods that can be used to enhance its hemocompatibility. Furthermore, this review summarizes the advantages and disadvantages of heparin-grafted methods. Furthermore, the influence of the heparin-immobilization method on the hemocompatibility and performance of the HD membrane was comprehensively analyzed. Finally, we conclude with the future perspectives for the strategies toward the heparinization and heparin-like/mimicking modification of membrane surfaces

2. Current Challenges of Heparin-Coated Dialysis Membranes

Heparin is a medication and naturally occurring glycosaminoglycan (i.e., a long linear polysaccharide consisting of repeating disaccharide units). The heparin structure is illustrated in Figure 1.

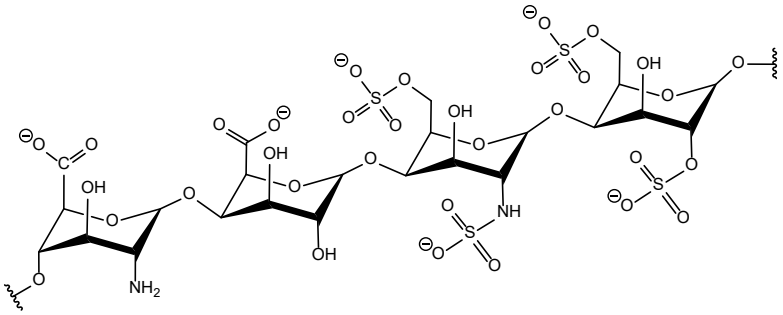

Figure 1. The structure of heparin.

Heparin is able to interact with coagulation factors XIa, IXa, Xa, and IIa (thrombin), and has been widely used as an anticoagulant reagent since 1935. Although the use of heparin has some side effects such as heparin-induced thrombocytopenia, hypertriglyceridemia, anaphylaxis, bone mineral disease, hyperkalemia, catheter-related sepsis, etc.

The most severe side effect is heparin-induced thrombocytopenia (HIT), which results in blood clotting. There are basically two types of HIT. The most dangerous and potentially life-threatening form is type II HIT, which results in both bleeding and thromboembolic complications. The mechanism of HIT includes several steps. At first, heparin binds with blood platelets with the release of platelet factor 4 (PF4). This PF4, in turn, is able to interact with heparin, resulting in the formation of the heparin–PF4 complex, which triggers blood antibodies (see Figure 2). This interaction between antibodies and the heparin–PF4 complex provokes cascade reactions, resulting in more platelet aggregation, which causes severe thrombocytopenia and further bleeding complications. Moreover, when these heparin-triggered antibodies bind with endothelial cells, it often results in paradoxical thrombus

formation with subsequent limb-threatening ischemia, or even fatal pulmonary emboli. Type II HIT usually occurs 5–12 days after heparin exposure, but can happen immediately in the case of re-exposure.

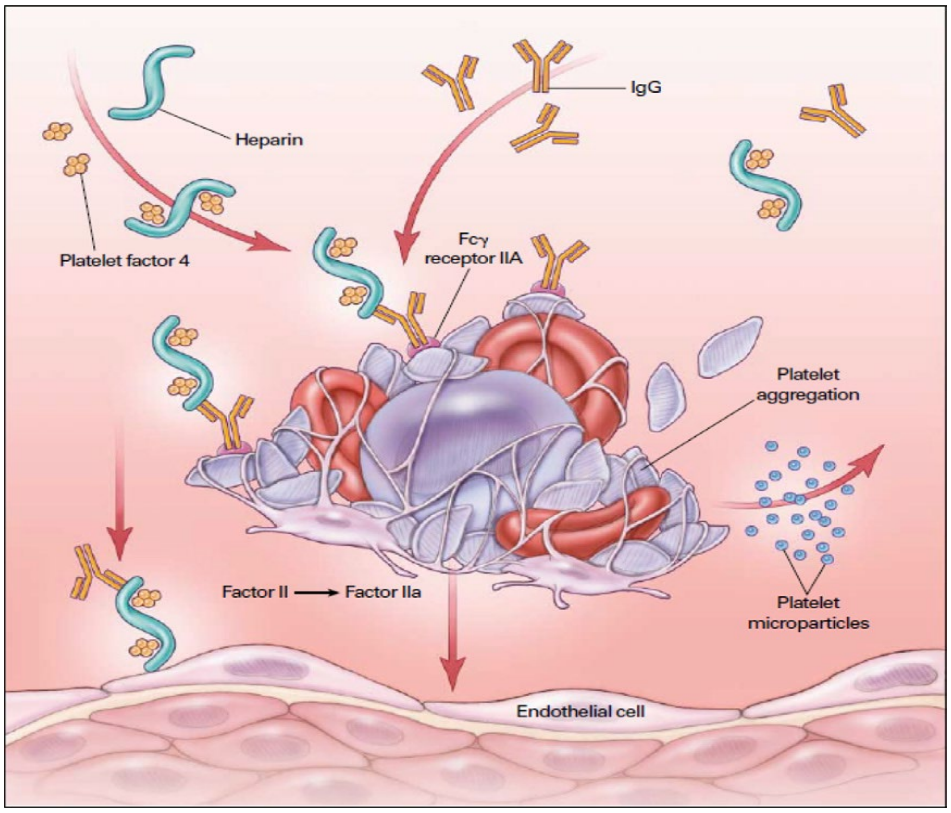

Figure 2. The mechanism of heparin-induced thrombocytopenia (HIT) with further thrombosis Reprinted/adapted with permission from Ref. [1], 2012, Shen and Winkelmayer.

The above-mentioned complications arise when heparin is injected into the blood during HD procedure and/or HD circuit parts are covered with heparin. Thus, after performing 120 HD sessions, 73% of them ended up with multiple fiber clotting (Grade 3) or clotting of the dialyzer (Grade 4) (see Figure 3) [2].

The opposite effect of heparin treatment as well as for all forms of anticoagulants is acute hemorrhaging [3]. Incidents of major bleeding during systematic heparinization are reported to occur with the rate of 7.3 to 16.7 per 100 person-years [4], causing major side effects such as osteopenia and drug intolerance aside from thrombocytopenia [5]. Even when heparinization is ceased, nearly a half of all patients that develop HIT experience thrombotic-related complications that result in a mortality rate up to 30% [6].

Furthermore, the use of heparin is also limited by its high price, activity degradation with time, and strong dependence on antithrombin, whose concentration broadly varies across patients with different diseases [7].

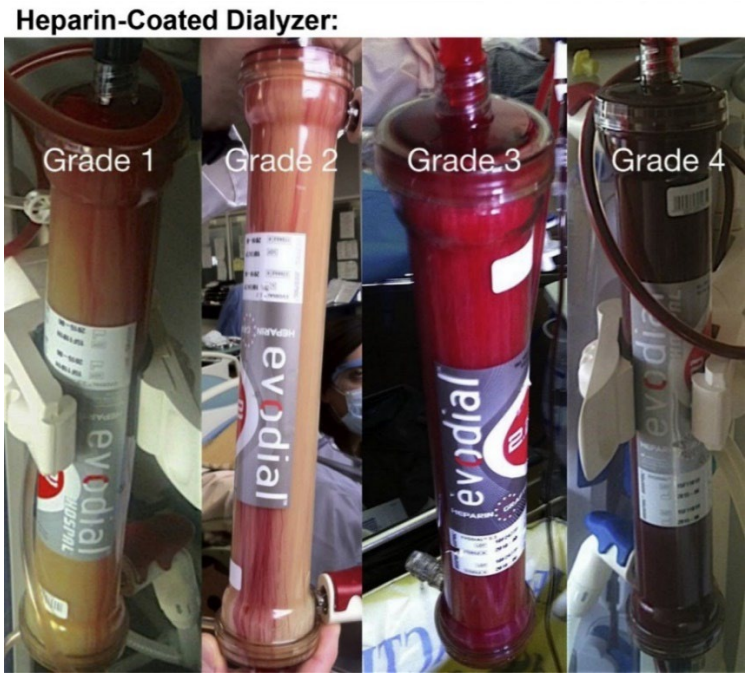

Figure 3. Examples of different grades (by visual inspection) of the heparin-coated dialyzer membrane modules after performing HD sessions. (Grade 1: clean dialyzer; Grade 2: ~5% of fibers clotting; Grade 3: multiple fiber clotting; Grade 4: total clotting).

3. Factors Affecting Hemocompatibility of Heparin-Grafted Membranes

One of the main reasons responsible for these side effects of using heparin is believed to be associated with the surface negative charge that arises when heparin is applied to cover the HD membrane surface. The negative charge of heparin arises from the inequality in the positive and negative charge groups (see Figure 4).

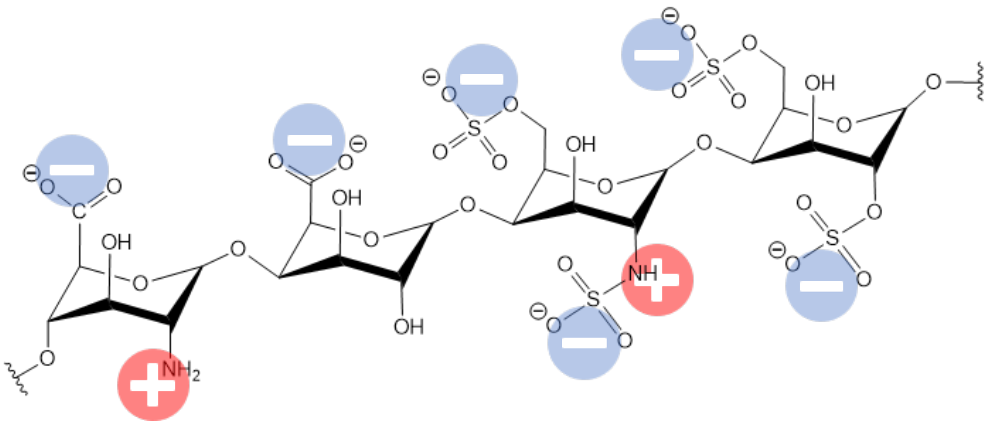

Figure 4. The distribution of the charged groups in the heparin molecule.

At first glance, the negatively charged membrane has a benefit in terms of protein repulsion, since the main human serum proteins are also charged negatively due to their pI (isoelectric) values (see Table 1) being lower than the blood pH. Despite this, there are frequent observations where negatively charged proteins can adsorb on a negatively charged membrane surface (i.e., in the "wrong" region of their isoelectric points) [8–11]. This phenomenon can be explained by the presence of rather large charged areas in the protein molecule due to the high molecular weight, and hence the size of the protein molecule. Thus, the protein can position positively charged areas toward the membrane

surface, resulting in electrostatic interaction, although the heparin-coated surfaces demonstrated a decreased affinity for particular blood proteins including C3, fibronectin, and fibrinogen [12]. The higher negative surface charge of the HD membrane indicates a high degree of hydrophilicity, which leads to the absorption of water from the blood circulatory system [11]. The dehydration of RBCs significantly contributes to the increased deformability and hemolysis of blood cells [11]. Nevertheless, the current trend in HD membrane development is to create near-zero charged surfaces to minimize any possible electrostatic interaction with human serum proteins or other molecules whose adsorption can provoke further cascade reactions and related undesired consequences. Thus, the above-mentioned heparin-induced thrombocytopenia results from the interaction of negatively charged heparin with positively charged platelet factor 4 (PF4) [13]. It should also be noted that roughness is a key in membrane morphology, which leads to blood cell rupture.

Table 1. The isoelectric points of the main human proteins.

Human Serum Protein	pI
Albumin (HSA)	~5
Fibrinogen (FB)	5.8
Transferrin (TRF)	~6
β-2 Microglobulin	5.3 and 5.7 (isoforms)

4. Methods for Enhancing Dialysis Membrane Hemocompatibility

All of the methods for improvements in the material biocompatibility applicable for membranes can be divided into two categories through achieving a bio-passive antifouling surface or bioactive surfaces.

4.1. Biopassive Antifouling Surface

This approach assumes the creation of surfaces that possess a minimal adsorption of proteins and blood cells, since this phenomenon is considered as the very first step for further thrombotic response, blood clotting, and biochemical cascade reaction, which result in severe health problems for HD patients. Although the aim of biopassive surfaces is to minimize triggering immune response reactions, the effectiveness of this approach for long-term applications is still a major concern. Hence, a bioinactive surface is hardly suitable for biomedical implants, but is a good option for short-term or single-use applications such as hemodialysis.

One example of a biopassive surface is a micropatterned surface that possesses superhydrophobic (SH) properties, resulting in antifouling behavior (so called "the lotus effect"). There are some reports, indicating good protein repulsion, decreased platelet adsorption, and reduced blood component activation [14,15]. The main concern regarding SH surfaces is the air pocket layer, which prevents liquid contact with the SH surface, which is able to provoke protein denaturation, causing coagulation cascade reactions and further distal thrombus formation [16]. Despite this concern, there has been a report showing a successful implementation of the SH surface for 8 days in the in vivo implant introduced into a sheep body without any sign of blood clotting or thrombosis [17].

Another example of a biopassive surface is a zwitterionic (ZW)-coated surface. Unlike SH surfaces, this type of surface is very hydrophilic. ZW molecules have an equal number of positive and negative charges, which results in near-zero total charge of the surface, thus minimizing the electrostatic interaction with proteins and other charged blood components. Moreover, the presence of charged moieties in ZW molecules creates a layer of bonded water molecules that creates obstacles for protein adsorption on the material surface, thus possessing antifouling properties [18,19]. These ZW molecules are now being developed for use to create the 3rd (the latest at the moment)-generation of HD membranes [20]. ZW coated materials have also been successfully used in implant applications, showing good bio- and hemocompatibility [21–23].

Another approach to create a biopassive surface utilizes the immobilization of specific physiological proteins on a material surface. In vivo experiments have demonstrated that protein adsorption on the surface of the nanoparticles results in the elimination of non-specific cellular uptake [24]. Moreover, the protein-covered surface being passive is believed to be associated, not with protein repellence as with other biopassive surface creation methods, but due to the affinity of the desired proteins due to surface functionalization [25]. However, the adsorbed proteins may change their conformation, revealing their active and antigenic sites, which may trigger cascade complement reactions and immune responses, resulting in undesired consequences [26,27]. Another issue that arises from using this approach is the Vroman effect (i.e., preliminary adsorbed proteins are able to be replaced with other proteins such as fibrinogen), which results in further platelet adhesion and blood clotting [28]. Even if protein is covalently immobilized on the material surface to prevent protein exchange, the adsorbed protein is subjected to degradation that also results in platelet adhesion with undesired further thrombotic events, which significantly limits of the long-term applications of this approach [29].

4.2. Bioactive Surfaces

This approach utilizes the immobilization of bioactive compounds that minimize the immune response by interacting with key blood components or by releasing bioactive compounds. Nitric oxide (NO) is a gaseous free radical molecule that attenuates the interaction of platelets to the adsorbed fibrinogen, von Willebrand factor, and other blood proteins, resulting in reduced platelet activation [30]. Moreover, this approach is based on the ability of the endothelial lining of blood vessel cells to synthesize and exhaust NO from L-arginine at an estimated flux of 0.5 to 4.0 $\times$ 10^{-10} mol/cm^2/min [31]. NO producing materials depend on the NO generation triggering type including physiologically, enzymatic, chemical, and thermal activated [32–35]. Ex vivo experiments have demonstrated a significant reduction in the thrombus formation in human blood and the inhibition of platelet aggregation in platelet rich plasma [36]. Earlier in vivo experiments in developing NO releasing materials allowed for a reduction in the thrombus area up to six times in a 7 h rabbit ECC model [37]. Recent work with NO releasing materials indicated the viability of this approach for ECC applications, wherein the maintenance of 90% of the baseline platelet count was achieved in a 4 h rabbit model using polyvinylchloride (PVC) tubing [38].

Indeed, the most widely known substance used to prevent blood coagulation is heparin, which has been used as systemic anticoagulant since 1935. Despite reducing the thrombin activity, heparin-coated surfaces are often not able to suppress other procoagulant activity including platelet activation.

One of the main reasons responsible for the side effects of using heparin is believed to be associated with the surface negative charge that arises when heparin is applied to cover the HD membrane surface. To overcome this, heparin should be attached to a positively charged substrate, resulting in near-zero surface charge (see Figure 5).

Using this approach, there have been several reports claiming the successful implementation of ionic complexes and near-zero charges in in vivo experiments, when no fibrosis was observed around the implanted foreign parts [21,39–41]. Furthermore, the above-mentioned complexes are reported to possess good hemocompatibility and near-zero adsorption of the platelets and fibrinogen, which is believed to be the first step in designing no-clotting HD membranes [40,42–51].

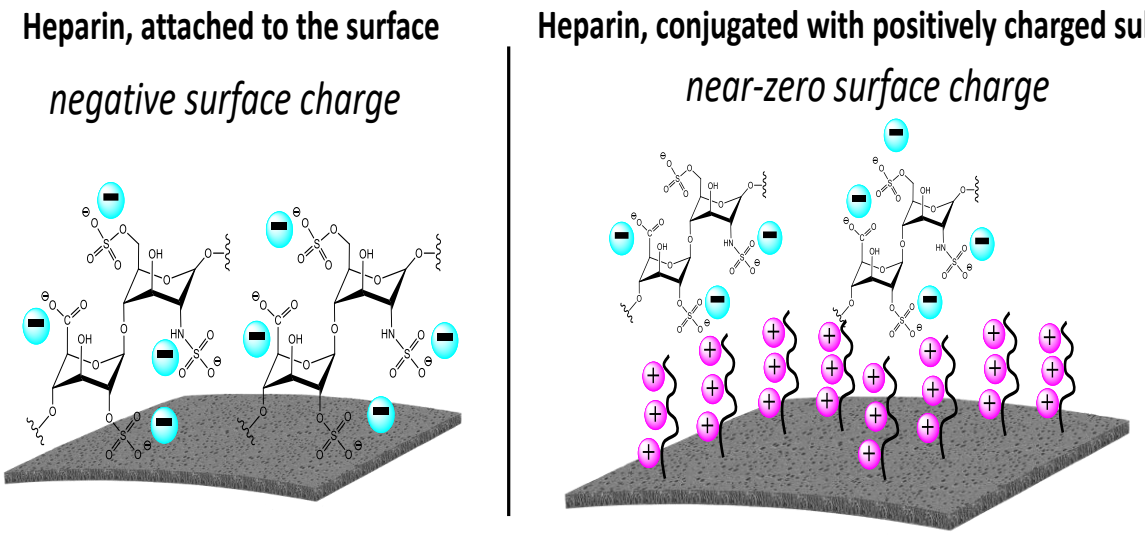

Figure 5. Approaches to immobilize heparin on the membrane surface.

5. Recent Development of Heparin-Immobilized Dialysis Membranes

A hollow-fiber oxygenator membrane was covalently coated with nitrous acid degraded heparin using aqueous free radical activation and oxygenation and the coupling of a polyethyleneimine spacer [52]. This coating technology allowed for a heparin surface density of 3.5 μg/cm^2 to be achieved. Protein adsorption was performed within 6 h. The binding mechanisms of the proteins were demonstrated to be changed for a heparin-coated surface that resulted in less protein adsorption, which was observed starting from 10 min of the experiment. However, complement system initiator proteins were detected to bind more to the heparinized membrane.

The Klotho (KL) gene was cross-linked with heparin to the acellular small intestinal submucosa (SIS) [53]. In vivo experiments demonstrated enhanced adhesion of the endothelial cells on the SIS membrane, resulting in increased patency rate, endothelialization, and smooth muscle regeneration, which indicates improved hemocompatibility. This approach of promoting endothelial cell growth on the implant surface demonstrates promising results, though at the moment, it is hardly applicable for the biocompatibility of hollow fiber-based HD membrane modules.

To simplify the membrane surface heparinization, a chitosan support layer was used [54]. Chitosan was directly added to the PES spinning solution, so further heparinization can be easily performed just by treating of hollow fibers with heparin solution. The authors proposed performing this procedure right before the HD session to minimize the immobilized heparin degradation. The resultant membranes were observed to possess a reduction in the thrombin–antithrombin complex, active complement component 3, and platelet factor 4 concentration, which indicates an improvement in hemocompatibility. Moreover, the above-mentioned modification with heparin increased the membrane flux (for pure water).

A similar approach in the simplification of heparin immobilization was used in another work [55]. Instead of chitosan, polydopamine (PDA) was used. It was demonstrated that aside from adding polydopamine in the bore spinning solution, it is also possible to coat PES hollow fiber membranes with PDA after membrane spinning, though it requires more steps compared to using PDA in the spinning process. Both ways resulted in obtaining a near-zero charged membrane, which is considered as a benefit. The resultant membranes are going to be used in hemocompatibility tests in future works.

Chitosan was also used for heparin immobilization on a thermo-responsive poly(N-isopropylacrylamide) (PNIPAM) polymer, that is, used for controlled drug release and tissue engineering [56]. Up to 10 layers of alternating layers of chitosan and heparin were created. To enhance the resultant complex stability layers were covalently cross-linked

using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and N-hydroxysuccinimide (NHS), which resulted in a reduced surface charge that is associated with the minimization of heparin and chitosan loss. Moreover, the cross-linked complex demonstrated better biocompatibility in terms of the growth of C3H10T1/2 cells after 24 h of cultivation. However, an uncross-linked chitosan/heparin complex was reported to be successfully used as an implant for 5 months for vascular regeneration [57]. In this study, a decellularized scaffold (DCS) vascular path was coated with poly(vinyl alcohol) (PVA) with the further immobilization of chitosan/heparin via layer-by-layer (LbL) self-assembly. At the same time, the in vitro hemocompatibility test showed that the APPT time increased only to 45 s for the heparin/chitosan coated vascular path, whereas the PVA-coated DCS possessed a 26 s APPT time. The same situation appeared for the PRT, PT, and TT times when the heparin/chitosan complex increased these times to 25–40 s, though the unmodified material demonstrated 15–20 s.

The layer-by-layer self-assembly (LbL) technique was used to immobilize heparin with the oppositely charged dihydroxy-iron (DHI) on the bovine pericardial scaffold (BPS) surface [58]. This cycle was repeated up to 10 times to create a multi-layer structure with alternating charged layers. The resultant complex was not stable and was able to gradually release heparin, thus resulting in 30 days of anticoagulant activity in the in vitro tests. As was previously discussed, the presence of heparin in human blood is able to provoke undesired consequences such as HIT. Heparin dosage is always a critical point for HD sessions, thus additional research is necessary to develop this approach.

Carbon nanotubes were used to carry heparin on their surface with further incorporation into the polyurethane (PU) matrix [59]. The resultant material showed increased APPT time (more than 120 s compared to 20 s for non-heparinized material), reduced platelet adhesion, and increased hydrophilicity.

Heparin was also used to improve the hemocompatibility and hydrophilicity of the extreme hydrophobic nature of poly(ε-caprolactone) (PCL) to create vascular graft implants [60]. Heparin-coated PCL nanofibrous scaffolds were prepared using gamma irradiation and N-(3-dimethylaminopropyl)-N′-ethyl carbodiimide hydrochloride/N-hydroxysuccinimide reaction chemistry on a preliminary 2-aminoethyl methacrylate (AEMA) hydrochloride grafted surface. The resultant modification reduced the fibrinogen adsorption to 4 $\mu g/mm^2$ (twice less compared with the unmodified PCL vascular graft). Moreover, improvement in the recovery of blood vessel function was observed for implanted heparin-coated vascular grafts into 24-month-old Sprague Dawley rats due to promoting the proliferation of endothelial cells and preventing thrombosis. The examples of using heparin through different approaches of its immobilization on various surfaces and the resulting outcomes are listed in Table 2.

Table 2. The effects of the different approaches of heparin immobilization.

No.	System	Preparation Method	Outcome in Hemocompatibility and Performance	Ref.
1	PTFE HD arteriovenous graft with attached heparin	Commercial product.	No benefit of using heparin. The number of cases of open or percutaneous thrombectomy was significantly higher for heparin-coated grafts as well as the number of any intervention performed to maintain graft patency. Kaplan–Meier survival curve also shows no positive effect of using heparin.	[61]
2	Low-molecular weight heparin injections		Heparin prevents blood coagulation.	[62]

Table 2. *Cont.*

No.	System	Preparation Method	Outcome in Hemocompatibility and Performance	Ref.
3	Heparin injections		Heparin increases the activated clotting time (ACT) from 150 s to 300 s depending on dosage. Survival is improved by increased heparin administration independent of the ACT.	[63]
4	Heparin (fractioned and unfractioned) injections		When fractioned heparin was used, it resulted in increasing the density of lipoproteins that is associated with atherosclerotic cardiovascular disease. Unfractionated heparin reduces these effects.	[64]
5	Barium alginate microcapsules with conjugate heparin	Alginate microcapsules were incubated with avidin with further treatment with heparin solution.	Immobilized heparin reduces pericapsular fibrotic overgrowth (PFO) both in syngeneic and allogeneic rat transplantation models by ~65% and ~43%, respectively (in-vivo experiments).	[39]
6	Pullulan acetate (PA)/polyethylene glycol (PEG) membrane with conjugated heparin	Heparin was immobilized using PEG spacer and N-hydroxysuccinimide.	Improved resistance to platelet adhesion.	[65]
7	Alginate capsules covered with poly-l-lysine (PLL) heparin	Alginate capsules were covered with positively charged poly-L-lysine with further immobilization of heparin or acrylic acid.	Use of heparin resulted in the appearance of fibroblasts and macrophages on the capsules (in-vivo rat tissues). When heparin was replaced by poly-acrylic acid, this effect was not observed.	[40]
8	Low-molecular weight heparin injections		Use of heparin in a coagulation preventive dose caused heparin-induced thrombocytopenia (HIT) type 1 and 2	[66–78]
9	Polyurethane (PU) coated with chitosan/heparin layer-by-layer.	Heparin / chitosan was immobilized on PU surface using 1,6-diisocyanatohexane in the presence of dibutyltin dilaurate.	Increase in blood clotting and recalcification time in the in vitro experiments. Thromboresistance was $83.94 \pm 8.12\% - 86.22 \pm 5.29\%$ after 20–240 min. In vivo hemolysis ratio was less than 0.01%.	[49]
10	Covalently attached heparin to membrane for artificial lung use.	Commercial product.	Heparin reduces activated coagulation time (ACT) from approx. 250 s to 150 s compared to the non-heparinized membrane. Lung performance parameters remained approximately the same	[79]
11	Heparin coated circuit parts	Commercial product.	Reduction in the terminal complement complexes when using heparin. Improvement in biocompatibility.	[80]
12	PTFE coated with bovine serum albumin (BSA)/heparin multilayers	Heparin/BSA was immobilized using cross-link by glutaraldehyde or without it.	The BSA/heparin layer, cross-linked by glutaraldehyde, prevented fibrinogen adsorption and platelet adherence on the PTFE surface.	[51]

Table 2. *Cont.*

No.	System	Preparation Method	Outcome in Hemocompatibility and Performance	Ref.
13	TiO_2 surface coated with heparin	TiO_2 surface was coated with conjugate of polydopamine (PDA) and poly(ethyleneimine) (PEI). Then heparin was attached to this conjugate using N-hydroxysuccinimide (NHS) and N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide (EDC).	Increase of activated partial thromboplastin time (APTT) from 35 s (pristine TiO_2) to 55–57 s for heparin-coated TiO_2. Heparin-coated TiO_2 also inhibited platelet adhesion.	[81]
14	Titan surface coated with laminin/heparin complex	Laminin/heparin complex was covalently immobilized onto poly-L-lysine (PLL) coated titan surface with help of 1-ethyl-3-dimethylaminopropyl carbodiimide (EDC), N-hydroxy-2,5-dioxopyrol-idine-3-sulfonicacid sodium salt (NHS) and 2-morpholinoethane sulfonic acid (MES).	The amount of immobilized heparin depends on the amount of used laminin. When high concentrations (more than 150 µg/mL) of laminin were used, it significantly increased the activated partial thromboplastin time (APTT) to more than 190 s while the uncoated Ti surface possessed an APTT of 30 s. A lower amount of laminin increased the APTT to 90–120 s.	[44]
15	PLA surface coated with heparin	Heparin was conjugated with chitosan coated polylactic acid (PLA) surface.	Chitosan/heparin complex prevented platelet adhesion and their activation in blood contact in the in vitro tests. At the same time, the L929 fibroblast adhesion test showed that the PLA surface adsorbed only 20% of cells, whereas the chitosan/heparin coating increased this value to 70%, which was greater than for the PLA coated with chitosan only (40% relative adsorption).	[43]
16	The extracorporeal circuit of low-flux cellulose dialyzers was rinsed with heparin solution	Commercial product.	75% of heparin-treated dialyzers showed a decrease in the vascular endothelial basic fibroblast growth factor VEGF165. It was more profound for patients with ischemic heart disease.	[82]
17	Fixation of heparin on biological tissue	Fresh porcine pericardia was used as biological tissue. For ionic immobilization, the tissue was treated with 2.1% protamine sulfate with further treatment with 0.625% glutaraldehyde or genipin. For covalent immobilization tissue was treated with 0.625% glutaraldehyde or genipin with further treatment with 2% water-soluble carbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride.	Heparin increased the surface hydrophilicity and reduced fibrinogen and platelet adsorption. At the same time, covalently attached heparin resulted in a greater hydrophobic surface and increased the amount of adsorbed fibrinogen and platelets compared with ionically immobilized heparin.	[42]
18	Polyurethane (PU) films coated with chitosan/heparin	PU film was treated with plasma with further growing polyacrylamide. Then, films were treated with glutaraldehyde with the further addition of chitosan (CH) and heparin (Hep).	Both surfaces were shown to possess antibacterial properties with some improvement for PU-CH-Hep.	[83]

Table 2. *Cont.*

No.	System	Preparation Method	Outcome in Hemocompatibility and Performance	Ref.
19	Glass and PVC surfaces coated with heparin	PVC surface was treated with radiofrequency SF_6 plasma with further chemical vapor deposition from heparin/isopropanol and heparin/hexamethyldisiloxane solutions.	The coagulation time of blood was increased by about 20–60%.	[84]
20	Electrospun bilayered bioresorbable small-diameter vascular grafts (SDVG) based on blends of poly(L-lactic acid) (PLLA) and segmented polyurethane (PHD), coated with heparin	Electrospun fibers were treated with allyl glycidyl ether with further addition of poly(ethylene glycol) bis(amine). Then heparin was immobilized with help of 2-(4-Morpholino) ethanesulfonic acid (MES), 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and N-hydroxysulfosuccinimide sodium salt (sNHS).	Heparin-coated surface promoted a stable and functional endothelial cell layer.	[85]
21	Alkylated polyelectrolyte thin film surface with immobilized heparin	Heparin was chemically modified by end-point conjugation to biotin and immobilized onto membrane-mimetic thin films via biotin–streptavidin interactions.	Heparin promoted ATIII-mediated thrombin inactivation.	[86]
22	Polysulfone (PSf) membrane coated with heparin/polydopamine (PDA)/polyethyleneimine (PEI)	PSf membranes were treated with PDA/PEI mixture. Then membrane was incubated into heparin and 1-Ethyl-3-(aminopropyl)carbodiimide (EDC)/N-hydroxysucciimide (NHS) mixture solutions	Heparin-modified PSf membranes possessed high selectivity for LDL removal and a reduction in the rate of platelet adhesion.	[87]
23	Stainless steel with covalently attached heparin-liposomes complex.	Stainless steel surfaces were treated with plasma with further deposition of acrylic acid and heparin-liposomes.	Increase in blood coagulation time.	[88]
24	PVC tubing coated with heparin	Commercial product.	It was demonstrated that the immobilization of heparin altered the composition of surface-adsorbed proteins and promoted the AT-mediated inhibition of surface adsorbed FXIIa and FXIa, unlike free heparin in solution.	[89]
25	Polyacrylonitrile HD membrane coated with chitosan/heparin conjugate	Chitosan (CS)/heparin (HEP) polyelectrolyte complex (PEC) was covalently immobilized onto the surface of polyacrylonitrile (PAN) membrane with help of glutaraldehyde and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC).	Coated PEC reduced protein adsorption, platelet adhesion, and thrombus formation. Additionally, immobilized PEC could suppress the proliferation of Pseudomonas aeruginosa.	[90]

Table 2. *Cont.*

No.	System	Preparation Method	Outcome in Hemocompatibility and Performance	Ref.
26	Graphene oxide with covered heparin, incorporated in polyetherimide membranes	Heparin was immobilized on the graphene oxide surface with the help of dopamine hydrochloride. Then, film and hollow fiber-based membranes with inclusions of modified graphene oxide were prepared.	Heparin reduced the platelet adhesion/activation (103 times), increased the blood clotting time (APPT 235 s), and lowered thrombin generation. Hemolysis ratio was less than 2%. Outstanding removal of uremic toxins after 4 h (Urea 77 ± 2.5%, creatinine 68 ± 2%, and lysozyme 44 ± 2%) and ~95% retention of human serum albumin was shown.	[91]
27	Heparin injections during HD		Skin necrosis due to the proposed acquired antithrombin III deficiency. Multiple erythematous, tender lesions developed over the abdomen.	[92]
28	HD procedure with heparin		Heparin-associated antiplatelet antibody (HAAb) positive patients experienced higher risk of thromboembolic and hemorrhagic complications (60% vs. 8.7% for control group) and higher related mortality (28.6% vs. 4.35% for control group).	[93]
29	Heparin-bonded polytetrafluorethylene HD arteriovenous graft (AVG)	Commercial product.	Rates of reintervention and thrombectomy were higher for the heparin-coated PTFE AVGs.	[94]
30	Heparin-coated polyacrylonitrile HD membrane	Heparin-coated polyacrylonitrile membrane (AN69ST) was compared with regional Citrate Anticoagulation.	Heparin-coated PAN membrane resulted in blood clotting in 39% of HD sessions, whereas no or 13% clotting occurred for citrate anticoagulation depending on citrate concentration.	[95]
31	Polyacrylonitrile (PAN) electrospun scaffold and heparin-poly(vinyl alcohol) (heparin-PVA) hydrogel coating HD membranes	Heparin was chemically attached to PVA with help of glutaraldehyde. Then, it was mixed with PAN and electrospun.	Heparin reduced membrane fouling with proteins and improved anticoagulation.	[96]
32	Immobilized heparin on PVDF membranes with microporous structures	First, polyacrylic acid was grafted on the PVDF surface. Then, heparin was covalently attached using (1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride.	Heparin reduced platelet adhesion	[97]
33	Dopamine-covered 316 L stainless steel surface coated with heparin/poly-L-lysine nanoparticles	Stainless steel was covered with dopamine with the further addition of heparin/poly-L-lysine nanoparticles.	Heparin prolonged the APTT and TT times, although a heparin density of more than 20 μg/cm^2 was unsuitable for vascular cell proliferation and endothelium regeneration.	[48]
34	Polycarbonate film with immobilized heparin	Heparin was attached to the PCL surface via aminolysis modification.	Heparin increased the surface negative charge, resulting in increased protein adsorption.	[98]

Table 2. *Cont.*

No.	System	Preparation Method	Outcome in Hemocompatibility and Performance	Ref.
35	GORE-TEX1 vascular grafts (PTFE) with immobilized heparin	Commercial product.	Heparin-coated PTFE grafts remained patent and had significantly greater thrombus-free luminal surface. The bioactivity of heparin was retained for a period of up to 12 weeks.	[99]
36	liquid crystalline hydroxypropyl cellulose ester film with immobilized heparin	Heparin was directly attached to cellulose surface using NaOH.	Heparin increased the activated partial thromboplastin time (APTT) and prothrombin time (PT) as well as the plasma re-calcification time (PRT) and reduced coagulation activation.	[100]
37	Alginate microbeads covered with polyallylamine (PAV)/macromolecular heparin conjugates	Heparin/PAV complex was attached to alginate microbeads using poly-L-lysine.	Heparin–PAV complex increased anticlot activity, lowered cytotoxicity, reduced elevated complement, leukocyte CD11b, and fibrotic overgrowth.	[50]
38	Hollow-fiber based PES HD membrane, modified with tannic acid (TA)/poly(2-ethyl-2-oxazoline) (PEtOx)/heparin	PES hollow fibers were covered with TA, then partially hydrolyzed PetOx was added with the further immobilization of heparin.	TA/PEtOx/Hep complex protected cardiomyocytes (H9C2) and vascular endothelial cells (HUVEC) from oxidative damage. Additionally, activated partial thromboplastin time was prolonged and complement activation was reduced.	[45]
39	Polyvinyl chloride (PVC) tubes and capillary membrane oxygenators with heparin-modified hollow fibers	Commercial product.	Immobilization of heparin resulted in reduced attachment of activated C3 and C5b-9 to the membrane surface in the invitro experiment and improved long-term hemocompatibility.	[101]
40	PVC surface coated with heparin and nitric oxide.	Heparin/copper nanoparticles and NO-generating substances were immobilized via tyrosinase (Tyr)-mediated reaction.	Heparin/copper nanoparticles/NO-generating generating complex demonstrated reduced inflammatory response and improved the adaptation of implants in vivo. Additionally, the complex promoted endothelialization and inhibited coagulation and platelet activation	[102]
41	PES HD membrane.	Heparin was added during HD.	In vitro, heparin reduced the rate of superoxide release from separated 12-myristate 13-acetate (PMA)-stimulated peripheral blood polymorphonuclear leukocytes (PMNLs). In vivo, the rate of superoxide release from PNMLs was significantly reduced for heparin use.	[103]
42	Cellulose membrane with covalently attached heparin	Visking@ dialysis tubes were modified with heparin (HE), dextran sulfate (DX), dermatan sulfate (DS), and endothelial cell surface heparan sulfate (ES-HS) using the photochemical heterobifunctional reagent 4-azido-lfluoro-2-nitrobenzene (AFNB).	Heparin-coated membrane showed 50% reduced platelet adhesion. ES-HS modified membranes demonstrated no platelet adhesion.	[104]

Table 2. *Cont.*

No.	System	Preparation Method	Outcome in Hemocompatibility and Performance	Ref.
43	Polyetherimide (PEI) with attached heparin	Heparin was covalently attached to the PEI surface via the amide group reaction.	Heparin caused a significant reduction in the platelet adhesion as well as the reduction in cell growth and metabolic activity	[105]
44	Bio-based poly(lactic acid) (PLA) membrane with attached heparin	Heparin was immobilized to the PLA membrane surface via reaction with dopamine.	Suppressed platelet adhesion, prolonged plasma recalcification time, and decreased the hemolysis ratio.	[106]
45	Styrene-butadiene-styrene (SBS) copolymer-based membrane with immobilized poly-vinylpyridine/heparin	Heparin was attached to polymer surface using poly-vinylpyridine.	Reduced adsorption of albumin and fibrinogen.	[46]
46	Polyvinyl chloride (PVC) based sodium selective membrane electrode coated with chitosan/heparin	Heparin/chitosan was attached using carbonyldiimidazole (CDI).	Reduced platelet adhesion	[107]
47	Heparin grafted HD dialyzers based on polyaryethersul-fone/polyamide, polysulfone, polyethersulfone, polyarylethersulfone, cellulose triacetate	Dialyzers from several manufacturers.	Increase in the success rate of the HD sessions for heparin-grafted dialyzers (68.5% versus 50.4% for the control group).	[108]
48	Gold covered SUS316L stainless steel (SS) sheet	Alternatively immobilized chondroitin 6-sulfate (ChS) and heparin (HEP) layers on gold-coated SS.	Increase in the blood clotting time	[109]
49	Titanium surface covered with chitosan (CS)/heparin (Hep)	Heparin was covalently immobilized on the alkali treated titanium surface with further immobilization of CS with electrostatic bonding.	Reduction in protein absorption, blood clot mass, and platelet adhesion. Additionally, antibacterial activity was observed.	[47]
50	Polyisobutylene-based thermoplastic elastomer (TPE) with immobilized heparin	Heparin was immobilized using 1-ethyl-3-(dimethyl-aminopropyl) carbodiimide hydrochloride (EDAC) and azidobenzoic acid/propine acid	Hindered accessibility of the heparin active site to antithrombin.	[110]
51	Hydrophobic polyethylene (PE) porous membrane covered with poly-dopamine/heparin	Heparin was covalently attached to the PE surface with dopamine.	Suppressed platelet adhesion and improved anticoagulation in vitro.	[111]
52	Polytetrafluoroethylene (PTFE) with a heparin-immobilized extracellular matrix (ECM) coating	Heparin was attached to the ECM coating.	Reduced endothelial cell (EC) growth and improved smooth muscle cell (SMC) proliferation, though platelet adhesion was observed at a low heparin surface density (4.89 ± 1.02 μg/cm^2).	[112]
53	Heparin-coated dialyzer membrane modules	Commercial dialyzers.	73% of HD sessions ended up with Grade 3 and Grade 4 clotting. No significant benefit of using heparin over vitamin E was shown.	[2]

6. Conclusions

The development of antifouling and anti-clotting materials is of great importance for hemodialysis and biomedical applications. The current tendency in the development of biocompatible materials is to design a membrane with near-zero charge due to the immobilization of zwitterionic molecules or pseudo-zwitterionic complexes. Achieving a near-zero charge dialysis membrane will minimize any possible electrostatic interaction with human serum proteins or other molecules, whose adsorption can provoke further cascade reactions and related undesired consequences.

The possibilities of current chemistry allow us to synthesize tunable structures with the desired properties that are potentially capable of replacing heparin and providing ultimate hemocompatibility. At the same time, it is also possible to use heparin for the creation of complex conjugates that eliminate heparin drawbacks, although this approach seems to be less promising than the controlled synthesis of heparin-mimicking polymers.

Achieving a biopassive antifouling surface that possesses minimal adsorption of proteins and blood cells is urgently required, since this phenomenon is considered as the very first step for further thrombotic response, blood clotting, and biochemical cascade reaction, which result in severe health problems for HD patients. Though the aim of biopassive surfaces is to minimize triggering immune response reactions, the effectiveness of this approach for long-term applications is still a major concern. Hence, a bioinactive surface is hardly suitable for biomedical implants, but is a good option for short-term or single-use applications such as hemodialysis. On the other hand, a bioactive surface utilizes the immobilization of bioactive compounds that minimize the immune response by interacting with key blood components or by releasing bioactive compounds.

Furthermore, with the methods mentioned in our study, it is more suitable for modifying flat-sheet membranes. However, studies to date on the heparin or heparin-mimicking modification of hollow fibers are not sufficient or well-tested. Therefore, in future studies, much more attention should be paid to the surface modification of hollow fiber membranes.

A few studies have succeeded in the mimicking of heparin conformation, since the anticoagulant of heparin is not only derived from the chemical groups, but also because the specific conformation of heparin may also promote the binding of coagulant factors. Thus, with a further understanding of heparin, the ultimate goal should be to design advanced heparin-mimicking polymers with both mimicking groups and conformations. It is believed that this review will evoke more attention toward the design of heparinized and heparin-like/mimicking membranes and encourage future advancements of this emerging research field.

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Abbreviations

Abbreviation	Meaning
HIT	Heparin-induced thrombocytopenia
PF4	Platelet factor 4
HD	Hemodialysis
C3	Complement component 3
HSA	Human serum albumin
FB	Fibrinogen
TRF	Transferrin
SH	Superhydrophobic
ZW	Zwitterionic
NO	Nitric oxide
ECC	Extracorporeal circuits
PVC	Polyvinyl chloride
KL	The Klotho Gene
SIS	Small intestinal submucosa
PES	Polyethersulfone
PDA	Polydopamine
PNIPAM	Poly(N-isopropylacrylamide
EDC	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
NHS	N-hydroxysuccinimide
DCS	Decellularized scaffold
PVA	Poly(vinyl alcohol)
LbL	Layer-by-layer
APTT	Activated partial thromboplastin time
PRT	Plasma recalcification time
PT	Prothrombin time
TT	Thrombin time
DHI	Dihydroxy-iron
BPSs	Bovine pericardial scaffolds
PU	Polyurethane
PCL	Poly(ε-caprolactone)
AEMA	2-aminoethyl methacrylate
PTFE	Poly-tetrafluoroethylene
ACT	Activated clotting time
PFO	Pericapsular fibrotic overgrowth
PA	Pullulan acetate
PEG	Polyethylene glycol
PLL	Poly-L-lysine
BSA	Bovine serum albumin
PEI	Poly(ethyleneimine)
MES	Morpholinoethane sulfonic acid
PLA	Polylactic acid
VEGF165	Vascular endothelial basic fibroblast growth factor
CH	Chitosan
Hep	Heparin
SDVG	Small-diameter vascular grafts
sNHS	N-hydroxysulfosuccinimide sodium salt
PSf	Polysulfone
PEC	Polyelectrolyte complex
PAN	Polyacrylonitrile
HAAb	Heparin-associated antiplatelet antibodies
AVG	Arteriovenous graft
PVDF	Poly-vinylidene fluoride
PAV	Polyallylamine
TA	Tannic acid
PEtOx	Poly(2-ethyl-2-oxazoline)

HUVEC	Human umbilical vein endothelial cells
Tyr	Tyrosinase
PMA	Phorbol 12-myristate 13-acetate
PMNLs	Polymorphonuclear leukocytes
DX	Dextran sulfate
DS	Dermatan sulfate
ES	Endothelial cell surface
HS	Heparan sulfate
AFNB	4-azido-lfluoro-2-nitrobenzene
SBS	Styrene-butadiene-styrene
CDI	Carbonyldiimidazole
SS	Stainless steel
ChS	Chondroitin 6-sulfate
TPE	Thermoplastic elastomer
EDAC	1-ethyl-3-(dimethyl-aminopropyl) carbodiimide hydrochloride
PE	Hydrophobic polyethylene
ECM	Extracellular matrix
SMC	Smooth muscle cells

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