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Review

Sulfonated Molecules and Their Latest Applications in the Field of Biomaterials: A Review

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Abstract: This review provides an overview of the latest applications of sulfonated molecules in biomaterials. Sulfonation, a chemical modification process introducing sulfonic acid groups, enhances biomaterial properties. This review explores the effect of sulfonation and recent innovations in biomaterial applications. It covers hydrogels, scaffolds, and nanoparticles, emphasizing sulfonation's unique advantages. The impact on cellular responses, including adhesion, proliferation, and differentiation, is discussed. This review also addresses sulfonated biomaterials' role in regenerative medicine, drug delivery, and tissue engineering challenges. It also provides a small overview of the sources and features of marine-derived sulfonated molecules, emphasizing their potential roles in advancing scientific research. As a novel aspect, an unconventional complex, "traditional Chinese medicine" and its sulfonation method have come to the forefront after a thousand years of history. This article concludes with a reflection on current research and future avenues, highlighting sulfonation's transformative potential in biomedicine.

Keywords: sulfonated molecules; sulfonation; biomaterial applications

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1. Introduction

A sulfonated molecule belongs to the category of organic compounds, being characterized by the existence of a sulfonic acid functional group. This functional group involves a sulfur atom bound to three oxygen atoms, with two of the oxygen atoms making bonds with a carbon atom [1].

The sulfonation process, involving the biotransformation of molecules, holds significant importance as a fundamental pathway. Sulfonation refers to the transfer of a sulfonate group from a universal sulfonate donor to an appropriate acceptor molecule [2]. Sulfonated compounds encompass a diverse range of substances, with molecular weights spanning from less than 10^3 to 10^6. These compounds undergo a notable alteration upon the introduction of the highly charged sulfonate group in their physiochemical properties. Sulfonation enhances water solubility [3] and can lead to conformational changes in molecules of varying molecular weights. Lipophilic molecules undergo conversion into amphiphiles, and, due to a pKα near 1.5, sulfonates maintain complete ionization across the pH range usually met in biological systems [4].

The significance of sulfonation is often underestimated, even though it plays a crucial role [5] in fundamental processes necessary for regular growth, development, and the maintenance of the internal environment. Sulfonated molecules, including proteoglycans and glycosaminoglycans, actively contribute to the connective tissue structures and formation of cell surface. Glycosaminoglycans, characterized by high acidity and hydrophilicity, exert a significant impact on tissue properties, such as hydration, elasticity, and cation composition [6]. Moreover, these molecules actively apply an extraordinary influence on the binding interactions of cell surface receptors, growth factors, extracellular matrix proteins, and enzymes. Additionally, they play an important role in transmembrane signaling [7].

The sulfonation of tyrosine residues emerges as a common posttranslational modification observed in numerous secretory and membrane proteins and peptides. This modification has the potential to exert a substantial impact on the functionality of these biomolecules [8].

The presence of sulfate groups in the sugar residues of glycoprotein hormones plays a crucial role in shaping their biological activity [9]. Sulfonation plays a crucial role [5] in the metabolic transformation of various small molecular mass hormones, such as vitamin C, catecholamine, and iodothyronines. Similarly, sulfonation stands out as a significant alteration for cholesterol and its derivatives, steroids, bile acid, and vitamin D [10]. It is very interesting that some traditional processes that have existed for thousands of years also endow compounds with sulfonic acid groups, playing an irreplaceable role in the fields of pharmacy and biomedicine. The above-mentioned content will be detailed and interpreted in this review.

2. Sulfonates

As we know, sulfonates involve the creation of a sulfur–carbon bond, although sulfation entails the creation of a carbon–oxygen–sulfur bond, as shown in Figure 1 [11].

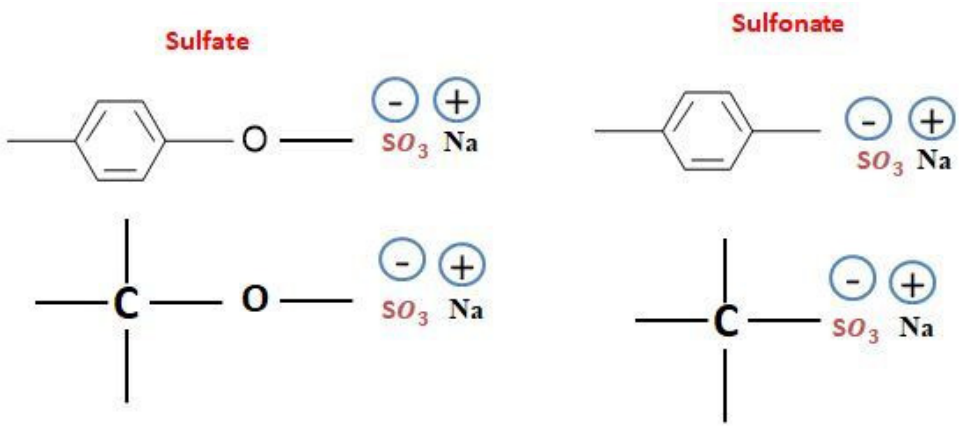

Figure 1. Sulfate and sulfonates dissimilarities [11].

Depending on their structure, polymers of sulfonate and sulfate can be produced using various chemical agents. These agents include those shown in Figure 2.

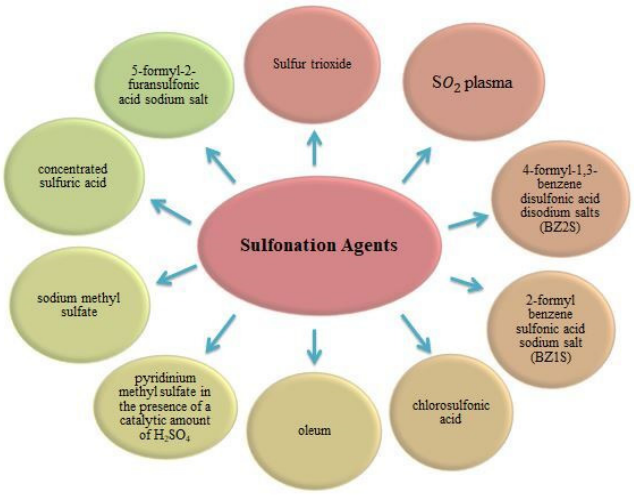

Figure 2. Sulfonation chemical agents [11].

The reagents shown above can be employed to generate sulfonated molecules or polymers under varied, semi-heterogeneous, or standardized conditions. However, it is noteworthy that strict circumstances may lead to polymer degradation, unwanted side

reactions, and poor reproducibility in some instances. Therefore, it is crucial to control the reaction conditions by adjusting constraints, including, for example, the degree of sulfonation, time, pH, temperature and solvent [11].

2.1. Sulfonated Kraft Lignin and Sulfonated Porous Surface of Tantalum Pentoxide/Polyimide Composite

Lignin exhibits nearly colorless characteristics in its natural wood state. However, technical lignin, including types such as kraft lignin or lignosulfonate, display a dark coloration. This dark coloration poses a significant challenge, hindering the widespread utilization of industrial lignin in high value applications, such as sunscreen or dyestuff dispersants. To broaden the range of applications for technical lignins, it is imperative to minimize their coloration. The production of lignin dispersant from soda lignin involves sulfonation. In certain instances, post-sulfonation modifications are undertaken to diminish coloration. An innovative, time- and energy-efficient sulfonating method has been reported. Eucalyptus (hardwood) kraft lignin undergoes sulfonation using 1, 4 butane sultone. This process simultaneously achieves sulfonation and color reduction under mild conditions, due to the phenolic hydroxyl blocking effect. The sulfonic group (SO_3H) content is determined through conductometric titration, and color performance is determined using a straightforward and quantifiable method. To augment decoloration efficiency, sodium borohydride is employed to modify the sulfonated sample, reacting rapidly and consuming minimal energy [12].

To enhance the surface bio-performance of polyimide (PI), composites of tantalum pent oxide (TPC) were synthesized, and the surface of tantalum pent oxide was modified using concentrated sulfuric acid. It is reported that sulfonated tantalum pent oxide displayed a microporous surface with pores approximately 3 μm in size, and -SO_3H groups were incorporated onto this microporous surface. Moreover, a multitude of submicroparticles of Ta_2O_5 emerged on the microporous surface, leading to the creation of micro-sub microstructures. In contrast to PI, the enhancements in surface roughness, hydrophilicity, surface energy, protein adsorption, and apatite mineralization were notably evident in sulfonated TPC (STPC) when immersed in simulated body fluid. These improvements demonstrated a proportional increase with the rising Ta_2O_5 content. Moreover, the antimicrobial properties of STPC were attributed to the presence of the -SO_3H group and Ta_2O_5. Additionally, the behaviors of rat bone marrow mesenchyme stem cells, including adhesion, proliferations, and differentiation, were significantly enhanced with the increasing Ta_2O_5 content. STPC with a Ta_2O_5 content of 50% (STPC 50), featuring a sulfonated microporous surface and micro-sub microstructures, exhibited antibacterial properties and stimulated favorable responses in cell behavior. The improved surface characteristics and cytocompatibility of STCP50 suggest a significant potential for applications in bone repair (Figure 3) [13].

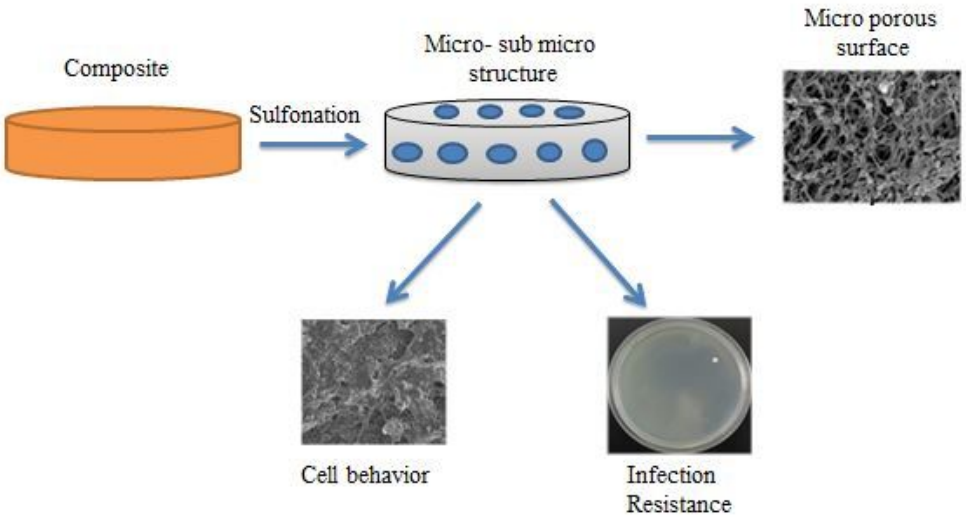

Figure 3. Sulfonated microporous surfaces of composites and their potential applications [13].

2.2. Sulfonated Polyetheretherketone

Polyetheretherketone (PEEK) is characterized by bio-inert properties and a comparatively hydrophobic nature, leading to challenges in achieving robust osseointegration, and thereby compromising its sustained clinical efficacy [14]. The successful integration between the implant surface and bone tissue is a crucial determinant for the effectiveness of orthopedic implants. In order to facilitate osseointegration, the surface of implant material must support the adhesion of osteoblasts cells essential for the construction of mineralized bone [15].

Studies have demonstrated that hydrophilic surfaces have been observed to enhance cell adhesion, while surface roughness provides additional sites for attachment and mechanical interlocking with osteoblasts. Porous structures play a vital role in facilitating nutrient and oxygen transport, creating a conducive environment for cellular activities. Furthermore, the introduction of bioactive groups, such as peptides or proteins, can emulate the extracellular matrix, fostering osteoblast responses and promoting the formation of bone tissue. In the realm of biomaterials design for applications such as bone tissue engineering or implants, the optimization of these factors is essential for encouraging favorable interactions with osteoblasts and ensuring the successful integration of implants with the surrounding bone tissue [16].

In specific, enhancement of PEEK's hydrophilicity can be achieved through the process of sulfonation, involving the introduction of charged sulfonate groups into the polymer backbone. Moreover, there is evidence supporting augmentation of non-specific interactions between polymeric scaffolds that carry sulfonate groups, such as polysulfonate copolymer hydrogels glycocalyx molecules present on the outer membrane of cells. This phenomenon contributes to the improved adhesion and proliferation of osteoblast-like cells on the scaffold [17].

The sulfonation process for PEEK is applicable either before or after the polymerization stage. When sulfonating PEEK monomers prior to polymerization, a significant sulfonation level can be attained. However, the resulting material exhibits diminished mechanical stability [18]. Consequently, post-polymerization sulfonation of PEEK is favored in applications involving bone implants, where maintaining mechanical integrity is crucial. Investigations into post-polymerization sulfonation of PEEK have primarily centered on completely transforming PEEK into membranes of sulfonated PEEK, particularly for use in applications involving fuel cell [19]. The sulfonation process has conventionally depended on prolonged reaction periods (exceeding 30 min) at higher temperatures (exceeding 258 °C) to attain the essential hydrophilicity in the resulting sulfonated tissue [20]. In recent research, surface-improved sulfonated PEEK, using a short period sulfonation technique, has demonstrated biocompatibility [21]. It has effectively triggered pre-osteoblast functions, such as proliferation, osteogenic differentiation, and proliferation in vitro. Additionally, it has significantly improved osseointegration and the strength of bone-implant attachments in vivo [22].

2.3. Sulfonated Chitosan Derivatives

Chitosan (CS) is a linear polysaccharide consisting of two repeating units, namely D-glucosamine and N-acetyl-D-glucosamine, connected by β-(1→4)-linkages as shown in Figure 4 [23]. CS is distinguished as the sole naturally occurring positively charged polysaccharide [24].

Its unique attribute stems from the abundance of free amino groups, specifically N%-*wt*, at 9.938% or 6.21 meq·g^{-1} for a chitosan sample with a degree of deacetylation (DDA) equal to 100%. This characteristic renders chitosan solvable in neutral or acidic aqueous media (pH less than 6), a solubility that varies based on factors such as origin, DDA, or the natural source. The presence of these functional groups provides CS with remarkable physicochemical and biological attributes, including but not limited to biocompatibility, hemostasis, biodegradability, and adsorption [25].

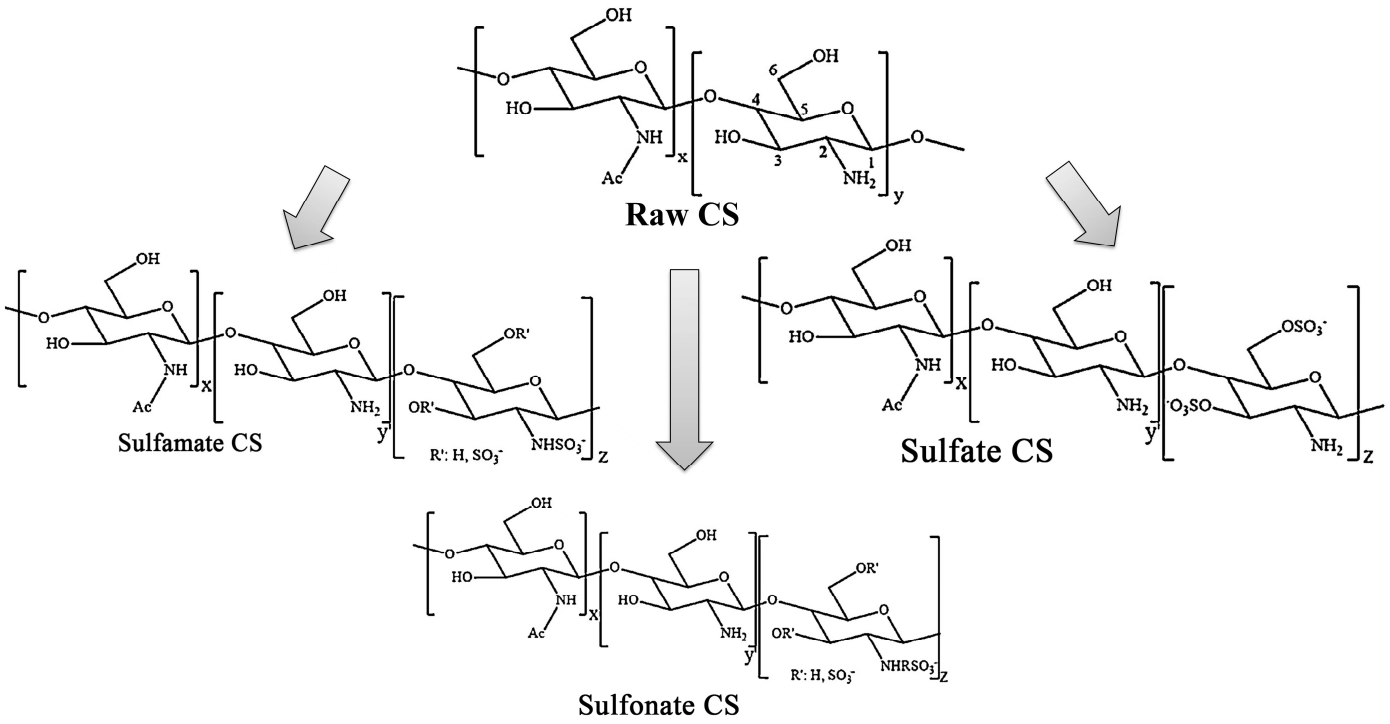

Figure 4. Chemical structure scheme of chitosan and its sulfonated derivatives [23].

The sulfonation of CS, explored in various publications, has been contemplated as a strategy to enhance its biological properties (Table 1). Sulfonated CS (SCS) derivatives are anticipated to capitalize on these outstanding biological characteristics, contingent on factors such as the degree of replacement. Notably, SCS derivatives have exhibited appealing characteristics, including antimicrobial characteristics, water solubility, and antioxidant properties. Additionally, SCS has been utilized for its blood anticoagulant characteristics, attributed to its chemical structure, resembling that of heparin. Furthermore, SCS has found application as a delivery system for tissue repair and regeneration, owing to its capability to fix to protein growth factors [26]. SCS has demonstrated high efficiency as derivatives for directing neural differentiation. Hence, SCS derivatives show great promise for various applications, including bone tissue engineering, blood contact devices and drug delivery [23].

Table 1. Conditions and properties influenced by the sulfonation modification of chitosan [23].

Experimental Conditions of Chemical Modification	Properties
pH	Solubility
Temperature	Molecular weight
Reaction time	Rheology
Sulfonate reagents	Degree of sulfation
Solvents	Zeta potential

2.4. Sulfonated Graphene

Sulfonated Graphene (oxide) (SGO) is a graphene imitative and a mixed catalyst. It is recognized for its sustainability and extensive applications in biology and chemical engineering [27,28]. Sulfonated graphene is synthesized through the sulfonation process of graphene oxide. Different sulfonating agents, including sulfuric acid, 4-diazobenzenesulfonic acid, and chlorosulfuric acid and 2-chloroethane sulfonic acid are employed in the preparation of sulfonated graphene [29]. SGO is synthesized through the oxidation and sulfonation processes applied to graphite powder. The chemical attributes of both sulfonated graphene and graphene oxide are influenced by the agents used for oxidation and sulfonation [30].

Sulfonated graphene refers to graphene featuring a frequent -SO_3H bound to its surface and sheet ends. This modification enhances the electron-withdrawing capacity from the carboxylic group (–COOH), thereby augmenting the electron concentration among sulfur and carbon atoms. This, in turn, improves the stability of the catalyst under demanding reaction conditions. Additionally, the sulfonic functional group serves as a proton carrier, suggesting the material's high density and potential application as a proton conductor [31]. The catalytic activity of SGO is 9.1 times higher compared to other solid acid catalysts and conventional sulfuric acid. The enhanced catalytic reactivity can be ascribed to the creation of hydrophobic pockets on the SGO surface. This is achieved through the integration of graphene nanosheets and oxygen-containing groups, enabling the catalyst to efficiently bind with substrates/reactants and significantly bolster proton transfer [32]. Various chemical uses have been documented employing graphene and its derivatives. Specifically, sugars like hexose, fructose, and glucose undergo decomposition into levulinic acid, through the use of a catalyst based on graphene oxide, which incorporates a -SO_3H group [33]. In a study conducted by Liu and colleagues in 2012, it was discovered that sulfated graphene exhibits excellent recyclability in the context of propylene oxide hydration [34]. The characteristics and potential applications of sulfonated graphene are depicted in Figure 5.

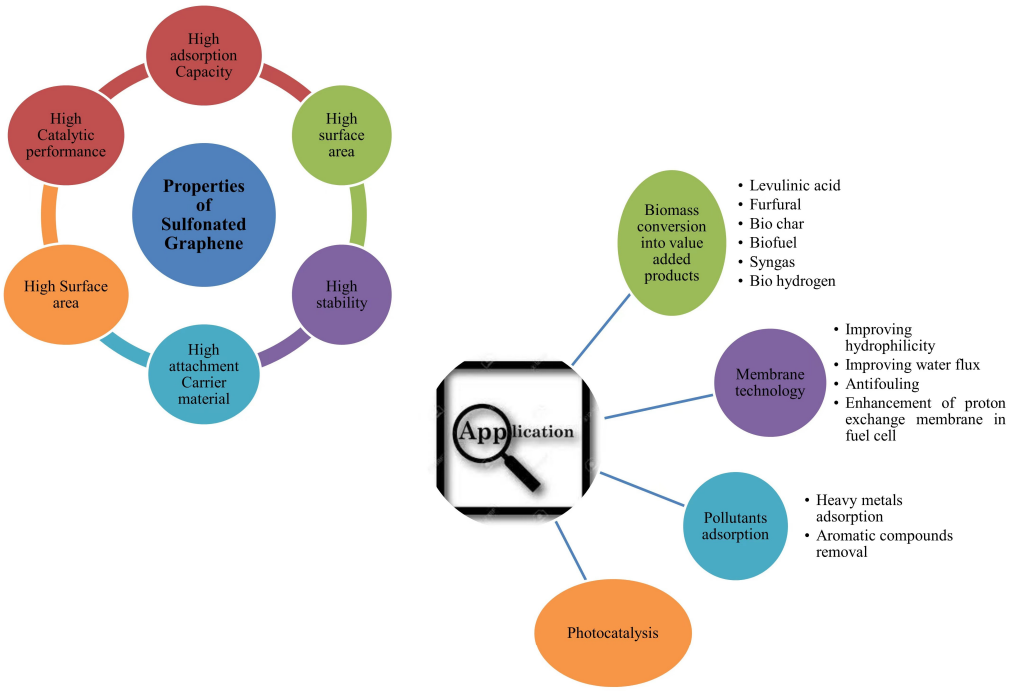

Figure 5. Properties and potential applications of sulfonated graphene [30].

2.5. A Thermo-Responsive Injectable Gel with Sulfonated Properties

Biomaterials designed for injection offer a versatile platform for delivering multiple proteins to address diverse pathologies associated with myocardial infarction (MI) [35]. These therapeutic interventions within the realm of biomedicine should target cardiac tissue regeneration, enhance cardiomyocyte survival, and alleviate ventricular wall stress. The overarching goal is to mitigate pathological remodeling and enhance cardiac function [36]. The effectiveness of intramyocardial biomaterial injections has been demonstrated in improving heart function and vascularization, diminishing infarct size and fibrosis, increasing the recruitment of progenitor cells, and reducing cardiomyocyte apoptosis [37].

A novel biomedical strategy includes administering therapeutic proteins through injectable materials in a controlled-release fashion to effectively address this condition. A thermo-responsive injectable gel, composed of chitosan conjugated with poly (N-isopropyl acrylamide) and sulfonate groups, was created for the purpose of spatiotemporal protein

delivery to protect cardiac function following MI [38,39]. Laboratory tests revealed that the thermo-responsive gel has the capability to deliver the vascular endothelial growth factor (VEGF), interleukin-10 (IL-10), and the platelet-derived growth factor (PDGF) in a sequential and sustained manner [40]. To evaluate the compatibility of the polymer and its therapeutic effects, an acute MI mouse model was employed. Immunohistochemistry analysis unveiled the biocompatibility of the hydrogel, showing that controlled protein delivery led to a reduction in macrophage infiltration and an enhancement in vascularization. Subsequent echocardiography indicated an enhancement in ejection fraction and fractional shortening following the injection of the thermo-responsive gel and proteins [41]. To enhance the delivery system, an experimental study was conducted, with a factorial design, aiming to determine the optimal combination and doses of proteins for enhanced stable vascularization and reduced inflammation [42]. This investigation utilized a subcutaneous injection mouse model [43]. The outcomes revealed noteworthy contributions from VEGF, IL-10, and FGF-2 in fostering long-term vascularization, while PDGF demonstrated minimal effects. Studies found the cardio-protective characteristics of S-GC-PNIPAM in treating MI and its capability to provide therapeutic proteins in a spatiotemporal manner, making it applicable to regenerative medication and tissue engineering (Figure 6) [38].

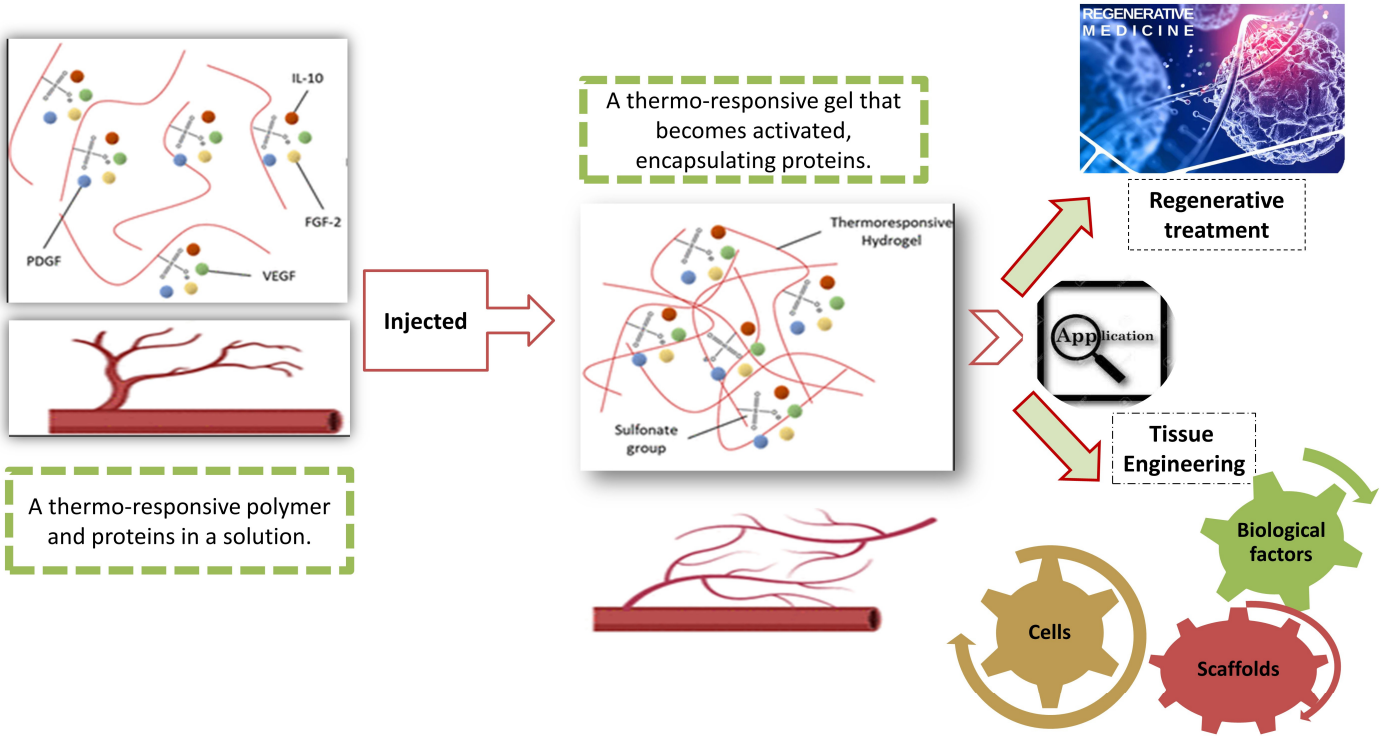

Figure 6. Design of experiments to optimize angiogenic protein therapy and applications [38].

2.6. Sulfonated Cladophora Nano-Cellulose Beads

Cellulose still requires much more exploration in material science and biomedical engineering [44]. Cellulose beads have been documented as absorbent materials for various purposes, such as the elimination of metals [45], dyes [46,47], and procedures related to blood [48–51]. Hemocompatibility stands out as a crucial characteristic for materials intended for blood contact. Interactions between blood and materials trigger the initiation of blood cascades, including coagulation and the complement system. Additionally, this interaction leads to the activation of platelets and leukocytes [52]. To avoid triggering the coagulation cascade during blood-related procedures, patients are administered the anticoagulant heparin. Nonetheless, prolonged use of heparin may result in adverse effects such as hyperkalemia, thrombocytopenia, and osteoporosis [53]. To address challenges associated with the systemic application of heparin, efforts have been directed toward

the creation of non-thrombogenicity materials. Various approaches have been suggested to impart anticoagulant characteristics to materials, including surface modifications using grafting of heparin-like molecules, anti-fouling agents, and heparin coatings [54,55]. Scholars have explored the integration of heparin-like structures into a diverse array of polymer materials, revealing that the presence of sulfate and sulfonate groups plays a role in influencing the anticoagulant activity of the material [56]. Sulfonated cellulose beads were created through the oxidation of Cladophora nano-cellulose to 2,3-dialdehyde cellulose, subsequently undergoing sulfonation through the use of bisulfite [57]. Nano-cellulose obtained from green algae of the Cladophora variety is an exceptionally versatile substance distinguished by a complex fibrous web structure, a notable specific surface area, heightened crystallinity, and remarkable rheological and mechanical characteristics [58]. The sulfonated Cladophora nano-cellulose beads exhibit characteristics that align with the properties illustrated in Figure 7. These attributes make them promising candidates for the creation of immunosorbent platforms, including applications in extracorporeal blood treatments. Furthermore, the inclusion of sulfonate groups in the polysaccharide chain has the potential to influence the thrombogenicity properties of Cladophora nano-cellulose [59]. The characteristics mentioned above have played a significant role in the advancement of materials based on Cladophora nano-cellulose for various biomedical purposes, as shown in Figure 7 below. These include the creation of drug delivery systems [60,61], as well as applications such as filters for removing viruses [62–64], membranes utilized for electrochemically-assisted hemodialysis [65–67], and DNA-immobilized immunosorbent membranes [68].

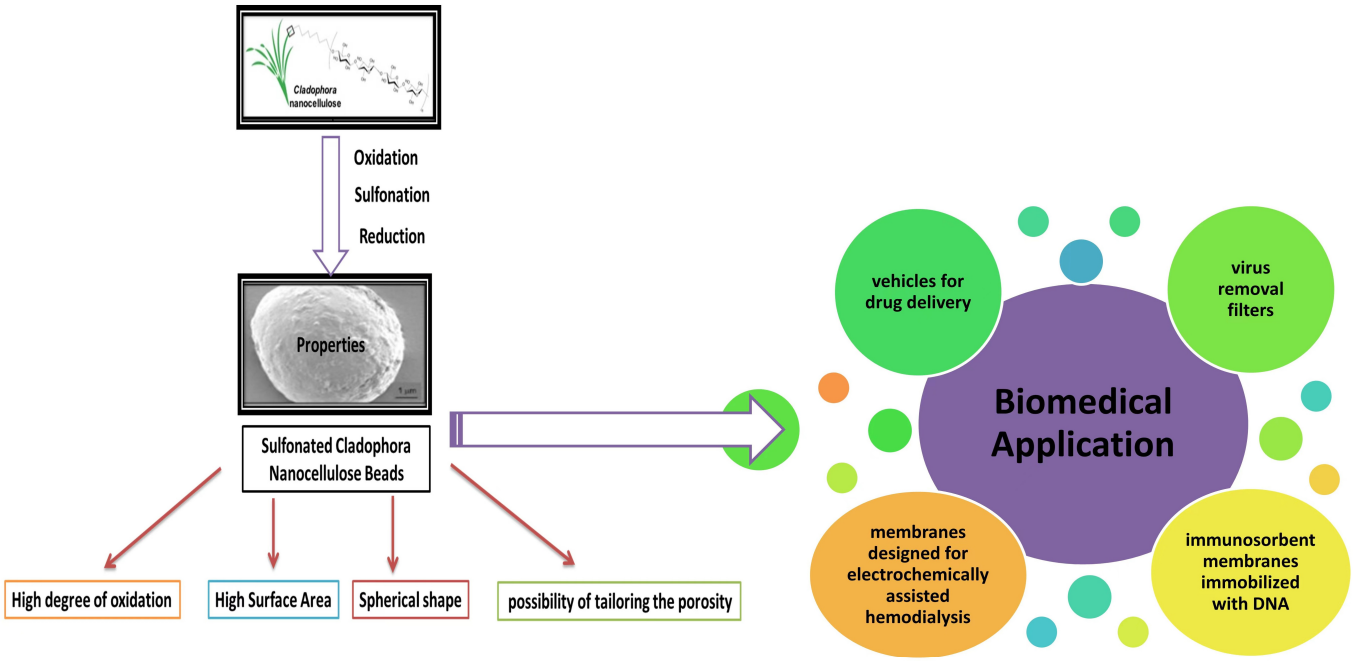

Figure 7. Properties of sulfonated Cladophora nano-cellulose beads [59].

2.7. Sulfonated Cryogel Scaffolds

The human brain possesses distinctive characteristics that pose challenges when attempting to investigate them through animal models, particularly concerning the intricate mechanisms involved in neurodevelopmental and psychiatric disorders [69–71]. While there have been notable strides in the development of human primary brain tissue culture systems, their application in unraveling the cellular mechanisms of diseases is constrained [72,73]. A primary obstacle is the scarcity of precise tools capable of consistently manipulating specific regions of the tissue [74]. It is reported that a novel approach involves the creation of entirely synthetic, line-shaped microscale cryogel. These cryogels are crafted from a combination of polyethylene glycol diacrylate (PEGDA) and the sulfonated

monomer 3-sulfopropyl acrylate (SPA), serving as an innovative tool for the focused and consistent marking of human tissue explants. The advantages of these materials include:

- A user-friendly scheme: this is attributed to their mechanical strength and sponge-like nature.
- Convenient storage: cryogels are easily stored before use.
- Simple loading process: agents can be loaded directly onto the dry materials, facilitating controlled release.
- Precise targeting: cryogels enable accurate and reproducible specific targeting.

The fabrication of line-shaped cryogels is achieved effortlessly within well-defined polydimethylsiloxane (PDMS) molds, featuring line-shaped cavities, with a hydrophilic surface. Micro-stereo lithography 3D printing is employed to create customized micron-sized master structures, offering a versatile technique to regulate cryogel shapes, with extraordinary description and reproducibility zones within tissue explants [75].

While the primary objective of this endeavor was to devise user-friendly implements for ex vivo tissue manipulation, there is speculation that the benefits of these cryogels could potentially broaden their utility across various research domains. The capacity to manipulate a specific region within the tissue could prove valuable in other 3D cell culture platforms, including spheroids and organoids. Such an application would empower researchers with finer spatial and temporal control over the administration of pharmacological agents in these cultures, facilitating the exploration of inquiries that are presently challenging [75]. Furthermore, the mechanical characteristics of these cryogels indicate a significant potential for the targeted delivery of therapeutic substances to the in vivo brain, both locally and regionally [76]. Numerous applications exist for controlled and directed drug delivery to the brain, offering solutions to challenges posed by the impermeability of the blood–brain barrier. These applications encompass treating traumatic brain damage, with silk biofilms presently undergoing testing in mouse models [77]. Additionally, addressing the nigrostriatal pathway caused by Parkinson's disease [78] involves localized drug delivery to a definite section of the brain.

In addition to their potential application in targeted treatments, cryogels could enhance models of focal damages. Researchers have newly demonstrated that cryogels serve as a tool to persuade focal demyelination of grey material both in mouse organotypic slice cultures [79] and in vivo [80]. This establishes board tools for both mechanistic survey and the assessment of remyelination therapeutics on behalf of various sclerosis. In cases where direct inoculation into the brain is necessary, it might be advantageous to explore another template for cryogel creation, such as, for instance, emulsion-templated spherical macroporous microcarriers [81].

Cryogels were specifically designed as a user-friendly method for regionally delivering to ex vivo brain slices, aiming to address the scarcity of tools obtainable for precisely operating brain tissue in slice cultures. However, with further refinement and advancement, these cryogels could be adapted for the mentioned in vivo applications, significantly increasing their possible influence and range of applications [75].

2.8. Sulfonated Hyaluronic Acid

Hyaluronic acid (HA) is recognized as the glycosaminoglycan characterized by the highest molecular weight, contributing to the facilitation of proliferation, tissue repair, adhesion, and cell migration [82]. In contrast to HA, sulfonated hyaluronic acid (S-HA) demonstrates a more favorable impact on cardiovascular cells and increased stability in the presence of hyaluronidase [83]. S-HA emerges as a promising biomaterial for delivering therapeutic agents aimed at facilitating the regeneration of injured or diseased tissues and organs. S-HA emerges as a favorable biomaterial for transporting therapeutic go-betweens aimed at facilitating the regeneration of damaged or diseased organs and tissues. Numerous studies have extensively investigated the reparative and therapeutic effects of S-HA on several cell types. Researchers have delved deeply into its impact on cell differentiation and formation processes, spanning keratinocytes [84], osteoclasts [85], astrocytes [86], macrophages [87], and more. Furthermore, S-HA collaborates synergistically with other substances to enhance its

role in these processes. Hennig et al. were the pioneers in exploring the therapeutic potential of sulfated angiogenic fragments, studying their effects in both cancer and non-cancer contexts. The results of their research indicate that these fragments may offer a valuable, non-toxic targeted treatment option for individuals with bladder cancer [88]. Gronbach et al. achieved protein clearance in DickkOPF-1 through the utilization of biomaterials based on macromolecular monomers covalently modified with S-HA. They carried out an in-depth examination of process, significances, and fate of binding proteins, representing the pioneering investigation of this particular aspect [89]. HA has been subjected to sulfonation for the creation of hydrogels, with researchers investigating its efficacy across multiple studies. In their research, Feng et al. suggest that S-HA hydrogel not only fosters chondrogenesis in human bone marrow mesenchymal stem cells (hMSCs) but also prevents hypertrophic differentiation produced by chondrogenesis [90]. The degree of sulfonation in S-HA has a notable impact on cell growth. Research has elucidated that highly sulfonated HA can sustain the undifferentiated state and pluripotency of human-induced pluripotent stem cells, even in the absence of feed and basic fibroblast growth factor (bFGF), as compared to un-sulfonated HA and low-sulfonated HA [91]. Lim et al. highlighted the critical role of sulfuration degree in the selective binding of vascular endothelial growth factor 165 (VEGF165) by sulfurating HA. Their synthesis resulted in a polymer with a strong attraction for angiogenic VEGF165a while showing no attraction beside angiogenic VEGF165b [92]. S-HA has demonstrated its potential in promoting endothelialization for the treatment of cardiovascular diseases, as evidenced by numerous investigations. Through a series of cell experiments, Xue et al. observed that the S-HA with a higher sulfur content not only showed a more robust capability to endorse the development and movement of endothelial cells but also demonstrated effectiveness in modifying the phenotype of smooth muscle cells, along with a heightened anti-inflammatory function. Additionally, all S-HA molecules were found to be extremely highly compatible with blood [93]. On this basis, Tong et al. prepared the S-HA into nanoparticles and conjugated the S-HA nanoparticles onto a magnesium alloy surface by the method of self-assembly [94]. The S-HA nanoparticle surface was covered with poly (L-lactic acid). They found that the thickness of the poly (L-lactic acid) coatings determined the S-HA nanoparticle release concentration, which further influenced surface biocompatibility. An excessive thickness of poly (L-lactic acid) coating can lead to insufficient biological function, but the absence of poly (L-lactic acid) coating can cause a sudden release of S-HA nanoparticles, leading to endothelial cell toxicity. Based on the above understanding, Xue et al. switched to using an electrostatic spraying method to graft S-HA nanoparticles onto the surface of magnesium alloy, in order to enhance the adhesion between S-HA nanoparticles and the substrate material, and thereby improve their biocompatibility under the condition of having no covering coatings [95]. Sun et al. prepared an S-HA drug-loading coating on the surface of magnesium alloy to load MOF-Cu, which catalyzes the release of appropriate amounts of nitric oxide (NO) from endogenous and exogenous donors in the microenvironment. The released NO significantly improves the biocompatibility of the magnesium alloy surface [96].

2.9. Marine-Derived Sulfonated Molecules

Marine-derived sulfonated molecules are also organic compounds that contain a $-SO_3H$ and are obtained from marine sources. These molecules are often isolated from various marine organisms, including algae, sponges, bacteria, worms, cnidarians (such as corals and jellyfish), and marine plants. They can exhibit diverse structures and biological activities, making them of interest in various scientific fields. Some common types of marine-derived sulfonated molecules include sulfated polysaccharides, sulfated sterols, and other sulfonated secondary metabolites [97]. Here are a few examples:

- *Fucoidans*
  Source: brown algae (Phaeophyta).
  Features: Fucoidans are sulfated polysaccharides with various biological activities, such as anticoagulant, antiviral, anti-inflammatory, and antioxidant properties. They have potential applications in pharmaceuticals, cosmetics, and biomaterials [98].

- *Carrageenans:*
  Source: red algae (Rhodophyta).
  Features: Carrageenans are sulfated polysaccharides widely used in the food industry as gelling and thickening agents. They also exhibit antiviral and anti-inflammatory properties. They have been studied for their various applications, including in tissue engineering, wound care, and drug delivery [99].
- *Glycosaminoglycans (GAGs):*
  Source: various marine organisms, including fish.
  Features: GAGs are sulfated polysaccharides with roles in cell adhesion, signaling, and tissue development. They have applications in medicine and biotechnology [100].
- *Sulfated Sterols:*
  Source: certain marine sponges.
  Features: Sulfated sterols from marine sponges may exhibit antibacterial, antifungal, and antiviral activities. They are studied for their potential in drug development [101].
- *Sulfonated aromatic compounds:*
  Source: various marine organisms.
  Features: some marine organisms produce sulfonated aromatic compounds with potential antioxidant, anti-inflammatory, and other bioactive properties [102].
- *Sulfonated peptides:*
  Source: marine organisms, including sponges and mollusks.
  Features: Sulfonated peptides may exhibit antimicrobial and antifungal activities. They are of interest in the development of novel therapeutic agents [103].
- *Sulfated nucleosides:*
  Source: marine microorganisms.
  Features: Sulfated nucleosides are compounds with antiviral and antitumor activities. They are studied for their potential in pharmaceutical applications [104].

The features of marine-derived sulfonated molecules vary widely, depending on their chemical structures and the specific marine organisms from which they are derived. These compounds often play essential roles in the marine organisms themselves, serving functions such as defense against pathogens or predators. Researchers are increasingly exploring the potential biomedical and industrial applications of these marine-derived sulfonated molecules due to their unique properties.

3. Sulfated or Sulfonated Compounds

Generally speaking, the sulfation or sulfonation of compounds or complexes is difficult to study because the physical and chemical properties, proportions, and targeted functional groups of different molecules in the compound during the actual operation can affect the sulfonation or sulfation process, leading to inaccuracies in the operation. However, the sulfation or sulfonation of compounds in a particular field may be achievable, and may have even existed for thousands of years. Traditional Chinese medicine has played an irreplaceable and noble role over the 5000 years of the history of Chinese civilization. The Shennong Materia Medica Classic, written before the Eastern Han Dynasty, is considered to be the earliest official record of traditional Chinese medicine. It states that an important step in the processing of traditional Chinese medicine is to use sulfur fumigation to pick and process the herbs after the initial processing. Its purpose is to kill parasites in traditional Chinese medicine and prevent mold growth. Traditional Chinese medicine itself is complex. However, modern natural medicinal chemistry has invented more time-saving and precise methods for killing insects and preventing mold, so sulfur fumigation technology has gradually lost its popularity in the field of traditional Chinese medicine processing. In addition, some experts believe that sulfur fumigation technology can lead to an increase in the toxicity of traditional Chinese medicine. However, it is precisely the traditional processing techniques of many authentic medicinal materials, such as sulfur fumigation, that contribute to the classification of traditional Chinese medicine as traditional. Sulfur fumigation causes many biomolecules in traditional Chinese medicine to be sulfated or

sulfonated, and the wonderful combination of these molecules is precisely the undisclosed secret to the therapeutic effect of traditional Chinese medicine for thousands of years.

4. Conclusions

In summary, this study emphasizes the significant progress and potential of sulfonated molecules in biomaterials. Sulfonation, a versatile chemical modification process, has demonstrated efficacy in enhancing biomaterial properties by introducing sulfonic acid groups. The exploration of sulfonation mechanisms, structural changes, and recent innovations in biomaterial categories, such as hydrogels, scaffolds, and nanoparticles showcases their broad applications.

This review particularly highlights the impact of sulfonated molecules on cellular responses, including cell adhesion, proliferation, and differentiation. This underscores the promising role of sulfonation in addressing challenges within regenerative medicine, drug delivery, and tissue engineering. The unique advantages identified in this review position sulfonation as a valuable avenue for future developments in the biomaterials field.

The importance of this review lies in the fact that the significant role it presents in the fields of biomaterials and biomedicine is often overlooked in specific application areas. Just as modern natural medicine science believes that sulfur fumigation is no longer important in the processing of traditional Chinese medicine, it is precisely the sulfur fumigation process that supports the soul of the efficacy of traditional Chinese medicine, endowing the compound with a sulfonic acid group.

5. Future Directions

Moving forward, there is a need for extensive research to deepen our understanding of specific aspects related to sulfonated biomaterials. Investigating the long-term biocompatibility, degradation kinetics, and potential immunogenicity of these modified biomaterials is crucial for ensuring their successful translation. Additionally, comprehending the scalability and cost-effectiveness of sulfonation processes will contribute to their practical utilization across various biomedical applications. The exploration of novel sulfonated molecules and their interactions with specific cell types presents an opportunity for customized biomaterial design. Collaborative efforts among researchers, clinicians, and industry stakeholders are essential for bridging the gap between laboratory innovations and clinical applications.

Sulfonation provides an opportunity for the multifunctionality of single molecule biomaterials. Through the sulfonation of single molecules, it endows them with the capabilities that were previously achieved through the synergistic action of multiple molecules. For example, HA has good cell compatibility, while sulfated S-HA has better enzyme stability and blood compatibility.

In summary, the ongoing exploration of sulfonated molecules in biomaterials offers a transformative potential in biomedicine. Future research should prioritize addressing existing knowledge gaps and refining the practical implementation of sulfonated biomaterials, ultimately leading to enhanced clinical outcomes.

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