Polysaccharides for Medical Technology: Properties and Applications

Pongpat Sukhavattanakul [a], Penwisa Pisitsak [a], Sarute Ummartyotin [a,*], and Ravin Narain [b,*]

[a] Department of Materials and Textile Technology, Faculty of Science and Technology, Thammasat University, Pathum Thani, 12120, Thailand

[b] Department of Chemical and Materials Engineering, University of Alberta, Edmonton, T6G1H9, Canada

Email: sarute@tu.ac.th (Sarute Ummartyotin)

narain@ualberta.ca (Ravin Narain)

Abstract

Over the past decade, the use of polysaccharides has gained tremendous attention in the field of medical technology. They have been applied in various sectors such as tissue engineering, drug delivery system, face mask, and bio-sensing. This review article provides an overview and background of polysaccharides for biomedical uses. Different types of polysaccharides e.g. cellulose and its derivatives, chitin and chitosan, hyaluronic acid, alginate, and pectin are presented. They are fabricated in various forms such as hydrogels, nanoparticles, membranes, and as porous mediums. Successful development and improvement of polysaccharide-based materials will effectively help users to enhance their quality of personal health, decrease cost, and eventually increase the quality of life with respect to sustainability.

Keywords: Polysaccharide-based material; Medical technology; Drug delivery system; Biosensor; Artificial face mask; Sustainability

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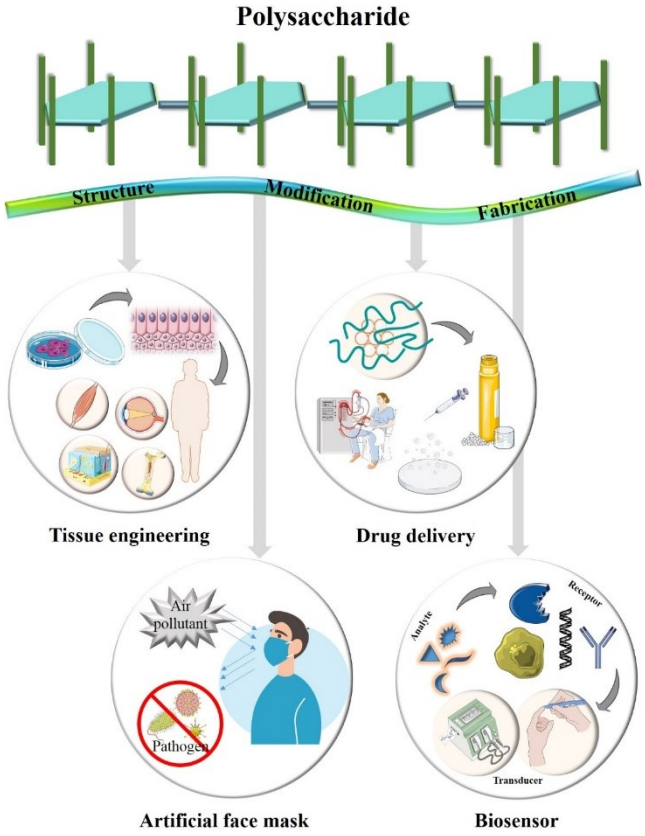
Graphical abstract



Development of polysaccharides in medical technology

Highlight

1) Cellulose, chitin-chitosan, hyaluronic acid, alginate, and pectin are presented.
2) Medical applications include drug delivery, tissue engineering, sensor, and face masks.
3) Applications as hydrogels, nanoparticles, membranes, and porous media.
4) Use of polysaccharides was encouraged by Sustainable Development Goal policy.

1) Overview

In the past few decades, the use of polysaccharide-based materials for biomedical technology has grown exponentially. The properties of polysaccharide-based materials can be tuned with respect to molecular weight, structural orientation as well as fabrication strategies.

Various fields of medical research areas include tissue engineering [1], drug delivery system [2], face masks [3] and biosensors [4].

By definition, a polysaccharide is a long chain of polymeric carbohydrates composed of monosaccharide units bound together by glycosidic linkages [5]. It can be hydrolyzed in water containing amylase enzyme producing sugars such as monosaccharides and oligosaccharides. The polysaccharide structure is versatile, from linear to branched structures. Polysaccharides can have either homostructure and heterostructure repeating units [6]. The use of polysaccharide significantly offers numerous benefits including good biocompatibility, low immunogenicity, low toxicity, good adsorption as well as degradability and hence suitable for applications in various medical fields [7-10]. It can be employed for health benefits [11] as well as for support of antifibrotic drug delivery [12].

One of the most abundant naturally occurring polysaccharides is cellulose which is found mainly in plants and some bacteria. It is a linear polymer chain of several hundred to thousands of β(1-4) linked D-glucose. It has high chemical resistance, excellent dimensional stability as well as high stiffness. The use of cellulose is therefore versatile in numerous sectors of industrial applications such as flexible electronics, chemical sensors and medical uses [13, 14].

Next to cellulose, the second abundant polysaccharides are chitin and chitosan. These copolymers are structurally defined as a long-chain polymer of *N*-acetylglucosamine and randomly distributed β-(1-4)-linked D-glucosamine and *N*-acetyl-D-glucosamine, respectively. They have excellent antimicrobial properties and are extensively used for food packaging and medical devices [15, 16]. Chitin is generally found in exoskeletons of arthropods and is converted to chitosan by deacetylation. Due to the presence of free amino groups, chitosan is a cationic polysaccharide which is soluble in acidic aqueous solution. It exhibits

antimicrobial, hemostatic and mucoadhesive properties beneficial for a variety of biomedical applications.

Alginate is an edible anionic polysaccharide generally obtained from brown algae. It is a linear copolymer with block of (1-4)-linked-β-D-mannuronate and α-L-guluronate residues, respectively. Alginate displays biocompatibility, low toxicity, and mild gelation by addition of divalent cations such as calcium ions. It has been conventionally used in pharmaceutics as thickening, gel forming, and stabilizing agents. They have been widely studied for wound healing, drug delivery and tissue engineering applications [17, 18].

Another important polysaccharide is hyaluronic acid. It is a polysaccharide composed of D-glucuronic acid and *N*-acetyl-D-glucosamine, linked by alternating β-(1-4) and β-(1-3) glycosidic bonds. Hyaluronic acid is a major component of skin extracellular matrix. Because hyaluronic acid is known to improve cell proliferation and migration, it has found applications in tissue engineering and cancer treatment [19, 20].

Pectin is a polysaccharide consisting mainly of galacturonic acid residues linked by α-1,4 glycosidic bonds. Some of the galacturonic acid chain partly esterified as methyl esters. It can be found in the cell walls of most plants and has been widely used as a thickener or stabilizer in food industry. The potential use of pectin in the biomedical field is related to its high-water content and ability to homogeneously immobilize cells. Tissue engineering, drug delivery, gene delivery, and wound healing patches are some examples of the promising applications of pectin [21]. Furthermore, polysaccharide can be effectively recovered from fungi [22] and seaweed [23]. The physico-chemical and biological properties were favorable.

Since polysaccharides are environmentally-friendly and sustainable biopolymers, which offer a wide variety of valuable physicochemical properties, they are good alternatives to petroleum-based polymers. Recently, polysaccharide for medical technology can be effectively prepared into hydrogel [24] and microcapsules [25]. Furthermore, manufacturing and

using polysaccharide-based products is considered the promising way of transiting towards low-carbon economy. Lowering the amount of carbon released into the atmosphere would mitigate the global climate change that is already having effects on our health, environment, and economy. Also, Advances in polysaccharide production technology is an important approach in pursuing the Sustainable Development Goals (SDGs). SGDs were established by the United Nations in 2015, with the aim to protect the planet in a socially and economically sustainable manner [26]. Two of the goals of SGDs include 1) responsible consumption and production and 2) good health and well-being. This could be achieved by eco-friendly technologies based on renewable sources.

In this review, we present an overview of different types of polysaccharides and the progress in biomedical applications including drug delivery systems, tissue engineering, face masks, and biosensors. The advantages and challenges of using a certain polysaccharide for each application are also discussed.

2) Background and Types of Polysaccharides

2.1) Cellulose and its derivatives

Cellulose is the most abundant renewable polymer mainly derived from plants and also some bacteria, e.g. *Acetobacterxylium*. It is made of glucose units linked by 1, 4-β-glucosidic bonds [27]. Due to intensive intermolecular hydrogen bonding, cellulose is difficult to dissolve. It is insoluble in water and only a few classes of solvents, such as *N,N*-dimethylacetamide (DMAc) in the presence of lithium chloride [28], ammonium fluorides/dimethylsulfoxide (DMSO), and also *N*-methyl-morpholine-N-oxide (NMMO) [29]. In general, the interesting properties of cellulose include high crystallinity, high stiffness, high chemical resistance, and high dimensional stability. They show good stability to fluctuations in pH and temperature [30].

When compared to plant cellulose, bacterial cellulose (BC) consists of a network of much finer fibers, in the nanoscale range. Plant-derived cellulose generally contains non-cellulosic materials that needs to be removed, for instance, lignin, hemicellulose, and pectin. On the contrary, BC consists of cellulose with high purity and also possesses larger water retention capacity and superior strength [27]. Either in its pure or modified form, BC has significant potential in various fields such as food ingredient, environmental remedies, electronics, and biomedical field. The beneficial properties of BC for wound healing materials include good biocompatibility, water retention, strength, and permeability to gas and liquid. It is also a promising platform for transdermal drug delivery [31].

Cellulose derivatives are obtained by chemical modification of cellulose, typically by esterification or etherification of the hydroxyl groups of cellulose. Derivatization of the native cellulose can result in cellulose derivatives with improved solubility and processibility. Therefore, cellulose derivatives have found extensive uses, ranging from construction products, ceramics, foods, cosmetics, and pharmaceuticals [32]. The physicochemical properties of cellulose derivatives can be adjusted to meet the criteria of the desired products.

One important class of cellulose derivatives is cellulose ethers, such as ethyl cellulose, hydroxy ethyl cellulose, methyl cellulose, sodium carboxy methyl cellulose. They are prepared by etherification of cellulose with aqueous sodium hydroxide followed by alkyl halide [32]. The other important class is cellulose esters, obtained by replacing all or a portion of hydroxyl groups of the cellulose with acetyl groups. Examples of cellulose esters are cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, and cellulose acetate phthalate [33].

The outstanding biocompatibility of cellulose and its derivative, combining with their low-cost and renewability, rendered them excellent candidates as biomedical materials. Although cellulose and its derivatives can be degraded by microorganisms in the

environment, they cannot be degraded *in vivo* due to the absence of suitable mammalian enzymes. In other words, cellulose and its derivatives are generally biodurable [27].

Cellulose has been used as a reinforcing agent for preparation of polymer composites to improve the mechanical properties of the biomedical devices. They can be prepared in various forms such as films, membranes, hydrogels, and nanoparticles.

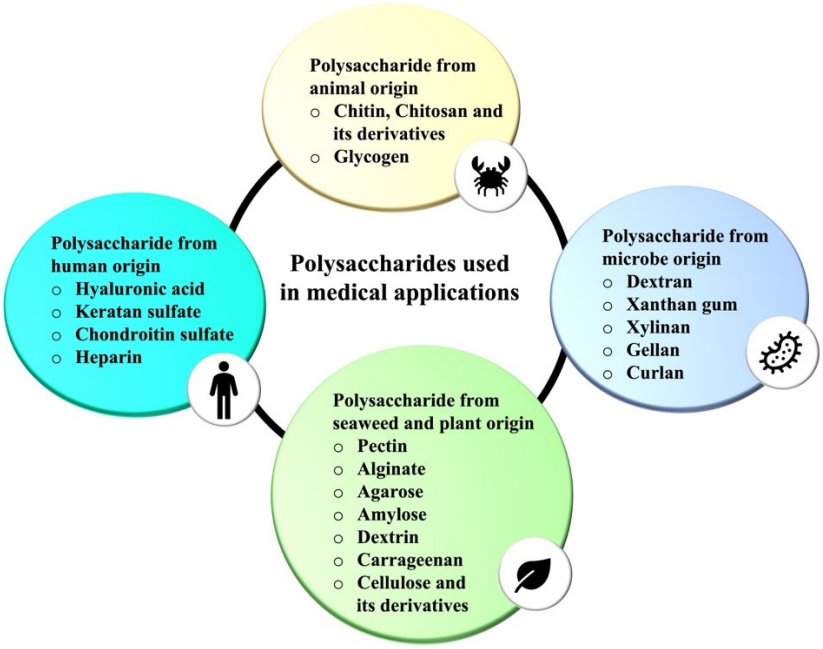


Figure 1 Polysaccharides used in medical applications

2.2) Chitin and chitosan

Chitin and chitosan are considered as the second most popular polysaccharides for biomedical research. Chitin consists of *N*-acetyl-D-glucosamine, an amide derivative of glucose. It is commonly found as a primary composition of cell wall in fungi and the exoskeletons of arthropods such as crustaceans and insects [34, 35]. Chitosan is obtained by partial deacetylation of chitin through enzymatic or chemical treatments[36], therefore chitosan contains randomly distributed β-(1→4)-linked D-glucosamine and *N*-acetyl-D-glucosamine, referred to as deacetylated units and acetylated units, respectively.

Chitosan is a polycation, because it contains free amino groups that can be protonated in acidic environment. Because of this, chitosan is soluble in acidic, but not in neutral or alkaline aqueous solutions[37]. Recently, Kulkarni et al [38] reviewed the role of chitosan in drug delivery systems. In addition to the excellent biocompatibility and biodegradability, chitosan exhibited anti-inflammatory and immunomodulatory properties. It has high potential for controlled drug release and can be designed into various forms for dosage such as pellets, microspheres as well as nanoparticles. Hamedi et al [39] highlighted the role of chitosan as mucosal adhesive essential property in biomedical uses. This feature of self-adhesion of chitosan for medical technology is attractive for sutureless surgery [40-42].

2.3) Hyaluronic acid

To date, one of the most important polysaccharides for medical research is hyaluronic acid, also called hyaluronan. Hyaluronic acid is a natural polysaccharide found in human cartilage. This polysaccharide is regarded as an essential part of extracellular matrix (ECM), a three-dimensional network consisting of extracellular macromolecules and minerals that provide the structural and biochemical integrity to cells [43, 44]. It is structurally defined as an anionic polymer and is a non-sulfated class of glycosaminoglycan (GAG). Hyaluronic acid composed of two repeating units, linear disaccharides β-(1→4) linked D-glucuronic acid, and β-(1→3) linked 2-acetamino-2-deoxy-D-glucopyranose [45-47]. Therefore, it is highly pH-dependent and under physiological conditions forms salts due to the presence of negative charges on the main chain. One of the most significant physical characteristics of hyaluronic acid is its very high water absorption capacity. This is due to the presence of hydrophilic -OH and -COOH groups which can create intramolecular hydrogen bonding within polymeric chain to form a three-dimensional network. Furthermore, it is highly water soluble. It forms a highly viscous solution upon dissolution and has a unique viscoelasticity [48, 49]. Recently, Zheng et al [50] reviewed the role of hyaluronic acid-based materials for bone regeneration.

Hyaluronic acid-based scaffolds have excellent potential for bone formation. They can be used as a drug delivery vehicle for bone repair. Harrer et al [19] also suggested that, due to biocompatibility and biodegradation, hyaluronic acid exhibited excellent properties for both *in vitro* and *in vivo* applications. It was therefore evaluated for the possible use in rheumatology, ophthalmology as well as for cancer treatment [20].

2.4) Alginate

Another extensively studied and used polysaccharides in the biomedical field is alginate, or algin. Alginate is an anionic and edible polysaccharide extracted from brown algae, called *Phaeophyceae, Ascophyllum, Durvillaea, Ecklonia and Laminaria* [17, 18, 51-53]. Various methods such as acid hydrolysis, enzymatic degradation, and microbial fermentation have been employed in the extraction of alginate oligosaccharides which present superior biological activities [54]. Also, bacterial biosynthesis may provide alginate with more defined structures and physical properties than algae-derived alginate[55]. Alginate has attracted considerable attention in pharmaceutical research because of its antitumor, antidiabetic, antimicrobial as well as antioxidant properties [56, 57]. Furthermore, it has been increasingly used for tissue engineering due to its ability to produce porous three-dimensional hydrogels, making it an ideal bio-inert matrix [58]. Besides being used as a stabilizing agent in the food industry, alginate also provides various health benefits. For example, it helps in cutting the health risks linked to induced metabolic disorders by lowering the absorption rate of nutrients. [59]. Recently, Raus et al [60] reviewed the role of alginate and its gelation in the formation of composites for biomedical applications. It is known that good mechanical properties of the alginate gels could be obtained by using the high-molecular-weight polymer. However, this results in high viscosity, not suitable for biomedical products. Viscosity could be minimally increased if using a mixture of high- and low-molecular weight-alginate polymers [55]. It has also been found that pristine alginate becomes softer when in contact

with physiological environment, making it unsuitable for soft tissue regeneration for load-bearing body parts. To overcome this issue, alginate-based composites were developed for superior dimensional stability. Mallakpour et al. [61] have explored the role of three dimensional printing process in alginate-based composites preparation. This technique can be scaled up for industrial commercialization, hence opening the possibility for mass production. This technique has also allowed the production of implant devices with controllable size and shape for healthcare products. These were prepared from bio-ink into which alginate was incorporated to allow for a fast and cytocompatible crosslinking after production as discussed by Ahlfeld et al. [62, 63].

2.5) Pectin

Pectin is a complex mixture of polysaccharides found in the primary cell walls of a wide variety of fruits and vegetables. It consists of a poly(D-galacturonic acid) with an average molecular weight of about 50–190 kDa[64]. Because pectin comprises of carboxylic acid and hydroxyl groups, it can be covalently bonded with other biomolecules or proteins[63]. Various enzymatic treatments have been employed to modify the pectin structure to make it suitable for medical applications [65]. Methods such as cold plasma, pressure-based technology, and high-speed shearing have been reported [66-68]. Not only widely used in food industry owing to its gelling activity, pectin has also found widespread use in the biomedical uses, mostly as drug delivery vehicles. For example, binding calcium salts to the enzymatically-degraded, water-resistant pectin derivatives, rendered the product a good candidate for colonic drug delivery [64]. The hydroxyl groups of pectin can be converted into the aldehyde groups capable of reducing metal salts into metal nanoparticles. Pectin-coated metal nanoparticles can be used to develop electrochemical sensors for environmental monitoring or disease diagnosis [63]. Recently, Agarwal et al [69] developed a pectin-based ink

formulation for three-dimensional printing, a technique which is promising for use in tissue engineering and food manufacturing.

2.6) Polysaccharide-based blends and composites

Although pristine polysaccharide-based materials provide numerous benefits for medical uses, some limitations still exist, such as difficulty of fabrication and low stability especially in strong acidic conditions or in the presence of enzymes. The design of blend and multifunctional composite materials has offered a great opportunity to overcome those limitations. Polymer blends are made of two or more types of polymers and can be classified as immiscible blend, compatible blend, and miscible blend [70-72]. Composites are produced from two or more constituent materials with different chemical and physical properties. A composite material consists of a continuous phase (a matrix phase) and a non-continuous phase (a reinforcing phase). There exists an interface between the two [73].

Polysaccharide blends and composites have been developed in order to tailor the critical and challenging properties needed for medical applications. For instance, pristine chitosan offers outstanding properties in terms of biocompatibility and antibacterial activity, yet it presented poor mechanical properties and low dimensional stability. Seidi et al [74] reviewed the modification of chitosan-based binary blends with various types of polysaccharides such as alginate, starch, cellulose, and dextran. Park et al summarized the medical applications of polysaccharide-based composites [75]. Nanocrystals and nanofibrils of bacterial cellulose (BC) as reinforcement in composite scaffolds have received considerable attention in the past few years. In addition, various metal nanoparticles such as Ag, ZnO and TiO_2 have been incorporated into the scaffolds to impart antimicrobial properties [76]. BC nanofiber clusters have shown to significantly improve strength and toughness of polyacrylamide because of extensive hydrogen bonding between the nanofiber clusters and the polymer matrix [77].

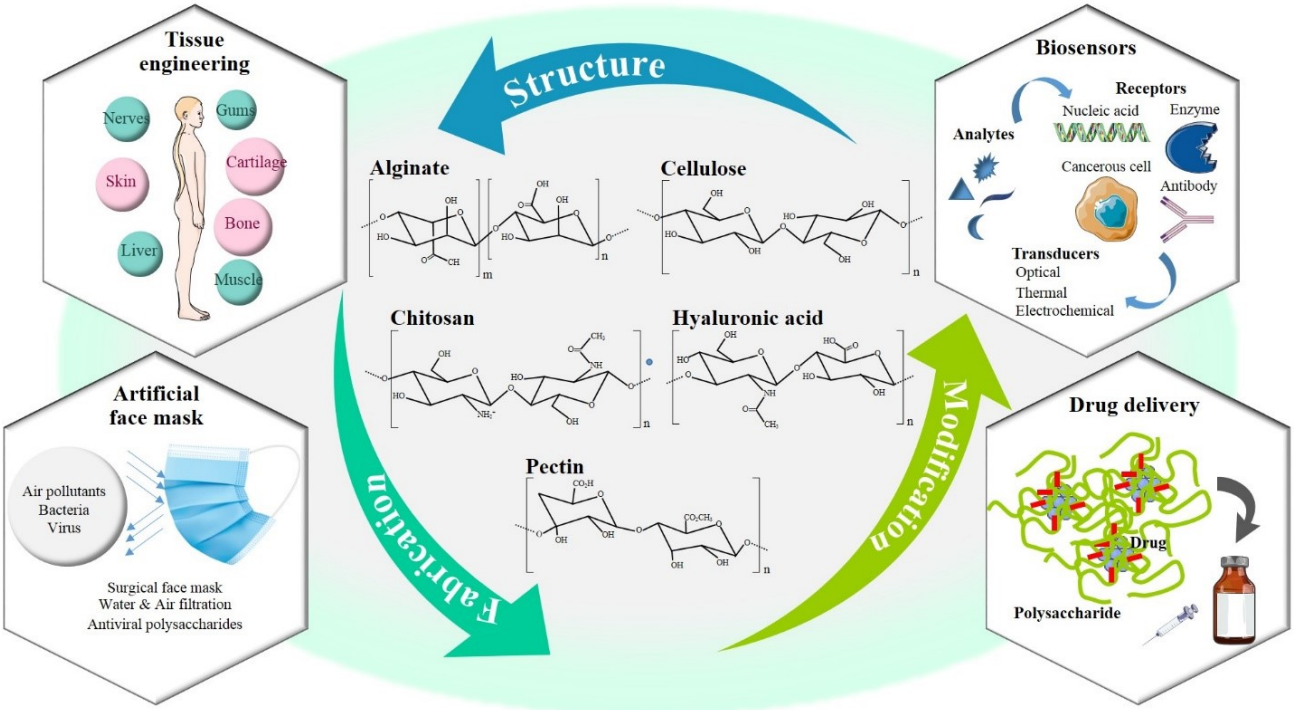


Figure 2 Molecular structures of polysaccharides and their biomedical applications

3) Types of materials used in medical applications

3.1) Hydrogels

Hydrogels are three dimensional networks of hydrophilic polymers capable of swelling and absorbing large amounts of water (at least 10% of the total weight or volume). Their ability to absorb water originates from the presence of hydrophilic groups of the polymer molecules such as $–NH_2$, -COOH, -OH and -CONH. Their resistance to dissolution is due to the presence of crosslinks between the polymer chains [78].

Hydrogels can be classified based on various criteria. They can be classified as naturally-derived or synthetic. Due to the great abundance, non-toxicity as well as biocompatibility of polysaccharides, these hydrogels have been widely used for medical and pharmaceutical technology [1]. Hydrogels can also be classified according to the crosslinking strategies used, that is, physical crosslinking and chemical crosslinking.

Physical crosslinking of hydrogels relies on strong intermolecular interactions such as electrostatic forces, hydrogen bonding and hydrophobic forces throughout the hydrogel network [79]. However, physically-crosslinked hydrogels can be disintegrated by changes in the environment conditions such as ionic strength, pH, and temperature. One important type of physical crosslinking is ionic crosslinking which occurs between two oppositely charged molecules or polyelectrolytes. Polyanions such as alginate can form ionic crosslinking with multivalent counterions (such as Ca^{2+}, Mg^{2+}, and Ba^{2+}) and with cationic polymers such as chitosan.

On the other hand, chemical crosslinking results in covalent bonding between smaller molecules to form a permanent hydrogel network. This is achieved using a chemical crosslinking agent or ionizing radiation [80]. The chemically-crosslinked hydrogels may be charged or non-charged depending on their functional groups. For charged hydrogels, their swelling behaviors are greatly affected by pH and they also display changes in shape when subject to electric field [81]. Formaldehydes and glutaraldehyde are effective covalent crosslinkers for polysaccharides through reactions with the hydroxyl groups of these biopolymers but their toxicity could present a risk to the biosafety of biomaterials. Some safer chemical crosslinkers have been reported such as cinnamaldehyde, citric acid, and several plant-derived phenolic compounds, including tannic acid [82]. Genipin, present in fruit of *Gardenia jasminoides*, is a biocompatible crosslinker for amino-containing polymers such as chitosan but its use results in a dark blue color of the crosslinkeed products[83].

Moreover, hydrogels can be created by interpenetrating networks (IPNs), which can be achieved by crosslinking/synthesizing at least one of the polymers in the presence of the other polymer(s), without forming covalent bonds between them. The polymers constituting IPNs cannot be separated unless chemical bonds are broken. A fully IPN can be obtained

when a crosslinker is used. In the absence of a crosslinker, a semi-IPN which is a network having linear polymers embedded within the first polymer network is formed [84].

Apart from high water absorbency, hydrogels also possess promising properties such as flexibility, porosity, stimuli-responsive and can be engineered to mimic natural tissues. Owing to the biocompatibility, biodegradability and great abundance of polysaccharides, the polysaccharide hydrogels are very attractive for biomedical applications. They can be processed into solid, semi-solid and liquid by adjusting their physicochemical properties and crosslinking conditions. At present, commercial hydrogel products are mainly in the medical field, for instance, drug delivery devices, wound dressings, contact lenses, scaffolds, and cosmetics [85]. Polysaccharide hydrogels as wound dressings can provide suitable moisture for the wound and act as a barrier against bacteria. To prepare cellulose hydrogels form native cellulose, chemical dissolution is required for example with ionic liquids or LiCl/dimethylacetamide, but hydrogels based on water-soluble cellulose derivatives (such as methyl cellulose and sodium carboxymethyl cellulose) can be prepared using water. A variety of hydrogels based on cellulose derivatives have been found promising for use in healthcare and hygienic products [86].

Chitosan hydrogels have been widely used for wound healing, drug delivery, and tissue engineering. They have been shown to improve the formation of bones, but blending with calcium phosphate or alginate was needed to improve their mechanical properties [87].

Hyaluronic acid hydrogels have been found to impart biological activity to cells, leading to changes in cellular behavior. Their potential use is in translational applications [88]. Injectable HA hydrogel exhibits good capacity for water absorption and high swelling ability, along with temporary mechanical integrity under physiological conditions. It was found to enhance cartilage-specific synthesis of extracellular matrix by stem cells [89].

Alginate-based hydrogels are interesting because alginate salts have been recommended by European Food Safety Authority in various foods for children [90] and help reducing glucose uptake and cholesterol [91]. They can protect and improve the probiotic functioning in a hostile environment, prolonging the release of probiotics and improve their viability in intestinal solution [92].

Pectin is hypoglycemic and hypochloresterolemic which is beneficial to human health. However, to its insufficient mechanical strength and too fast degradation rate for use as drug delivery devices and scaffolds, so the pectin-based hydrogels required the combination with other organic or inorganic compounds to improve these properties [93].

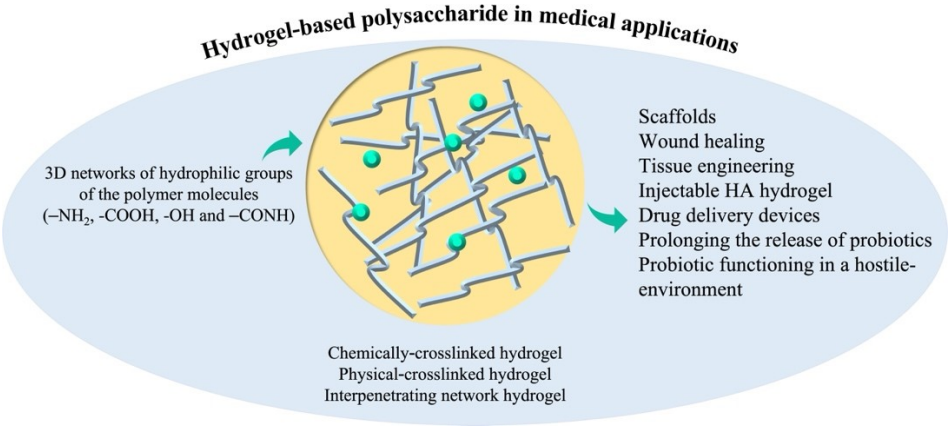


Figure 3. Hydrogel-based polysaccharides in medical applications

3.2) Nanoparticles

Nanoparticles are ultrafine particles whose size ranges from 1 to 100 nanometers (nm), but the term can be applied for larger particle sizes expressed in nm [94]. Development of nanoparticle-based technology has been steadily growing in biomedical, pharmaceutical, cosmeceutical, and food industry [95]. Numerous applications are possible with nanoparticles,

especially in the biomedical field. This includes therapeutics, diagnostics, imaging, and drug delivery. By using smart nanoprobes, disease diagnosis could be done inside the body or by analyzing the biological fluids such as blood or urine. Nano-based drug delivery systems such as polymeric nanoparticles, liposomes, and dendrimers are being intensively studied [96]. Nanoparticles used for targeted drug delivery allow for therapeutic substances to be encapsulated and thus protected from the surroundings, before being transported to specific sites [94]. They have also found applications in tissue engineering and regenerative medicine [96].

Polysaccharide-based nanoparticles are beneficial in terms of good stability and low toxicity in physiological environment. They are biodegradable, biocompatible, and are derived from sustainable feedstocks. The carboxyl and hydroxyl groups distributed along their backbones facilitate chemical modification to achieve certain properties required for specific applications [95].

Common strategies for the synthesis of polysaccharide-based nanoparticles are ionic/chemical crosslinking, self-assembly of hydrophobically modified polysaccharides, forming polysaccharide-drug conjugates, and complexation of polyelectrolytes with opposite charges [94] as shown in Figure 4.

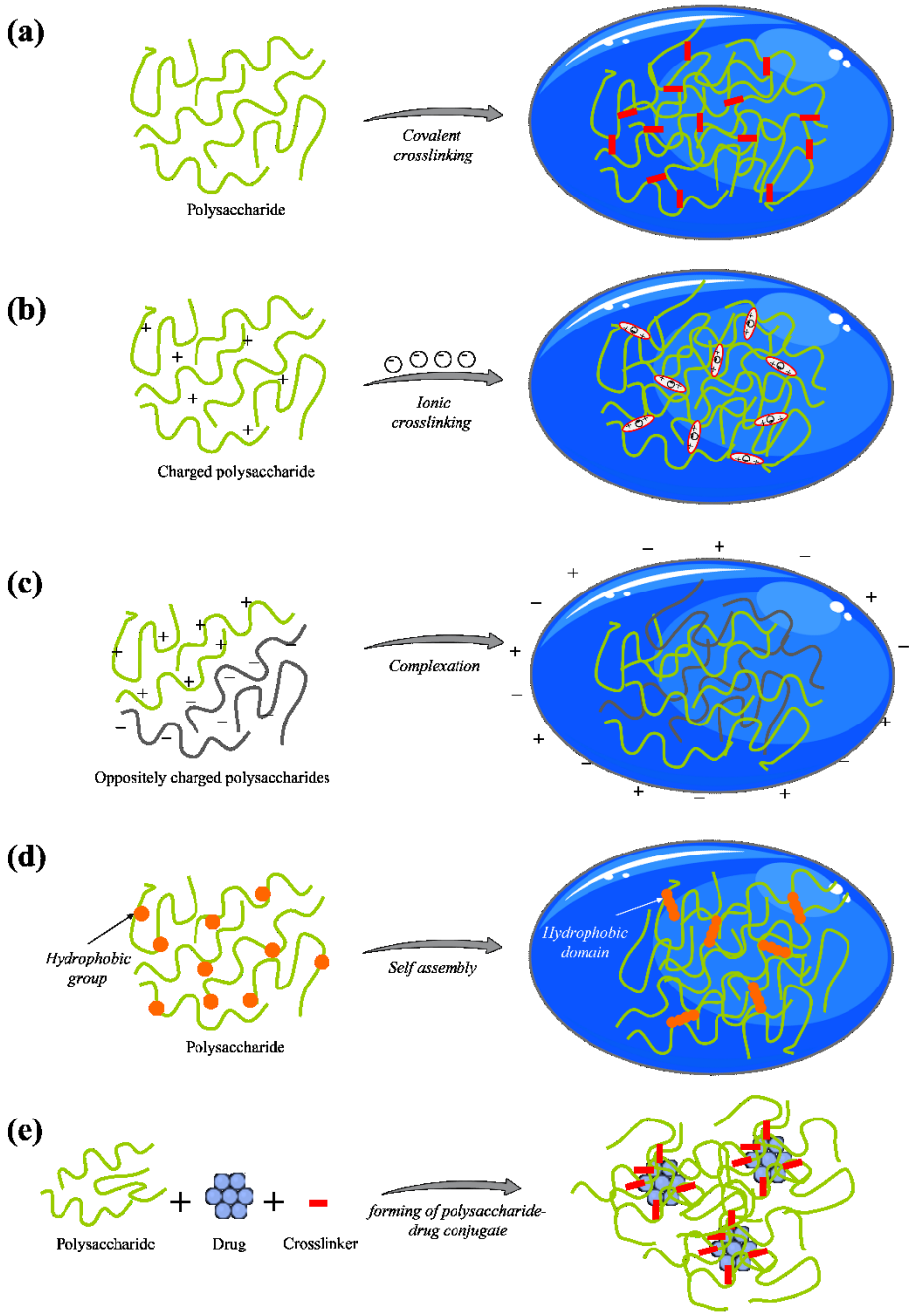


Figure 4 Strategies for the formation of polysaccharide-based nanoparticles: (a) covalent crosslinking (b) ionic crosslinking (c) complexation (d) self-assembly and (e) forming of polysaccharide-drug conjugate [95, 97].

Preparation techniques widely used for the formation of nanoparticles are nanoprecipitation, complex coacervation, and emulsification. In brief, nanoprecipitation is conducted by dissolving both the polymer and the hydrophobic solute in the organic solvent,

then adding the non-solvent such as water. This leads to a rapid precipitation of polymer occurs in the form of nanoparticles with the solute inside [95, 98]. Complex coacervation is a widely used technique for preparing polysaccharide nanoparticles. It is carried out by mixing aqueous solutions of two polymers with opposite charges such as a cationic chitosan and anionic hyaluronic acid [95]. This technique has advantages of simplicity and no organic solvent is required. Emulsification is the generation of mixtures of two or more immiscible liquids in which one or more liquids are dispersed in another liquid. Emulsions can be classified as a direct system - water-in-oil, suitable for encapsulation of hydrophobic solutes, or inverse system- oil-in-water, which is suitable for encapsulation of hydrophilic solutes. More complex emulsions such as oil-in-water-in-oil and water-on-oil-in-water also exist [99]. Typically, surfactants and stabilizers are used to stabilize emulsion droplets. Elzayat et al. [100] has published a great review which summarize the principles of emulsification techniques for the synthesis of biomedical carriers.

Although it is expected that nanoparticles are more effective than conventional drugs due to their larger surface area, the nanoparticles tend to aggregate, leading to poor flow properties. It has been proposed that transforming nanoparticles into core-shell nanocomposite microparticles could solve the aggregation issue of nanoparticles, which could be done by combining nanoparticles on inert carrier pellets via a polymeric coating dispersion [101, 102].

Recently, Carrasco-Sandoval et al. [103] studied the properties of alginate and chitosan coated zein nanoparticles. Encapsulation of phenolic compounds was carried out by nanoprecipitation. Zein nanoparticles were then coated with alginate and chitosan by electrostatic deposition. Excellent encapsulation efficiency and bio accessibility were developed for medicinal usage. Xu et al. [104] developed hyaluronic-based nanoparticles for

tissue engineering. Lactoferrin was successfully coated onto hyaluronic molecule. *Ex vivo* image presented the excellent properties to targeted cell for brain.

3.3) Membranes

Membranes refer to a selective barrier that allows certain molecules, ions and small particles to pass through. They can be classified based on their pore size into conventional filtration (from 100-10 μm), microfiltration (from 10 to 0.1 μm), ultrafiltration (from 0.1 μm to approx. 50 Å), nanofiltration and reverse osmosis (pore size down to approx. 1 Å) [105]. Apart from separation by size, using membranes with electrical charges enables better control of membrane selectivity between the membrane and the charged components due to electrostatic interactions. Adjusting voltage, pressure, and concentration gradient can be done to control the mobility molecules, ions and particles [106].

The advantage of membranes is particularly due to high porosity and selectivity for specific molecules. To date, various types of polysaccharides have been employed to design selective membranes for medical usage. Polysaccharide-based membranes have been primarily fabricated by various techniques including solution regeneration, electrospinning, vacuum filtration and phase inversion, as suggested by many previous literatures [107, 108]. Furthermore, they can be prepared into various ranges of thickness, with homogeneous and heterogeneous structure. Li et al [109] developed chitosan based selective membranes with antioxidant and antibacterial activity. They also exhibited biocompatibility and biodegradability, therefore showing good potential in practical applications such as in wound dressing.

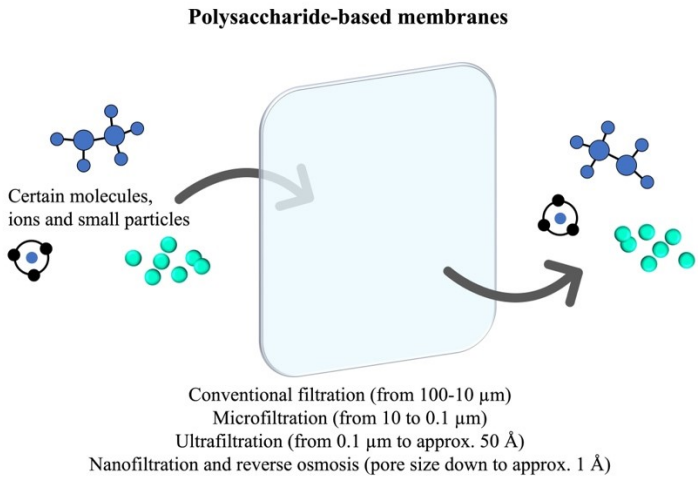


Figure 5 Polysaccharide-based membranes

3.4) Porous media

Porous media and/or porous materials are materials containing pores typically filled with a fluid. The main portion of these materials is called a matrix. The existence of porosity can be employed as a tank for liquid storage, while solid part serves as framework [110, 111]. This feature offers the potential use in wound dressing and drug delivery applications. Recently, Zhang et al. [112] developed chitosan and cellulose blends into a three-dimensional porous network by self-assembly technique which showed excellent biocompatibility and bioactivity for wound healing process. Wang et al. [113], successfully prepared an alginate-based porous network as hemostatic sponges which can accelerate the blood coagulation of artery bleeding.

Various types of polysaccharides were prepared for medical uses. Figure 6 summarizes the different forms of polysaccharide used for medical technology.

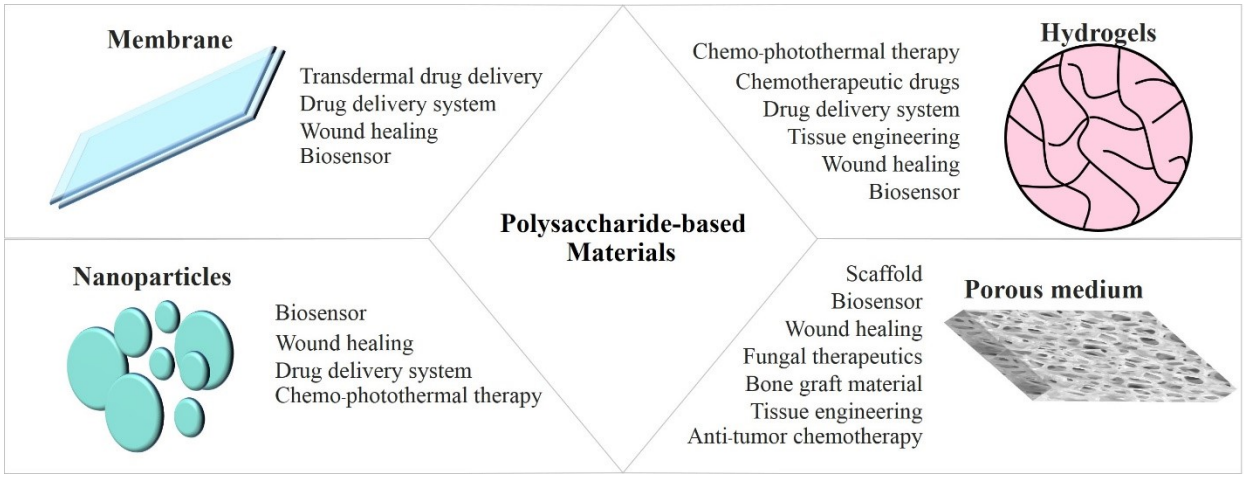


Figure 6. Forms of polysaccharide-based materials for medical technology

Table 1 Summary of polysaccharide materials for medical technology

Materials	**Form of material**	**Application**	**References**
Cellulose and derivatives			
Cellulose nanofibril	Hydrogel	Chemo-photothermal therapy	[114]
Antimicrobial cellulose	Hydrogel	Wound healing	[115]
Regenerative cellulose	Hydrogel	Drug delivery system	[116]
Bacterial cellulose	Membrane	Wound healing	[117]
Cellulose sheet	Porous medium	Scaffold	[118]
Deacetylated cellulose acetate	Nanoparticle	Wound healing	[119]
Carboxymethyl cellulose	Nanoparticle	Chemo-photothermal therapy	[120]
Cellulose nanofiber	Porous medium	Biosensor	[121]
Cellulose	Porous medium	Wound healing	[122]

Bacterial cellulose	Porous medium	Tissue engineering	[123]
Chitin-chitosan			
Chitin	Nanoparticle	Drug delivery system	[124]
Carboxymethyl chitin	Porous medium	Anti-tumor chemotherapy	[125]
Chitin nanowhisker	Hydrogel	Drug delivery system	[126]
Amorphous chitin	Nanoparticle	Drug delivery system	[127]
Chitin	Hydrogel	Drug delivery system	[128]
Chitosan/cefazolin coatings on Ti	Membrane	Drug delivery system	[129]
Carboxylated chitosan	Porous medium	Drug delivery system	[130]
Chondro-inductive chitosan	Hydrogel	Tissue engineering	[131]
Vanillin-bioglass-chitosan	Porous medium	Tissue engineering	[132]
Polycaprolactone (PCL)-chitosan	Porous medium	Tissue engineering	[133]
Hyaluronic acid			
Hyaluronic acid	Hydrogel	Chemotherapeutic drugs	[134]
Hyaluronic acid	Membrane	Transdermal drug delivery	[135]
Hyaluronic acid-functionalized halloysite nanotube	Porous medium	CD44-overexpressing cancer cells	[136]
Hyaluronic acid loaded with silica particle	Porous medium	Drug delivery system	[137]

Hyaluronic acid/poly vinyl alcohol	Membrane	Biosensor	[138]
Polydopamine/hyaluronic acid	Membrane	Biosensor	[139]
Polypyrrole-sulfonated graphene/hyaluronic acid	Porous medium	Biosensor	[140]
Hyaluronic acid/chitosan	Hydrogel	Wound healing	[141]
Hyaluronic acid bilayers	Scaffold	Osteochondral defect regeneration	[142]
Hyaluronic acid/chitosan	Scaffold	Cartilage tissue engineering	[143]
Alginate			
Alginate/chitosan/hydroxyapatite	Scaffold	Cartilage regeneration	[144]
Alginate coated lactose modified chitosan	Scaffold	Dental pulp stem cells proliferation and differentiation	[145]
Bioglass/chitosan/alginate	Porous medium	Bone graft material	[146]
Alginate/silica particle	Porous medium	Fungal therapeutics	[147]
Alginate/folate	Hydrogel	Drug delivery system	[148]
Alginate with 5-fluorouracil	Nanoparticle	Drug delivery system	[149]
Sterculia gum-alginate-carbopol	Hydrogel	Drug delivery system	[150]
Starch modified alginate	Nanoparticle	Drug delivery system	[151]
Alginate/graphene oxide/polyacrylamide	Hydrogel	Biosensor	[152]
Alginate/methylcellulose	Hydrogel	Biosensor	[153]

Pectin			
Citrus pectin modified carbon paste	Porous medium	Biosensor	[154]
Pectin/xanthan	Membrane	Biosensor	[155]
Pectin/alginate	Porous medium	Tissue engineering	[156]
Apatite/chitin/pectin	Porous medium	Tissue engineering	[157]
Metal oxide/pectin	Porous medium	Tissue engineering	[158]
Pectin/chitosan	Hydrogel	Drug delivery system	[159]
Pectin/modified copper-based metal-organic framework	Membrane	Drug delivery system	[160]
Pectin/modified nano-carbon sphere	Hydrogel	Drug delivery system	[161]
Pectin-deoxycholic acid	Hydrogel	Anticancer drug delivery	[162]
Pectin/chitosan bead	Hydrogel	Colon targeted drug delivery	[163]

4) Applications of polysaccharide in medical technology

4.1) Tissue engineering

Tissue engineering is a powerful tool for repairing, regeneration, and replacement of damaged tissues or organs. The tissue engineering scaffolds provide a template for reconstruction of damaged tissue, promoting cell attachment, cell proliferation and also restoration of extracellular matrix (ECM). They are porous or fibrous to ensure high surface-to-volume ratio, therefore are capable of supporting cell attachment and allowing transport of body fluids and gases. Scaffolds with pores larger than 100 μm allow tissue growth and

vascularization, 10-75 μm accommodate only fibrous tissue, pores between 2-50 nm facilitate cell adhesion and resorbability at controlled rates [164]. Scaffolds can be permanent or biodegradable depending on their applications. For biodegradable scaffolds, suitable and controlled degradation rate is required without toxic products generated. Also, immunological response should not occur. Factors that need to be considered for the preparation of scaffolds include mechanical, physicochemical, and biological properties. Biological events following the injury can be mimicked and controlled by adding bioactive species (such as growth factors, peptides, genes, antibodies and drugs, etc.) to the scaffolds[165]. Fabrication methods that have been developed for scaffold preparation include solvent casting, porogen leaching, self-assembly, gas foaming, electrospinning, phase preparation, rapid prototyping, fiber mesh, fiber bonding, melt molding, and membrane lamination [166]. Recently, 3D bioprinting of bio-inks made from polysaccharide has been employed to precisely controlling the microstructure of scaffolds, capable of generating biomimetic complex tissue architecture [167].

The structural and functional diversity of polysaccharides and their biocompatible and biodegradable properties have attracted increasing research interest in the tissue engineering field.[165]. Significant progress has been made in the production of polysaccharide-based scaffolds but each type of polysaccharide has its own advantages and limitations. Some important aspects to consider for the design of polysaccharide-based scaffolds are provided.

4.1.1) Effects of polysaccharide characteristics on the properties of scaffolds

4.1.1.1 Cellulose and its derivatives

Cellulose and cellulose derivatives have been extensively used in biomedical field. Novel cellulosic materials, in particular, those having nanoscale fibrillar structure are receiving considerable attention in the growing field of tissue engineering. Biocompatibility and ease of surface modification along with the reasonable cost make the cellulose and

cellulose derivative-based scaffolds attractive. However, it has been found that the high degree of crystallinity and lack of cellulolytic enzymes in the mammalian tissues lead to low or non-biodegradability of cellulose. However good thermal stability allows for ease of sterilization. To improve biodegradability, incorporation of a suitable enzyme such as cellulase into the scaffolds as well as irradiation with γ beam or electron beam have been reported [168]. Cellulose derivatives have also been widely studied for scaffold materials. The water-soluble ones are preferred for biomedical applications. Their favorable features include solubility, viscosity, surface activity, and thermoplastic-like behaviors [30].

Torgbo and Sukyai [169] fabricated nanocomposite scaffolds based on bacterial cellulose, Fe_3O_4, and hydroxyapatite nanoparticles which were generated through ultrasonic radiation. The prepared scaffolds had a high potential for osteogenesis. In the case of corneal tissue engineering, pure bacterial cellulose film was evaluated as a scaffold for corneal stroma restoration. Epithelial and stromal cells grew well on bacterial cellulose film and showed acceptable cell morphologies. The optical clarity of the corneal stroma was preserved [170]. Abouzeid et al. [171] designed a 3D printed composite scaffold for bone regeneration using alginate and tempo-oxidized cellulose nanofiber. The tempo-oxidized cellulose nanofiber performed essential functions in this scaffold and can be used to create a dual network with alginate to improve the mechanical strength of the hydrogels, but this has no effect on the printability of the composite printing inks. Tempo-induced carboxyl groups, on the other hand, have a beneficial effect on the nucleation of hydroxyapatite in simulated bodily fluid. In several studies, cellulose has been used as reinforcement in composite scaffolds. For example, Abudula et al. [172] created electrospun composite scaffolds made of polylactic acid and polybutylene succinate, which were reinforced with cellulose nanofibers. The composite scaffolds showed improvements in mechanical properties and cell adhesion, indicating their potential in vascular tissue engineering applications. Carboxymethyl cellulose

was crosslinked with citric acid and subjected to freeze-drying process. The prepared scaffolds were promising for bone tissue engineering application [173].

4.1.1.2 Chitosan

Chitosan is widely used for the fabrication of scaffolds due to the present of abundant amino and hydroxyl groups along the chains. These groups can participate in various physical effects and chemical reactions, to meet the application requirements. The presence of cationic moieties along the chains makes chitosan an antimicrobial biopolymer, which is a desirable characteristic for scaffolds. By conjugating chitosan with catechol or catechol derivatives have been shown to improve adhesive properties of the chitosan-based scaffolds [167]. As chitosan has a similar structure to glycosaminoglycans, which are the major components of bone tissue's extracellular matrix, chitosan and its derivatives have gained much research interest in the field of bone tissue engineering [174]. They have been found to promote cellular differentiation and expression of extracellular matrix (ECM) proteins in osteoblasts and chondrocytes to facilitate osseointegration [175]. Chitosan has also been employed for surface modification of metallic implants, to enhance corrosion resistance. to metal implants and biocomposite scaffolds in bone tissue engineering [175].

Sadeghi et al. [176] created conductive scaffolds based on poly(ε-caprolactone) and polypyrrole for neural tissue engineering, and found that incorporation of chitosan significantly improved hydrophilicity of the scaffold. Prabhakaran et al. [177] discovered that PCL/chitosan nanofibrous scaffolds were more biocompatible and capable of cell proliferation with rat Schwann cells than PCL scaffolds. Saekhor et al. [178] developed an injectable chitosan-based hydrogel by first modifying chitosan with carboxymethyl chloride. The obtained carboxymethyl-chitosan was then conjugated with α-cyclodextrin to produce water-soluble conjugates capable of forming thixotropic gels with polyethylene glycol. The gel was shown to be compatible with human osteoblastic cells (SaOS-2 cells), indicating that

it might be used as an injectable scaffold in bone healing. Pezeshki-Modaress *et al.* [179] investigated the role of chitosan in gelatin/chitosan scaffolds in skin tissue engineering. Human dermal fibroblast cells were successfully adhered and disseminated on macroporous scaffolds with chitosan content (approximately 30%) optimized as a scaffold condition. Maturavongsadit et al. [180] created the first chitosan-based injectable hydrogel incorporating cellulose nanocrystals (CNC) as a reinforcing agent and β-glycerophosphate and hydroxyethyl cellulose as gelling agents. The CNC-chitosan hydrogel displayed immediate gelling behavior at body temperature and high encapsulated cell viability. In vivo tests revealed that neither acute nor chronic systemic inflammation developed in any of the hydrogel groups after injection. This innovative scaffold has the potential to promote bone regeneration by in situ injection of encapsulated stem cells from patients.

4.1.1.3 Hyaluronic acid

Hyaluronic acid (HA) and HA derivatives are considered excellent candidate as scaffold materials. HA plays an important role in cell signaling and wound healing processes and therefore is capable of creating the scaffolds that can mimic the structure and function of the native extracellular matrix. The structure of HA is composed of multiple negatively charged hyaluronic acid, enabling HA to bind with water and therefore providing support to the extracellular matrix. They have been widely used in the medical industry for various therapeutic purposes. To promote cell migration and proliferation, HA in the form of nanofibers are advantages but due to the high viscosity and surface tension of HA, electrospinning of HA is difficult. Introducing other polymers such as collagen [181] and gelatin [182] have been found to facilitate electrospinning, otherwise applying high temperature and additional pulling force to the electrospinning process (blowing-assisted electrospinning) could also be done. Polycations could be blended with HA in order to

counteract the negative charges of HA, consequently improving the scaffold's adhesive properties[183].

4.1.1.4 Alginate

Alginate-based hydrogels are a widely studied polysaccharide scaffolds in tissue engineering, with bone regeneration being one of the most important applications [184, 185]. Alginate has many favorable properties such as tunable mechanical properties and good scaffold forming properties. Poor mechanical properties can be improved by crosslinking of alginate by physical method, usually using divalent ions (e.g. Ca^{2+}, Sr^{2+} and Ba^{2+}), but the resulting mechanical properties are inferior to those crosslinked by a chemical method. It should be noted that Ca^{2+} is the most widely used physical crosslinking agent for alginate because of its non-toxicity [186]. Divalent cations of alginate, such as Ca^{2+}, has been found to significantly improve alginate solution viscosity and gelation, as well as strengthen the intermolecular connection [187]. Recently, crosslinking alginate with Fe^{3+} has gained increasing research interest as the obtained material exhibits different properties comparing to those obtained using other ionic crosslinking agents. However, eventual leaching of Fe^{3+} from alginate also prevent long-term application generally required for scaffolds[188].

Garske et al. [189] investigated the regeneration capability of rat mesenchymal stromal cell -laden porous alginate hydrogels in animal models. The results showed that MSCs encapsulated in this alginate hydrogel system had stronger paracrine signaling and fewer inflammatory cells than hydrogels containing stromal cell-derived factor–1α, indicating that alginate hydrogels can be useful in delivering MSCs and thus recruiting endogenous cells via paracrine signaling. Alginate-based composite scaffolds may also be useful in the creation of dermal replacements for skin formation [184, 190, 191]. Solovieva et al.[184] employed freeze-drying to create alginate/fibrinogen composite sponge scaffolds. The hydrogel was treated with thrombin and e-aminocaproic acid (ε-Ac), and crosslinked by Ca^{2+} and Mg^{2+}. Scaffolds

with a 15% fibrinogen content showed the maximum adhesiveness and survival rates for all cell types, demonstrating that they are an effective and low-cost alternative to mammalian collagen as biodegradable scaffolds in large wound skin healing and regeneration. For articular regeneration [192, 193], a novel living hyaline cartilage graft (LhCG) with pure cartilaginous elements was produced. As 3D culture microenvironments for chondrocyte encapsulation, alginate hydrogels crosslinked by Ca^{2+} were applied. The alginate hydrogels may be de-cross-linked by sodium citrate when the cartilage matrix had sufficiently formed and joined. This design has been shown to be useful in constructing pure tissue using temporary scaffolds.

4.1.1.5 Pectin

Pectin contained carboxyl groups in its molecular structure. Due to the presence of negative charges, pectin is soluble in water. Its solubility could be suppressed by adding salt or decreasing pH, leading to gelation [37]. Pectin has not gained as much attention for the preparation of scaffolds as for other polysaccharides described in this review. Literature reports have demonstrated that electrostatic interactions between carboxylate anion of pectin and Ca^{2+} of $Ca(PO_4)_3$ can be adjusted to improve the properties of the bone tissue engineering scaffolds [194].

Pectin hydrogel nanofiber scaffolds were prepared by electrospinning. Periodate oxidation and crosslinking with adipic acid dihydrazide were performed to improve mechanical properties. It was found that the electrospun pectin-based fibers promoted differentiation of mesenchymal stem cells into endothelial cells or into vascular cells[195]. Lapomarda et al [196] prepared pectin-based scaffolds by 3D bioprinting followed by freeze-drying. The pectin solution was cross-linked with 3-glycidyloxypropyl) trimethoxysilane (GPTMS). By controlling the amount of GPTMS, the printability of pectin was improved

owing to higher viscosity and yield stress and the complex shaped-scaffolds with interconnected pores could be achieved.

Table 2 Recent tissue engineering applications of some polysaccharides

Polysaccharide	**Application examples/Target tissue**	**Functions of polysaccharides in the examples**	**Fabrication process**	**References**
Cellulose	As an artificial corneal layer, a pure bacterial cellulose film is used/ Corneal	Provide high light transmittance and superior mechanical qualities	Fermentation synthesis	[180]
Cellulose	Cellulose nanofiber-reinforced polylactic acid-poly (butylene succinate) composite scaffolds/Vessel	Improve cell adhesion and mechanical strength	Electrospinning	[193]
Cellulose	As 3D printing inks, temp-oxidized cellulose nanofiber combined with alginate can construct dual network hydrogel/Bone	Formation of a dual network with alginate and -COOH groups has a beneficial effect on the nucleation of hydroxyapatite	3D printing	[181]
Chitosan	Injectable cellulose nanocrystal/chitosan hydrogel can simulate the bone microenvironment/Bone	At body temperature, chitosan solution can go through the sol-gel transition	Gelling caused by heat	[180]
Chitosan	To functionalize the surface of titanium grafts, chitosan-bovine serum albumin micropatterns were fabricated/Bone	Surface modifier to promote osteoblast attachment & proliferation	Using the Schiff base reaction, chitosan was grafted onto titanium	[197]

Polysaccharide	Application examples/Target tissue	Functions of polysaccharides in the examples	Fabrication process	References
Chitosan	Human osteoblastic cells (SaOS-2) cells were biocompatible with injectable modified chitosan-polyethylene glycol hydrogel/Bone	Injectable hydrogel structure of chitosan was molecularly created	Blending	[178]
Hyaluronic acid	Thiolated hyaluronic acid based composite scaffolds to support human neural stem or progenitor cell function/Neural & vessel	Reduce the rate of fibrin breakdown	Blending	[198]
Hyaluronic acid	Engineered cartilage constructed from hyaluronic acid-based hydrogel/Cartilage	Cell encapsulation	Blending	[199]
Hyaluronic acid	Hyaluronic acid, corn, silk extract, β-tricalcium phosphate-containing thermosensitive, & injectable scaffolds/Bone	Injectable hyaluronic acid hydrogel	Blending	[200]
Alginate	Alginate is used as a sacrificial scaffold in the production of living hyaline cartilage graft/Cartilage	Aid in the preservation of phenotypic cartilage, ionic crosslink ability, non-cytotoxicity & detachability	Ionic crosslinking	[193]
Alginate	Alginate/fibrinogen composite sponge scaffolds with strong cell-binding	Provide biocompatibility & biodegradability	Freeze drying technique, ionic crosslinking	[184]

Polysaccharide	Application examples/Target tissue	Functions of polysaccharides in the examples	Fabrication process	References
	properties/Skin			
Alginate	Microbeads made of alginate and 3D printed fibers to generate porous & channel structures/Adipose	Provide ionic crosslinkability & detachability	3D printing, ionic crosslinking	[201]
Pectin	Pectin grafted with arginylglycylaspartic acid or RGD and spun to form 3D fibrous salf-standing patches capable of supporting muscle tissue regeneration/ muscle	Gelation with Ca^{2+} to form stable microfibers and promote cell proliferation through grafting with RGD peptides	Simple coaxial flow wet-spinning system	[202]

4.2) Drug delivery

Polysaccharides are natural inexpensive biomaterials with promising properties for drug delivery applications, such as biocompatibility, biodegradability, low immunogenicity. They have been used as excipients for traditional pharmaceutical formulations [203, 204]. Due to their diversified structural properties, they exhibit a wide range of functional properties, e.g. solubility and rheology. This allows for fabrication of various forms of drug delivery vehicles, for instance, smart nanocarriers, which have gained increasing interest for cancer treatment. As polysaccharides are derived from natural sources, they may display broad or mixed molecular weight and variable chemistry, which must be taken into account for the design of drug delivery vehicles.

Polysaccharide-based drug delivery systems may be classified based on methods of preparation as: (i) drug-loaded polysaccharide hydrogels, (ii) drug-loaded self-assembled polysaccharide particles (iii) polysaccharide-drug conjugates via cleavable bonds. The third category relies on chemical bonding such as covalent bonding, or physical interactions such as ionic forces. Figure 7 depicts the primary design strategies of polysaccharide-based drug delivery systems[205]. It is noted that controlled drug delivery systems designed to release drugs over a prolong period of time can reduce the side effects and improve therapeutic efficacy[206].

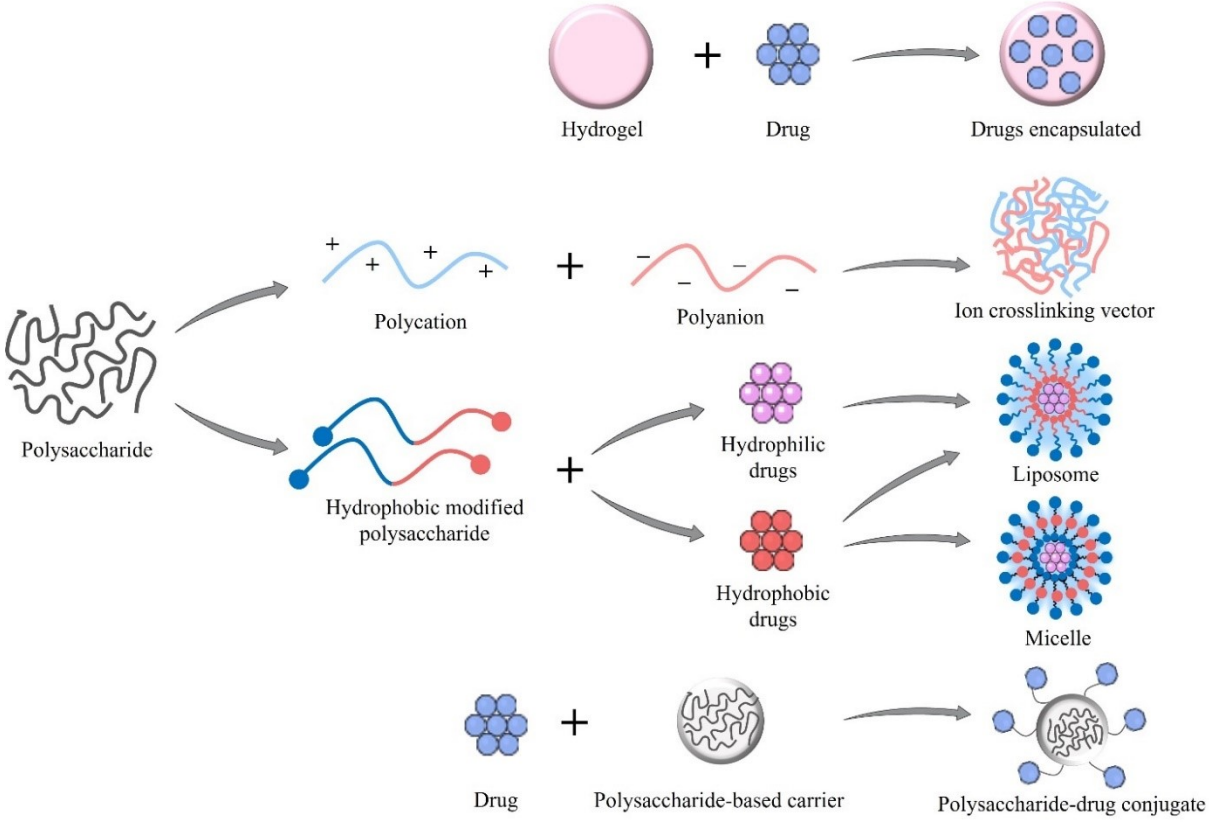


Figure 7 Three major categories of polysaccharide-based drug delivery systems [205]

4.2.1 Classification of polysaccharide-based drug delivery systems

4.2.1.1 Drug-loaded polysaccharide hydrogels

Polysaccharide-based hydrogels are excellent candidates for drug delivery systems due to their biocompatibility, facile modification methods, and ease of adjusting swelling degree. They are characterized by their highly hydrated and porous architecture, capable of encapsulation and controlled release of therapeutic agents. To be able to encapsulate drug, the hydrogels need to be crosslinked [204]. By controlling the structure and composition of polysaccharide-based hydrogels, loading, swelling, and releasing of drug can be adjusted to meet the desired applications. Drugs can be loaded into hydrogels by in-situ polymerizing and crosslinking of monomers in the present of drug to obtain drug-carrier hydrogels. The other approach is by placing a preformed hydrogel in the drug solution and allowing for the swollen hydrogel to reach equilibrium. The drug-loaded hydrogel is then dried. The second approach is preferred if in-situ polymerization would negatively affect the drug properties and purity of the prepared drug delivery device [207].

4.2.1.2 Drug-loaded self-assembled polysaccharide particles

Self-assembly is defined as the process by which a system's components spontaneously form an organized structure or patterns. The process is driven by noncovalent interactions, such as the van der Waals and hydrogen bonding forces, and the hydrophobic effect [208, 209]. Applying self-assembly to form physical-crosslinked polysaccharide-based hydrogels are advantageous in terms of simple and mild preparation conditions. It should be noted that self-assembly of polysaccharides does not always results in the formation of hydrogels. For instance, delta inulin is capable of self-assembling into semi crystalline microparticles useful for pharmaceutical applications [204].

Self-assembly of polysaccharide to yield nanostructures can be generally achieved by two approaches. First, by modification of native polysaccharides to obtain amphiphilic molecules. The hydrophobic species used for modification can be small or macromolecules with suitable reactive functional groups. These amphiphilic molecules self-assemble to form

micellar aggregates in aqueous solution with a hydrated outer layer and an isolate hydrophobic core in which the hydrophobic drug molecules are solubilized [209, 210]. Self-assembly of amphiphilic polymer with bilayer membrane(s) leads to the formation of a spherical molecular aggregates, known as liposomes [205]. The hydrophilic head groups exposed to the aqueous environment, and the hydrophobic moieties assembled within the interior[211]. Liposome is capable of encapsulating hydrophobic drug within the bilayer(s) and hydrophobic drug within its core [205]. The second approach relies on electrostatic interaction between polyelectrolytes of opposite charges [209]. This is a simple and facile approach for preparation of polysaccharide nanoparticles. Ionic strength and pH of the medium influence their self-assembly behavior significantly [209]. Ion complexation of polysaccharides containing carboxylic acid or amine groups are of great interest in drug delivery applications. An example of this is the self-assembly of positively charged chitosan and negatively charged carboxymethyl cellulose [205].

4.2.1.3 Polysaccharide-drug conjugates

Possible leaching of the physically encapsulated hydrophobic drug during systemic circulation leads to depletion of drug content within the nanoparticles. To solve this problem, polysaccharide-drug conjugates provide higher drug loading capacity, drug stability and prolonged plasma half-life. By this approach, a site specific, cleavable linker between the drug and polymer is used for chemical conjugation of the drug to the polysaccharide carrier [212]. Smart linkers are cleaved in responses to specific internal and external stimuli, such as enzyme, acid magnetic field, temperature, and light. This allows release of the drug from the conjugate at a target site. Furthermore, linkers can be used to connect the drug molecules with functional moieties to improve stability of the drug, selectivity to target, and sensitivity to stimuli [213]. For instance, curcumin is a natural compound with anticancer properties. By

chemical conjugation of curcumin to chitosan through imine formation leads to improvement in the solubility and stability of curcumin [214].

4.2.2 Polysaccharides used in drug delivery systems

4.2.2.1 Cellulose-based drug delivery systems

Cellulose is not soluble in water and common solvents due to its extensive intermolecular hydrogen-bonding. Cellulose derivatives have therefore been developed to allow ease of functionalization and fabrication into various forms suitable for drug delivery applications. Cellulose ethers have been traditionally used as excipient for oral administration because of its swelling properties. Hydroxypropyl methylcellulose is the most commonly used as a hydrophilic excipient and is approved by FDA. It exhibits good solubility at low temperature but gels at high temperature. Cellulose acetate phthalate, which is a type of cellulose ester, has been used extensively as the enteric coating of tablets or capsules as it solubility is pH-dependent, allowing for pH-controlled release e [28].

Cellulose nanocarriers have great potential for drug delivery applications. They are classified as cellulose nanofibers (CNFs), cellulose nanocrystals (CNCs), and bacterial cellulose (BC) [28]. CNFs are characterized by long chains, typically more than 1 um long, and diameters of 3-100 nm with both crystalline and amorphous regions. They are obtained by mechanical treatment of lignocellulosic materials [215]. CNCs, also known as cellulose nanowhiskers, are obtained by several processes to remove the amorphous part and preserve the crystalline part. They are inflexible rods with nanoscale length. BC is produced by bacteria in the form of fibrous networks with a fiber diameter of 20-100 nm, and is of high purity, in contrast to CNFs and CNCs which are usually contaminated with lignin, pectin, and hemicellulose [215]. Various bacterial strains, either gram-positive or gram-negative, can be used to produce BC, such as *Acetobacter xylinum*. BC is in the form of nanofibrous network with a fiber diameter of 20-100 [215].

Owing to the high surface area-to-volume ratio, nanocellulose provides high loading and binding capacity for therapeutic agents. Drug release behaviors can be controlled by adjusting water retention, adhesion, rheology and film forming ability of the cellulose nanocarriers. Nanocellulose in different forms have been found to improve bioavailability and enable sustained and controlled drug [215]. For instance, the addition of CNC to alginate was found to extend ocular residence time and mechanical strength of the CNC/alginate nanoparticle hydrogels in ophthalmic drug delivery systems [216]. Oral, ocular, intratumoral, and transdermal drug delivery systems have been found to benefit from the incorporation of nanocellulose [215].

4.2.2.2 Chitosan-based drug delivery systems

Chitosan is a cationic polysaccharide which possesses antimicrobial, anti-coagulant, and mucoadhesive properties. It has also been found to accelerate wound healing. Low-molecular-weight chitosan displays antitumor activity with lesser toxicity on normal cells [217]. Chitosan is very promising as oral drug carriers for proteins since it is able to prevent enzymatic degradation of the drug in the gastrointestinal system while facilitate mucoadhesion to the intestinal mucus layer [218]. Due to the presence of positive charges of the protonated chitosan, drug carrier systems based on electrostatic assembly between the positively-charged chitosan and negatively charge compounds are possible [219]. The majority of the *in vitro* and *in vivo* studies revealed that bulk chitosan and chitosan nanoparticles displayed low toxicity regardless of particle composition, derivatives, cytotoxicity assay, cell lines and animals [218]. Both cell permeability and mucoadhesion of chitosan are advantages for drug delivery devices through ocular, transdermal and nasal routes [217]. Chemical modification of chitosan could improve solubility and bioavailability, e.g. grafting of hydrophobic moieties into chitosan can enhance its self-aggregation properties, facilitating the encapsulation of anticancer drug [220]. Chitosan-drug conjugates have also attracted

considerable attention. Recently, a chitosan derivative-drug conjugate based on carboxymethyl chitosan and norcantharidin (anti-tumor compound) has been reported to show enhanced solubility and decreased the systemic toxicity of free norcantharidin, thus possibly increasing bioavailability and anti-tumor efficacy compared to the free drug [221].

Skorik et al. [222] employed chitosan-based nanoparticles as nanocarriers to transport paclitaxel (PTX) and docetaxel (DTX). The drug-charged succinyl and glutaryl chitosan nanoparticles exhibited significant cytotoxicity toward gastrointestinal cell lines, increasing their anticancer efficacy as compared to free medications. Chen et al. [223] reported hydrophobic doxorubicin (DOX)-chitosan nanoconjugates with pH-sensitive drug release that were created by combining the DOX with the acid-cleavable hydrazone link. According to the studies, the chitosan-DOX conjugates with the acid-cleavable hydrazone linkage became stable at neutral pH and dissolved at pH 5.0, which contributed significantly to the release of DOX into HeLa cells.

4.2.2.3 Hyaluronic acid-based drug delivery systems

Hyaluronic acid contains hydroxyl, *N*-acetyl, and carboxylic groups that allows for a variety of chemical modification methods. Because of this, HA-drug conjugate could be synthesized with stronger anti-cancer activity. It has been reported that HA is capable of binding with certain tumor cells, particularly tumor-initiating cells, making it suitable for use as targeted-drug delivery. HA-based drug delivery vehicles are generally in the forms of hydrogel or micelles [214]. Yan et al [224] successfully prepared micelles based on hyaluronic acid-tetraphenyl ethylene conjugate (HA-SS-TPE) with glutathione (GSH) for targeted drug delivery of doxorubicin (DOX). Doxorubicin was incorporated during the self-assembly of HA-SS-TPE, to form DOX-loaded micelles. They observed fluorescent emission, and fast glutathione-triggered dissociation to unload DOX by responding of the micelles to tumor microenvironments. Wu et al [225] developed a pH/near-infrared (NIR) multi-responsive drug

delivery platform consisted of hollow hydroxyapatite, chitosan /hyaluronic acid multilayers, gold nanorods and MXene via a layer-by-layer (LbL) technique. Chitosan and hyaluronic acid were alternately coated on hollow hydroxyapatite to avoid the initial burst release of DOX. MXene and gold nanorods which are NIR responsive, were capped on the surface of the multilayer microcapsules. The microcapsules displayed pH/NIR dual-responsive drug delivery characteristics, high drug loading efficiency, as well as biocompatibility. Le et al. [226] synthesized hyaluronic acid-BHQ3 conjugates that, through self-assembly, formed HA-BHQ3 nanoparticles. DOX-encapsulated HA-BHQ3 contained azo bonds which were cleaved under hypoxic conditions resulting the release of DOX. I*n vivo* studies indicated that HA-BHQ3 nanoparticles might possess a potent tumor targetability.

4.2.3.4. Alginate-based drug delivery systems

Alginate is an anionic polysaccharide widely used as a carrier for delivering proteins and small drug molecules. It exhibits moderate gelation when in contact with cations and is adhesive to mucosal surfaces. In the form of nanoparticles, alginate can be stabilized by cationic polyelectrolytes. These properties are beneficial for use as a drug carrier. Drug delivery devices based on alginate hydrogels can be taken orally or injected. Various forms of alginate drug delivery vehicles have been prepared, such as microspheres, tablets, and nanoparticles [214].

Kianersi at al. [227] prepared alginate nanoparticles for the delivery of betamethasone sodium phosphate, an anti-inflammatory drug via electrospraying, emulsification, and a combination of these two methods. Cationic polymers, chitosan and gelatin were used as nanoparticle coatings. The highest mucoadhesive strength (approx.75%) was found for gelatin-coated alginate nanoparticles. They obtained sustained drug release *in vitro* for a period of 120h. Hu et al. [228] developed a new double-layer, pH-sensitive, composite hydrogel sustained-release system. Alginate and carboxymethyl cellulose crosslinked with

Ca^{2+} were used as the inner layer while the outer layer was made from synthetic materials of poly (acrylamide) or its derivative. Sustained-release effect of the hydrogels could be achieved for large-molecule proteins of bovine serum albumin (BSA). They suggested that sequential or multi drug release are possible when using the double layer structure. Azad et al [229] utilized an organic solvent-free and environment-friendly electrohydrodynamic assisted (EHDA) technique to prepare peppermint oil -loaded alginate microbeads. They claimed that the microbeads are promising as anti-inflammatory therapeutic strategy for treating irritable bowel syndrome.

4.2.3.5. Pectin-based drug delivery systems

A complicated chemical structure of pectin had negative impact on its mechanical properties and chemical reactivity. However, the presence of various saccharide residues give rise to some health benefits and unique biomedical properties for drug delivery applications. [230].

Pectin has been shown to produce hypocholesterolemia effect (reducing cholesterol levels) and anticancer effect (suppression of the proliferation of cancer cells)[230]. Since pure pectin-based materials generally possess undesirable swelling and corrosion properties, drug delivery vehicles based on pectin are mostly obtained through chemical/physical modifications or prepared in the forms of hybrid materials.

Chemical modification of pectin can be achieved through reactions between the nucleophilic hydroxyl and carboxylic acid groups of pectin and the electrophilic compounds. These reactions are esterification, amidation, silanization, and etherification. Formation of coordination bonds between hydroxyl or free carboxyl groups with polyvalent metal ions such as Ca^{2+}, Zn^{2+} and Fe^{2+} produces ionically-crosslinked hydrogels. However, the coordination bonds are labile leading to the poor strength and toughness, and also the possibility of undergoing ion-exchange in aqueous solution. Covalent crosslinking is a

superior strategy to obtain hydrogels with good mechanical properties and well-controlled

Polysaccharide /Other components	**Therapeutic agents/Type of targeting/Cell types**	**Functions of the drug delivery system**	**Model of study**	**References**

crosslinking reactions. One interesting example is the oxidation of adjacent hydroxyl groups in pectin by periodate, to obtain dialdehyde, and then conjugation between the oxidized pectin with chitosan via Schiff's base reaction in the presence of magnetic nanoparticles to generate injectable, self-healing hydrogels. The prepared hydrogels were pH- and temperature-responsive [231]. Recently Ergin et al. [232]reported a novel pectin-based drug delivery system in the form of nanoparticles-in-microparticles (NIMs) using fluidized bed technology. They successfully improved the bioavailability of S-adenoxyl-L methionine (SAMe) for colon-targeted delivery both *in vitro* and *in vivo*. Li et al. [159] developed pH-responsive, self-healing hydrogels based on pectin and chitosan via Diels-Alder reaction. They found higher cross-linking density by the Diels-Alder reaction. High loading efficiency and sustained release performance as well as great cytocompatibility of the hydrogels were observed. Lemos et al. [233] prepared multi-responsive magnetic-pectin microspheres coated with chitosan for the release of metamizole. Release experiments performed in simulated gastric and intestinal fluids indicated that the release process was pH-dependent and also responsive to an external magnetic field.

The recent uses of polysaccharides in drug delivery applications are shown in Table 3.

Table 3 Drug delivery applications based on polysaccharides

Dialdehyde cellulose-Chitosan	Lipophilic compound β-carotene/Passive/Oral delivery & Stomach	Lipophilic beta-carotene slows release in the stomach and much slower releases in the intestines	*In vitro*	[234]
Chitosan	Suramin & DOX/ Passive/Breast cancer cell line (MDAMB231)	Breast and lung metastases can be prevented	*In vitro & in vivo*	[235]
Chitosan-Carboxymethyl dextran	DOX and IL17RB siRNA/Passive/Breast cancer cell line (MDA-MB361)	Reduce tumor cellular viability, limits tumor cell growth, migration, and proliferation	*In vitro*	[236]
Chitosan- N-acetyl histidine and arginine	DOX/Passive/Breast cancer cell lines MCF-7	Increase cytotoxicity and cell uptake	*In vitro*	[237]
Chitosan-Hyaluronic acid-sulfobutyl-ether- β-cyclodextrin	Curcumin/Passive/Colon cancer cell line (HT29)	Cellular absorption is increased, cellular proliferation is decreased, and toxicity is elevated	*In vitro*	[238]
Hyaluronic acid/Polyamido amine	Doxorubicin & Cisplatin/Active/Breast cancer cell lines (MDAMB231&MCF-7)	At low drug doses, tumor growth inhibitor	*In vitro & in vivo*	[239]
Hyaluronic acid/Silicapolye thyleneimine	TWIST-siRNAs (Transcription factors with basic helix-loop-helix structure)/Active/ Ovarian cancer cell line (Ovcar-8)	Cancer development and cell survival can be reduced as a result of selective targeting	*In vitro & in vivo*	[240]
Hyaluronic acid/Silica	5-Fluorouracil/Active/ Colon cancer cell line (HT29)	Tumor inhibition, tumor accumulation via specific targeting, and high cytotoxicity	*In vitro & in vivo*	[241]
Hyaluronic acid/Silica	Paclitaxel/Active/ Breast cancer cell line (MCF-7)	Increase consumption and drug accumulating, as	*In vitro & in vivo*	[242]

		well as improve cancer growth slowing		
Hyaluronic acid-/Poly-lactic-coglycolic acid	Paclitaxel & curcumin /Active/Breast cancer cell line (MCF-7)	Pharmacokinetics are prolonged, and cellular accumulation is enhanced	*In vitro & in vivo*	[243]
Hyaluronic acid-Chitosan	5-Fluorouracil/Active/ Lung cell line (A549) & liver cell line (HepG2)	Increase cell apoptosis and drug accumulation in cells	*In vitro*	[244]
Alginate-Chitosan	DOX/Active/Breast cancer cell line (MCF-7)	Tumor progression and cellular growth can be inhibited	*In vitro*	[245]
Alginate	DOX/Passive/ Melanoma cell line (B16)	Tumor growth inhibition, increase cellular absorption, and high cytotoxicity	*In vitro & in vivo*	[246]
Alginate	Paclitaxel/Passive/ Different breast cancer cell	Increase cell cycle arrest, promote apoptosis, and decrease bioavailability	*In vitro & in vivo*	[247]
Alginate	1-[4-(2-aminoethyl) phenoxy] zinc (II) phthalocyanine/Active/J 774A.1 and HepG2 cells	Photodynamic treatment with tumor-associated phagocyte targeting enhancement	*In vivo*	[248]
Alginate	Gold nanoparticles (AuNPs) & cisplatin/Passive/ Colon cancer cell line (CT26	Tumor growth inhibition is high, and survival is improved	*In vitro & in vivo*	[249]
Pectin	S-adenosyl-l-methionine (SAMe)/Colon targeted delivery	Increase bioavailability of SAMe by pectin nanoparticles-in-microparticles	*In vitro & in vivo*	[232]

4.3) Artificial face mask

The Chinese Center for Disease Control and Prevention (CCDC)discovered a new beta-coronavirus named 2019-nCoV, COVID-19, or formally known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in December 2019 [250]. To combat the spread of the virus, countries throughout the world have used non-pharmaceutical therapies, including social distance and the wearing of masks in public. SARS-CoV-2 viruses have diameters around 100 nm making them easily dispersed in aerosols or droplets out of humans' breaths. To avoid COVID-19 infection, various types of masks, i.e., cloth masks (cotton or gauze), medical masks (medical, surgical or procedural), and respirators (N95, N99, N100, P2, P3, FFP2, and FFP3) have been used. The respirators show the highest protection efficiency since they can provide good fitting around the face and also have higher filtering capacity than face masks. However, this is accompanied by lower breathability and discomfort during use [251]. The protective effects against respiratory infection have been well studied for surgical masks and respirators but not for cloth masks. While the medical masks and respirators are recommended for healthcare workers, cloth masks are more suitable for the general public in community [252]. Among the different types of face masks, surgical masks are most widely used. They often have 3-4 layers, including two electrostatic nonwoven fabric layers and a melt blown polymer layer between them. The fabric material is generally produced from synthetic polymers, with polypropylene as the most widely used. Other usable but less common synthetic polymers are polystyrene, polycarbonate, or polyester [252]. Synthetic commodity polymers have good properties such as ease of processability. They are suitable for the manufacturing of disposable face masks because of their low cost. However, in terms of sustainability, worldwide use of disposable products manufactured from petrochemical raw materials may pose serious environmental impacts as they take a very long time to degrade. It has been reported that global warming contribution

factors from a disposable medical mask being ranked as raw material supply, followed by packaging, and then production [253]. It is therefore interesting to find more environmental-friendly alternatives to the synthetic polymers for the manufacturing of face masks. Numerous patented and commercially accessible biodegradable filtering media for face masks have been reported in recent years. These include polysaccharides and proteins [291]. Polysaccharide-based biomaterials such as alginate, chitin, chitosan, cellulose acetate, and their blends are suitable and sustainable for the creation of facemasks [254].

While not all polysaccharides have antiviral properties, some have been shown to exhibit direct antiviral activity, for instance, chitosan and algae-derived polysaccharides (carrageenan, laminaran, alginate, fucan, laminaran, and naviculan) [255-257]. Cellulose, however, does not exhibit virucidal activity [258] and therefore coating or surface modification using antimicrobial agents would be required to achieve direct antiviral effects. Incorporation of silver nanoparticles and graphene have been found to impart antimicrobial properties to face masks [252]. Surface functionalization of cellulose can be carried out through oxidation, esterification or etherification involving the hydroxyl groups of cellulose, introducing new functional groups such as aldehyde, quaternary ammonium, metal or metal oxide nanoparticles, and chitosan. Deng et al. reported the use of guanidine-based polymer and neomycin sulfate (NEO) for chemical grafting onto the surface of cellulose nonwovens, imparting antiviral and antibacterial properties to the nonwovens with promising high virucidal activity (> 99.35%) [259]. Catel-Ferreira et al. found that modifying nonwoven cellulose filter with catechin polyphenol imparted excellent antiviral activity against the T4D bacteriophage virus [260]. Table 5 lists the materials in polysaccharide for artificial face mask applications.

Table 5 Polysaccharides for the artificial face mask applications

Bio-based polysaccharide media	Structure and materials	Application	References
Cellulose	Non-woven cellulosic fiber & catechin polyphenol	Face mask	[261]
Cellulose	Banana stem fiber	Face mask	[262]
Cellulose	3-ply cotton-polyvinyl alcohol-cotton layered & polyphenol	Face mask	[263]
Cellulose	Fungal hyphae (wood), cellulose fibers (hemp) & lignicolous basidiomycetes	Personal protective equipment (PPE) materials apart from synthetic melt & spun-blown	[264]
Cellulose	Nanomembrane lyocell fibrous of poly(acrylonitrile) & zinc oxide	Surgical face mask	[265]
Cellulose	Cellulose non-woven layers functionalized with poly(ethylenimine)	Surgical face mask	[266]
Cellulose	Cellulose acetate nanofibers & cetylpyridinium bromide	Air filtration	[267]
Chitosan	Chitosan nanowhiskers and microfiber & nanofiber developed from poly (butylene succinate)	Face mask filter	[268]
Chitosan	Chitosan/PEO blend coated spunbonded non-woven polypropylene	Water and air filtration	[269]

Antiviral polysaccharides can be highly effective against pathogenic viruses. Sulfated polysaccharides (SP) are present in the cell wall of seaweeds or marine algae. They are negatively charged and constitute mostly of cellulose and hemicellulose with high

carbohydrate content but low fat content [270]. Sulfated polysaccharides are capable of binding to the viral protein hence preventing the virus from entering the host cell. High antiviral activity has been found from the sea cucumber sulfated polysaccharide, carrageenan, and fucoidan with the sea cucumber sulfated polysaccharide showing the highest efficiency in fighting against COVID-19 virus [271]. Otto and Villiers [272] suggested that coating face masks with mucopolysaccharides, also known as glycosaminoglycans (GAGs), which has the ability to bind with pathogens, may be a promising approach to obtain antiviral face masks. GAGs are negatively charged linear polysaccharides found in extracellular matrix of the mammalian tissue. They are classified into 4 groups, namely heparin/heparin sulfate, chondroitin/dermatan sulfate, keratan sulfate, and hyaluronic acid. Coating of GAGs onto substrates may be done by a layer-by-layer technique [272].

4.4) Biosensors

A biosensor is a self-contained device with significant sensitivity and specificity for evaluating the toxicity of a particular substance or organism [273]. The biosensor's physiochemical transducing element provides a quantifiable measurement of the analyte in the form of an electric signal. It should be specific, sensitive, portable, and not affected by physical elements such as pH or temperature. They can test analytes in complicated matrices with little sample preparation and can be used both in vivo and in vitro [274, 275]. Functional proteins, nucleic acids, cell organelles, or even whole living cells are immobilized on a physicochemical transducer surface that can translate the strong interaction of the immobilized bio-entity with its associated binding partner analyte into measurable, concentration-dependent electrical signals. The focus in this review will be on polysaccharide-based compounds for biosensor. It will report various types of polysaccharides such as cellulose, chitin-chitosan and alginate. Polysaccharides having the unique ability to create hydrogels. Because of their hydrophilicity, strong protein affinity,

heavy metal ion chelation, biocompatibility, simplicity of modifying the surface chemical group, low cost, acceptable mechanical characteristics, and simple synthesis procedure, these polysaccharide hydrogels are appealing biomaterials for biosensors [276]. There is a lot of evidence that polysaccharide-based hydrogels can be used as immobilized biomaterials to manufacture bioreceptors [277]. Immobilizing bio receptors on the hydrogel surface can be accomplished by physical absorption, trapping, covalent bonding, crosslinking, and other methods. Irreversible immobilization of the bioreceptor prevents it from detaching from the biosensor, and if this happens, the hydrogel microstructure or bio-receptor activity is damaged [278].

4.4.1) Biosensors based on chitin and chitosan

Chitosan is soluble in slightly acidic aqueous media and hence can be processed under physiological conditions, although chitin requires harsh organic solvents for dissolving and manufacturing. Despite this distinction, chitosan has been more generally utilized in the construction of electrochemical biosensors than chitin. However, chitin has been employed as a tunable electrode modification in a number of investigations, and the examples below show some of the possibilities. Thin chitin or chitin dispersed in carbon/platinum paste are appropriate matrices for electrostatic immobilization of enzymes [279]. In order to improve its electrical characteristics for sensing applications, chitosan is combined with nanoparticles such as graphene, multiwall carbon nanotubes, polypyrrole, and polyaniline. The glutaraldehyde amino-reactive cross-linker can be used to covalently link enzyme molecules to the surface of a chitin membrane. An electrochemical flowcell was successfully developed with choline oxidase modified chitin films positioned on a platinum disk electrode as part of an electrochemical flow cell. A choline-sensing flow injection analysis system for evaluating the cholinesterase inhibitory effects of synthetic compounds or natural items was successfully developed [280]. Glucose oxidase (GOD)-loaded chitin films, as well as

GOD/chitin/carbon/platinum pastes, worked well as glucose biosensors on the surface of Clark-type oxygen or noble metal hydrogen peroxide electrodes. Two more studies used partially deacetylated chitin's amine and hydroxyl functionalities, with glyoxal, carbodiimide, or epichlorohydrin used to cross-link individual chitin chains and to bind enzymes to chitin networks [281, 282]. Shen et al. [283] reported a chitosan-based electrochemical biosensor using graphene that showed good sensitivity and a low detection limit of 0.29 μM for the detection of dopamine. Moreover, chitin films can be employed as immobilizing platforms for enzymes as well as other protein-based biological recognition elements. This was achieved in a study in which streptavidin was electrostatically bonded to chitin electrode coverings and the effective fixation of the biomolecule was demonstrated by pulse voltammetry measurements in biotin solutions containing daunomycin as an electroactive redox indicator [284].

In electrochemical nucleic acid biosensors, biosensors with DNA chips are used to screen biological materials for segments of single-stranded target complementary DNA (cDNA) or short-chain oligonucleotide (OND) ladders that have been found as markers for the development or presentation of a range of common diseases, indicators of pathogenic pathogen infection, or symptoms of contamination with other harmful biological matter in clinical trials. The production of genomic nucleotide probes such as synthesis of sections of end-modified single-stranded cDNA, oligonucleotides (ONDs), or peptide nucleic acids (PNAs) and their precise immobilization on the analytical platform are the key issues for solving diagnostic tasks with blood, urine, or tissue extracts. For example, chitosan-based DNA biosensors are generated by attaching the anionic phosphate of biotinylated probe DNA to the cationic amino group of chitosan by affinity conjugation or covalent bonding. According to Singh et al. report [285], this sensor was utilized to detect gonorrhea (a sexually transmitted infection). Furthermore, Singh et al. [286] used a chitosan-based nucleic acid biosensor to detect *Salmonella Typhi* by immobilizing the infectious agent's single -stranded

DNA on a graphene oxide/chitosan/ indium tin oxide (ITO) nanocomposite. The biosensor can discriminate between complementary, noncomplementary, and one-base mismatch sequences. A comparable electrochemical DNA biosensor for sensing E. coli 0157:H7 was developed by immobilizing *SS E. coli* DNA using a graphene oxide chitosan hybrid nanocomposite [287]. Recent studies have shown that chitosan can be utilized to immobilize DNA probes and even detect hybridization, whether employed as a coating system or as a composite material with other nanoparticles such as carbon nanotubes (CNTs) or metal/metal oxide nanoparticles. Polycationic chitosan scaffolds attracted and bonded anionic nucleic acid strands at slightly acidic pH values; however, switching to alkaline conditions and deprotonation of the chitosan allowed successful elution of the DNA from the beads. Nucleic acid fragments can be immobilized on biosensor surfaces using this form of ionic interaction. Fish sperm double-stranded DNA, for example, was electrostatically bound on chitosan/CNT-modified screen-printed carbon [288] and graphite [289] electrodes, and the arrangement permitted detection of profound DNA damage using a redox marker.

Electrochemical immunosensors take advantage of the particular identification of antigen molecules by corresponding antibodies, deciding whether to use electrochemical or other detection systems such as immunoglobulins. Antibodies or antigens are immobilized on the electrode surface of chitosan to develop electrochemical immunosensors. One of the advantages of chitosan is that the number of amino sites available for covalent protein attachment to chitosan materials can be adjusted across a wide range simply by varying the degree of deacetylation. The strong Ab-Ag binding (dissociation constants, K_D, of -10^{-7} M) [290] and the high specificity of protein complex formation are the basis of the outstanding analytical performance of existing immunological tests. DNA biosensors [291, 292] have comparable sensitivity since they are affinity-based devices with responses driven by strong binding properties. For example, biomarkers for hepatitis B, various malignancies,

pregnancy, blood iron levels, the food contaminant ochratoxin A, and diarrhea-causing microorganisms (*Shigella flexneri*) have all been detected using electrochemical immunosensors supported by chitosan [293]. On chitosan-modified electrochemical platforms, the antigen/antibody interaction is normally transformed into a signal that may be measured by amperometry, voltammetry, or electrochemical impedance spectroscopy. Potentiometric measures have been proven for detection of the hepatitis B surface antigen (HBsAg) [294] and prostate-specific [295] antigens. Chitosan can be covalently modified with synthesized functional groups for application in immunosensor fabrication. For example, an initial covalent attachment of the redox mediator ferrocene to chitosan chains was conducted out [296] to reduce leakage of integrated electroactive molecules. Prior covalent attachment of thionine to chitosan, on the other hand, was employed to improve the polymer's chemisorption affinity for gold nanoparticles on the immunosensor's electrode surface [297].

In order to highlight the potential of chitosan in enzyme biosensor development, case examples will be presented. The majority of the recently proposed designs are multicomponent systems that combine simple or chemically premodified chitosan variants with a specific enzyme and additional functional materials, including carbon nanotubes, graphene sheets, metal/metal oxide nanoparticles, ionic liquids, and clay, to mention only some. The enzyme used depends on the analyte specificity required: oxidases, peroxidases, acetylcholine esterases, laccases, dehydrogenases, tyrosinases, reductases, hydrolases, and phosphatases have all been used. The majority of the described enzyme-chitosan linking techniques have employed standard cross-linking reagents like glutaraldehyde, carbodiimides, hydroxysuccinimide, epichlorohydrin, or glyoxal, although specific cross-linkers like cyanuric chloride [298] have also proved effective. Chitosan emerges as a porous polymer with polycationic chains that bind enzymes to provide a biosensor. This attachment is appropriate for cross-linking pharmaceuticals such as GL, carbodiimide, NH,

epichlorohydrin, or GL, NH, or cyanuric acid, for example. The adhesion has no effect on enzyme activity or movement. The quantity of functional groups and pH solubility are essential factors in linking chitosan with diverse chemical groups. Several uses for chitosan-based electrochemical enzyme biosensors have been reported, including measuring dopamine release in rats' brains [299], laccase immobilized on ZnO-chitosan nanocomposite for chlorophenol determination [300], and hydrogen peroxide detection using catalase immobilized on chitosan-b-cyclodextrin [301]. A current study that focuses on the behavior of *Agrocybe aegerita* peroxygenase on the surface of a glassy carbon electrode modified with chitosan-capped gold nanoparticles indicates how direct electron transfer between chitosan-tailored electrodes and enzymes [302] could be achieved. In traditional beaker-type electrochemical cells, the tips of chitosan-based enzyme biosensors have macroscopic dimensions and are utilized for analyte measurements in the bulk phase of solutions. A dopamine biosensor utilized for amperometric detection of localized dopamine release in the brains of rats [303] is an example of a biosensor with a tiny, needle-like tip. The detection of bacterial contamination in milk [304], water quality estimation, and biomedical applications are all possible with alginate-based biosensors. The alginate microsphere glucose oxidase-based biosensor, which employs the glucose oxidase enzyme to estimate glucose in vivo glucose monitoring system, was developed to detect glucose levels in the blood [305].

In voltametric electrodes for trace analysis, natural or chemically modified polysaccharides, especially chitosan, are an effective sorbent material for heavy metals, pesticides, and dyes due to potential chelation by inherent oxygen and nitrogen atoms with free electron pairs. Analyte species are drawn out of solution into top layers of the material on voltametric electrodes in the removal of environmental pollutants from contaminated wastewater, and analysis can be done without the electrodeposition step used in anodic stripping voltammetry of heavy metals such as lead, cadmium, and zinc using mercury or

bismuth film electrodes. Janegitza et al. [306] observed the sensitivity of chitosan-supported adsorptive stripping voltammetry in the electrochemical analysis of heavy metals. Infectious pathogens such as *E. coli* and *S. Typhi* have been detected using a nickel oxide associated chitosan electrochemical biosensor in ambient and clinical samples [307].

4.4.2) Biosensors based on cellulose and its derivatives

Biosensors developed from cellulose and its derivatives have a high degree of biocompatibility, making them appropriate substrates for the addition of biologically active ingredients. The use of a cellulose matrix is appropriate for chemical covalent bonding as well as physical adsorption and immobilization since a typical carrier substrate for an enzyme should be stable, inert, and resistant to mechanical changes [7, 8]. With their unique chemical structure, cellulose and its derivatives have been shown to be adaptable materials, providing a high-quality foundation for completing the immobilization process of physiologically active molecules into biosensors [9]. Optical and electrochemical biosensors based on cellulose may be classified into two main types based on the sort of biosensors they utilize [9].

For cellulose optical biosensors, cellulose is generally used in an optical biosensor as a supporting substrate for the incorporation of biological components, including enzymes, aptamers, and antibodies [10]. For enzyme immobilization, cellulose may often be reacted with, which can enhance the biological element incorporation process or improve sensor efficiency. Different enzymes can then be immobilized on the treated cellulose [9]. In order to create an optical fiber-based fluorescence biosensor, Wang et al. [11] reported applying cholesterol oxidase enzyme to a cellulose acetate membrane that had previously activated by sodium periodate, ethylenediamine, and glutaraldehyde. The development of a novel fiber-optic glucose biosensor employing glucose oxidase enzymes and fluorescent carbon quantum dots immobilized through dip-coating on a cellulose acetate film biosensor was recently reported by Yu et al. [12]. For the purpose of continuous online monitoring of low glucose

concentrations, the suggested optical fiber sensor displayed superior sensitivity and recyclability. Ethyl cellulose membrane, oxazine 170 perchlorate fluorophore, and enzymes immobilized in a matrix of ethyl cellulose membrane and polyurethane hydrogel were used to construct ratiometric fluorescent l-arginine and l-asparagine biosensors reported by An et al. [13]. The hydrolysis reaction of urea and l-arginine in the presence of urease and arginase as catalysts was the basis for the sensory mechanism. As a result, ammonia was produced in the presence of a membrane made of l-arginine. In the case of the l-asparaginase-based membrane, the l-asparagine hydrolysis process was also seen under l-asparaginase catalysis. The l-arginine and l-asparagine concentrations in the range of 0.1 to 10 mM were proportionate to the variations in the fluorescence intensity between 565 and 625 nm, which occurred as a result of the interaction between the produced ammonia and the ethyl cellulose membrane-based biosensor. The reversibility, stability, and reaction time of the biosensing membranes all showed outstanding quality.

As in cellulose-based electrochemical biosensors, cellulose cannot serve as an amperometric sensor's main support. This kind of biosensor often includes a transducer. For this reason, cellulose modification is crucial for the immobilization of enzymes in amperometric sensors [14, 15]. Using a dialdehyde derivative of cellulose nanocrystals (CNCs) immobilized with gold nanoparticles (AuNPs) via an aminothiophenol crosslinking agent and glucose oxidase (GOx) enzymes via thioctic acid as a double crosslinker, Saeed et al. [16] recently developed a non-invasive biosensor for human salivary glucose. Thiol chemistry was used to link the gold nanoparticles to the cellulose. The same person's blood glucose was compared to the observed salivary glucose. In the presence of typical glucose interferences, including uric acid, ascorbic acid, and dopamine, it had a high selectivity for glucose. This biosensor demonstrated decent performance and may be used to analyze actual samples. Besides developing a low-cost, disposable glucose biosensor, Mahadeva et al. [17]

reported immobilizing glucose oxidase onto cellulose/tin oxide (SnO_2) hybrid nanocomposite. A potentiometric biosensor for cholesterol was recently published by Pandey et al. [18] employing cholesterol oxidase enzymes mounted on single-walled carbon nanotubes that were then put on a cellulose acetate membrane. In comparison to the cholesterol oxidase/cellulose acetate biosensor, the cholesterol oxidase/carbon nanotubes/cellulose acetate biosensor outperformed in terms of electrocatalytic responsiveness to detect cholesterol. Consequently, cellulose as well as cellulose's nano-or micro-structure allows for the immobilization of nanoparticles. Innovative methods for enhancing analytical efficiency are provided by biosensors. Numerous cellulose-based biosensors have been designed for a variety of laboratory-scale applications.

4.4.3) Biosensors based on alginate hydrogels

Alginate hydrogels stand out as attractive alternatives to satisfy the demand for biocompatible wearable, implantable, and injectable biomedical devices. Alginate hydrogels have been utilized as a matrix to immobilize proteins, sensitive polymers, and nanoparticles [308]. Ionotropic alginate hydrogel biosensors typically function by diffusing the analyte into the hydrogel's free volume, in which the mechanism of biomolecular binding is converted into a detectable signal [308]. Biorecognition is generally performed by an enzyme, and the transduction is accomplished by integrating sensitive polymers or nanoparticles inside the hydrogel to create (nano)composites. Various types of biosensors have been developed that use the enzymes lactate oxidase (LOx) and glucose oxidase (GOx) as the biorecognition components to detect lactate and glucose. In the presence of synthetic sweat, lactate was present, and in the presence of O_2 that is reduced to H_2O_2, the lactate was oxidized by LOx to pyruvate. The high selectivity of lactate monitoring during numerous cycles was achieved by the sensitivity to changes in oxygen levels. The co-encapsulated catalase enzyme used up the H_2O_2 that was created as a byproduct during the biorecognition event [309]. To create an

optical sensor, Garcia-Rey et al. [310] immobilized LOx and horseradish peroxidase (HRP). 3,3′, 5,5′-tetramethylbenzidine (TMB), which was catalyzed by HRP, was utilized to produce H_2O_2, which resulted in the sensor's color changing proportionately to the lactate concentration. The sensor performed incredibly well with actual human sweat samples. For in vivo applications, more complex alginate hydrogel-based devices have been developed. In order to modify a layer-by-layer electrode sensor, Zhou and colleagues [311] developed chitosan, alginate, and a hollow polysulfone membrane (PSfHM) with GOx serving as the biorecognition component. To allow for controllable glucose diffusion, the membrane's porosity was modified. The sensor was implanted in vivo in the tail of a mouse, where it could detect glucose fluctuations efficiently for weeks with no sensitivity decrease. Iverson and colleagues [312] encapsulated nitric oxide (NO)-specific DNA oligonucleotide-ligated single-walled carbon nanotubes (AAAT)7-SWNTs in Ba(II)-alginate hydrogels. The sensor was subcutaneously implanted for monitoring epidermal NO in inflammatory tissue, and it can provide data for up to 400 days while the hydrogel is still in situ and the fluorescent signal is unaffected. When compared to the PEG hydrogel analog sensor that was also examined in this work, the (AAAT)7-SWNTs alginate hydrogel's long-term durability was notably greater. Recently, a soft calcium (Ca)-alginate hydrogel was linked with a multimodal sensing platform based on fibers to imitate brain tissue. When implanted in a mouse's brain, the fibers can produce optical, electrical, and fluidic signals in response to opto-electrophysiological and behavioral tests [312]. This study investigated several hydrogel matrixes and concluded that Ca-alginate mixed with polyacrylamide (PAAm) displayed low interfacial toughness, low fracture toughness, and long-term stability in physiological settings. Consequently, a summary of the sampling of principal approaches for developing polysaccharide-based materials for medical applications is described in this section in Figure 8.

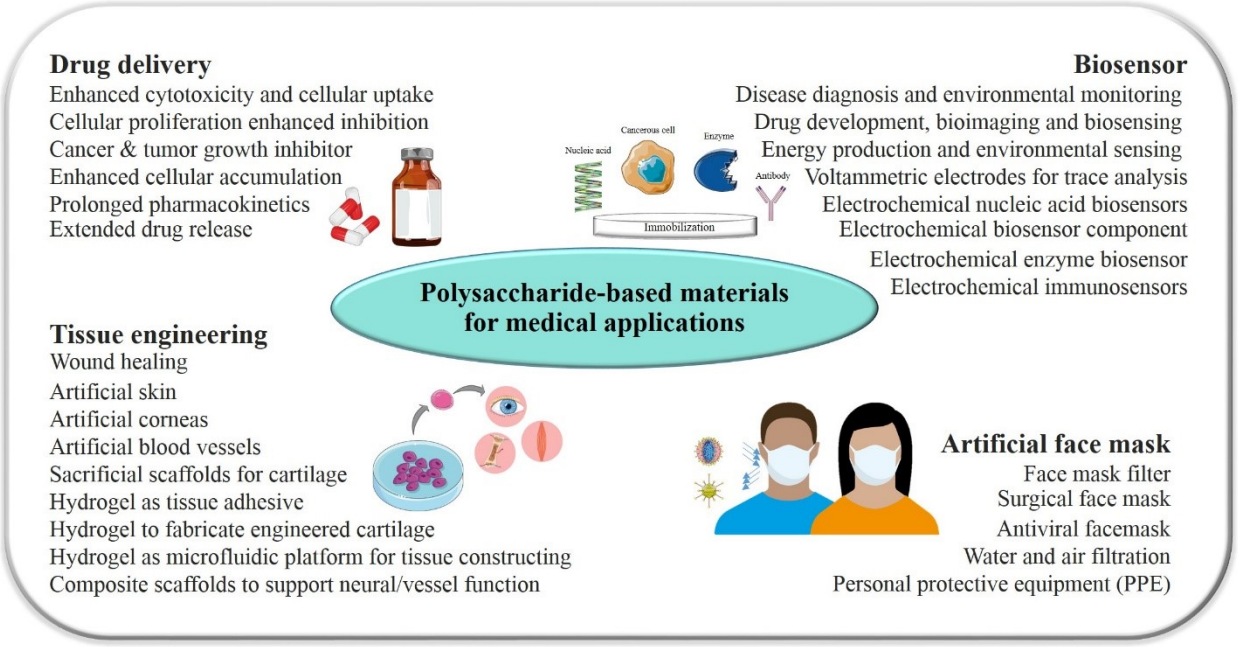


Figure 8 Summary of principal approaches for developing polysaccharide-based materials for medical applications

5) Summary

5.1) Conclusion

This review article described the recent development and improvement of polysaccharide-based materials for medical technology. Cellulose and its derivatives, chitin and chitosan, hyaluronic acid, and pectin continue to be the subject of intensive research in the biomedical field because of their abundance and biocompatibility. Their diverse structure and ease of modification through their reactive functional groups allow for adjusting the final properties to meet the desired applications.

Some of the polysaccharide has inherent therapeutic effects. They are used in combination with other materials for additional or improved physicochemical properties of the products. While having its own limitations, each polysaccharide described in this review may have inherent properties that are particularly beneficial to a certain biomedical

application. For instance, chitosan and its derivatives possess mucoadhesive, hemostatic, and antimicrobial properties, which render them promising candidates for tissue engineering. Bacterial cellulose consists of nanofibrous cellulose and therefore having high surface area, high water retention, and in-situ moldability, but its resistance to biodegradability *in vivo* limits its use as tissue engineering scaffolds. Alginate easily undergoes gelation when in contact with metal cations, but the mechanical properties of the resulting gels are usually low. Choosing high molecular-weight alginate polymer might provide superior mechanical properties but the rise in viscosity may make it impractical for biomedical applications. Therefore, producing alginate-based composites or blends may be a better alternative. Hyaluronic acid possesses wound healing, hydrating, and antioxidative properties, therefore it has been widely used clinically in medical products. Pectin has recently been demonstrated to show antitumor and anti-inflammation effects, leading to growing interest in its potential use in the biomedical field.

Over the past few decades, significant advancements in the biomedical field have been made. Injectable hydrogels have been developed for use as therapeutic implants as they are less invasive than traditional preformed hydrogels. Then the idea of self-healing hydrogels has attracted great attention with the aim to avoid mechanical deterioration of the hydrogels after injection into the body. Three-dimensional (3D) scaffolds have been produced to effectively imitate the complex tissue of the host. Numerous studies on the modification of polysaccharides have been carried out for use as targeted drug delivery devices. The introduction of stimuli-responsive groups enables site-specific drug delivery and prolongs bioavailability of the drug carrier. Drug delivery systems based on nanoparticles have been used to facilitate the transport of small therapeutic molecules to the site of action and to reduce off-target side effects. Recently, a new generation of drug delivery devices not only deliver small-molecule drugs, but also new classes of therapeutics, which include but not

limited to, proteins and peptides, monoclonal antibodies, nucleic acids and live cells to provide new therapeutic functions. This evolution adds new challenges to the development of drug delivery devices based on polysaccharides.

In biosensor applications based on polysaccharides, biomolecules can be immobilized on a polysaccharide's physicochemical transducer surface, which can convert the biomolecule's strong contact with the analyte that serves as its binding partner into quantifiable, concentration-dependent electrical signals. Because of their hydrophilicity, high protein affinity, heavy metal ion chelation, biocompatibility, ease of surface chemical group modification, low cost, superior mechanical properties, and straightforward production process, polysaccharides exhibit a unique ability. Thus, polysaccharides can be desirable biosensor materials.

Polysaccharide-based biomedical materials have tremendous potential for the future due to their flexibility and diversity of physicochemical and biological properties. As they are also biodegradable, sustainable, and renewable, development of novel polysaccharide-based materials contributes to Sustainable Development Goals (SDGs) adopted by the United Nations, i.e. responsible consumption and production, and good health and well-being.

5.2) Future outlook

Considering the various benefits of polysaccharides for medical technology as highlighted in the previous sections, and with the exponential growth of world population and greater need for health products, the processing, advanced design and fabrication of polysaccharide biomaterials need further optimization for large scale explotation. For instance, it is essential to improve the efficiency of isolating the pure polysaccharide materials and their modifications. However, one of the challenges of polysaccharide utilization is typically related to variation of its original source. In addition, the properties can

vary and are still difficult to be controlled and hence polysaccharide-based materials with controllable properties is considered as one of the most important future goals.

From the industrial development viewpoint, although polysaccharide-based materials were successfully prepared from lab-scale with physico-chemical and biological properties, there is still concern over the purity and mass production. Therefore, considerable effort need to be devoted for safe, well-characterized and large scale production of polysaccharide for medical purposes.

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7) Conflict of Interest

The author declares no conflict of interest.

8) Biography

Dr. Pongpat Sukhavattanakul

Pongpat Sukhavattanakul is currently working as a postdoctoral fellowship research associate at Thammasat University Research Unit in Textile and Polymer Chemistry, Department of Materials and Textile Technology, Faculty of Science and Technology, Thammasat University, Thailand. He obtained his Ph.D. degree from The Petroleum and Petrochemical College, Chulalongkorn University, Thailand. He spent a year as a visiting scholar at University of Bayreuth, Germany. His current research interest focuses on the development of polysaccharide-based composite for medical material.

Dr. Penwisa Pisitsak

Penwisa Pisitsak is currently an associate professor in Department of Materials and Textile Technology, Faculty of Science and Technology, Thammasat University, Thailand. She received her PhD in polymer science from The Petroleum and Petrochemical College, Chulalongkorn University, Thailand. She spent a year as a visiting scholar at The University of Akron, OH, USA. Her current research interest focuses on the development of biocomposites and chemical modification of fibers.

Dr. **Sarute Ummartyotin**

Sarute Ummartyotin is currently associate professor in Department of Materials and Textile Technology, Faculty of Science and Technology, Thammasat University, Thailand. He received his PhD in polymer science from The Petroleum and Petrochemical College, Chulalongkorn University, Thailand, and spent a year as postdoctoral fellowship research associate at Center of Biocomposite and Biomaterials Processing, University of Toronto, Canada. His research interest focuses on development of fiber-based composite.

Dr. **Ravin Narain**

Ravin Narain, PhD, P.Eng, FRSC is a Professor in the Department of Chemical and Materials Engineering, University of Alberta, Canada. Prof. Narain has made significant contributions to research on the design, fabrication, and characterization of novel carbohydrate-based materials (glycopolymers, hydrogels and nanomaterials) for a wide range of applications. His research has also covered biomaterials, nanomedicine and regenerative medicine, with an emphasis on developing advanced materials as cancer therapeutics, anti-fouling and anti-microbial uses, and cell/tissue engineering advances. He has published over 180 articles in peer-reviewed and high impact journals and has edited several books namely Engineered Carbohydrate-Based Materials for Biomedical Applications (Wiley), Chemistry of Bioconjugates (Wiley), Glycopolymers: Synthesis and Applications (Smithers & Rapra), and Polymers and Nanomaterials for Gene Therapy (Woodhead Publishing & Elsevier). He was

section editor for the second edition of the book – Comprehensive Glycoscience (Elsevier). He is also on the Editorial Board for Frontiers in Chemistry (Polymer Chemistry), Polymer Chemistry (RSC), Biomacromolecules (ACS) and Polymers (MDPI). He was the recipient for a Distinguished Visiting Scientist Award from CSIRO (Manufacturing), Melbourne, Australia (2017-2018).

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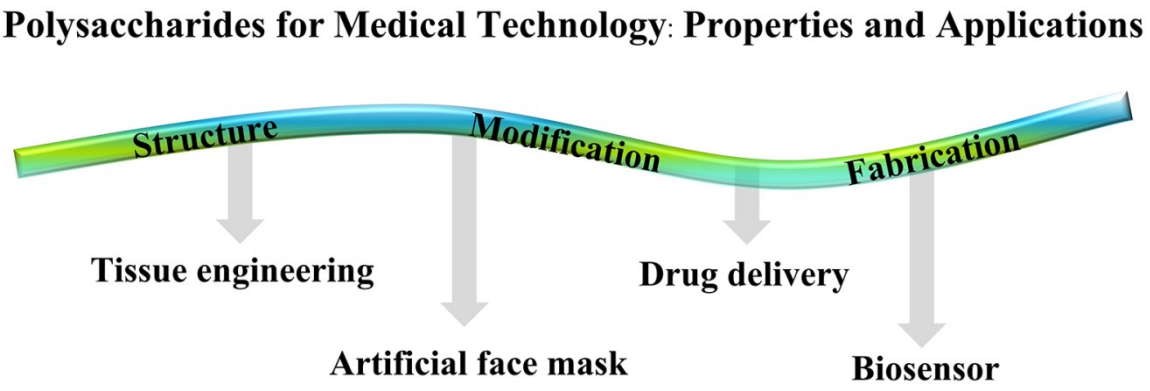
ToC Text



This review article provides a detailed overview of different types of polysaccharides and their medical applications ranging from drug delivery, tissue engineering, sensing and face masks. Different types of formulations of the polysaccharides are discussed such as hydrogels, nanoparticles and membranes.