Polysaccharide Based Implantable Drug Delivery

Subjects: Transplantation

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Implantable drug delivery systems advocate a wide array of potential benefits, including effective administration of drugs at lower concentrations and fewer side-effects whilst increasing patient compliance. Amongst several polymers used for fabricating implants, biopolymers such as polysaccharides are known for modulating drug delivery attributes as desired.

implants polysaccharides biopolymers drug delivery

1. Introduction

Implantable drug delivery systems offer wide therapeutic applications by providing targeted local delivery of drugs and long-term therapeutic effects. This effective delivery with lower drug concentrations results in minimizing the potential side-effects and ultimately enhancing the efficacy of treatment [1][2]. Drugs that would ordinarily be inappropriate for oral administration can be delivered as implants since, following implantation, the drugs would circumvent hepatic first pass metabolism and would also escape chemical degradation in the intestine and stomach, resulting in improved bioavailability. Controlled drug release over an extended period of time can be achieved by employing this system. The fluctuations in plasma drug concentrations such as attainment of peaks and valleys that occur from repeated intermediate dosing are avoided [2][3].

From the standpoint of patient compliance, the implantation might be relatively invasive, but good compliance can be achieved owing to a single-time implantation. Further, occurrence of any adverse effect that necessitates termination of treatment can be achieved by early removal of the implants. Moreover, hospitalization or persistent monitoring by healthcare staff might not be necessary for chronic conditions [2][3]. **Figure 1** illustrates the advantages of an implantable drug delivery system.

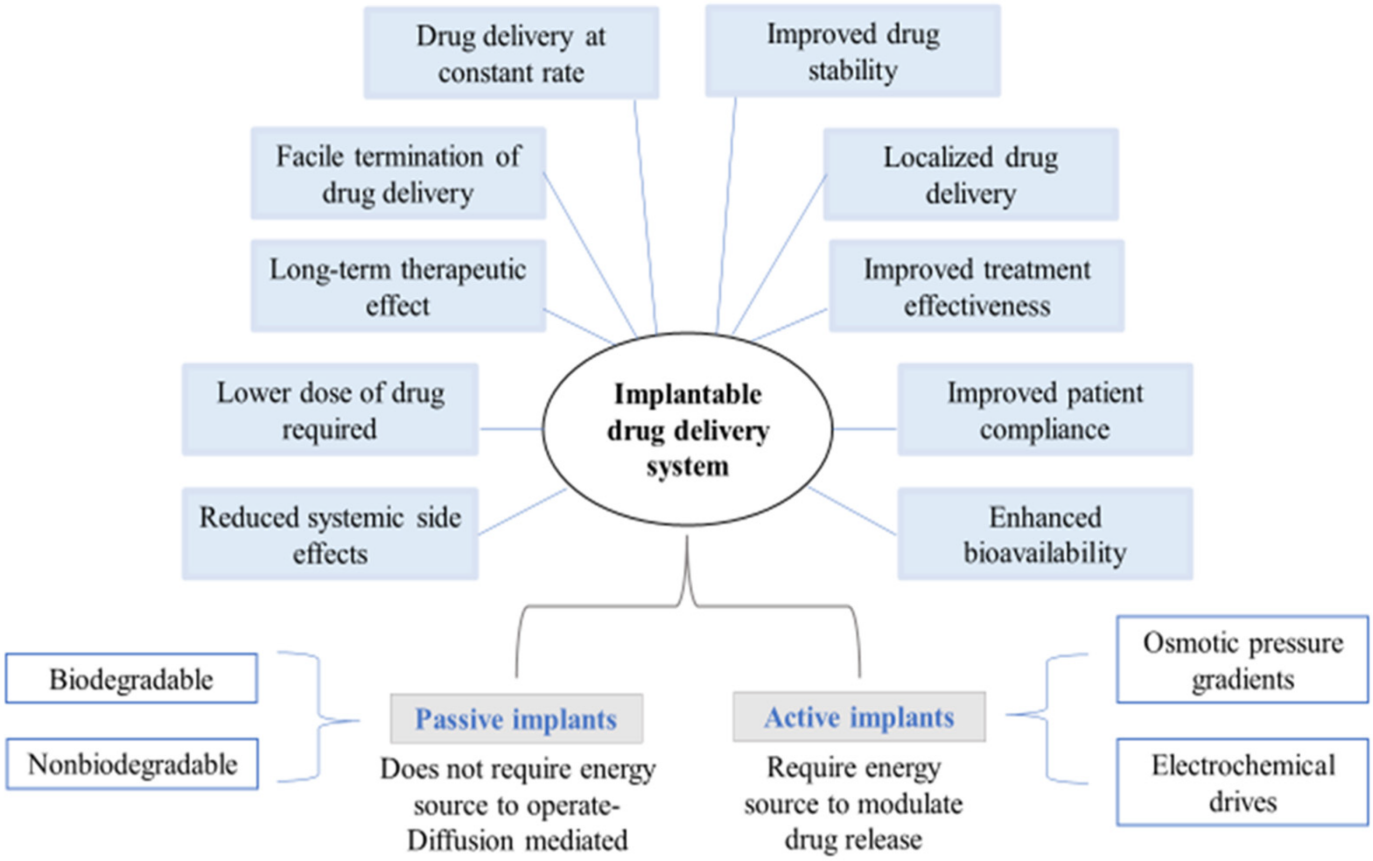

Figure 1. Design features of implantable drug delivery system.

2. Classification of Implantable Drug Delivery Devices

Implantable devices for drug delivery can be broadly categorized into two major groups: active implants and passive implants. Passive implants depend upon a diffusion-controlled phenomena to achieve drug release, whereas active systems are dependent on energy that serves as the key driving factor to control drug release. Further, passive systems are biodegradable or non-biodegradable and are simple with no moving parts. They use different kinds of polymers that enable to achieve membrane-controlled drug release kinetics from the delivery systems. Active or dynamic drug delivery implants are relatively complex but offer greater control over the drug release [1][2].

Biopolymers arise from living organisms whose degradation products are not immunogenic. Biopolymers offer several benefits over synthetic polymers, including a well-organized structure, degradability, and renewability, all of which possess the ability to be utilised in the design of therapeutic devices like implants. A wide range of alternative uses of biopolymers are also evident, including their use as scaffolds for tissue engineering owing to its three-dimensional porous structures, as controlled or sustained release vehicles for drug delivery, and as temporary prostheses [4][5] (**Figure 2**).

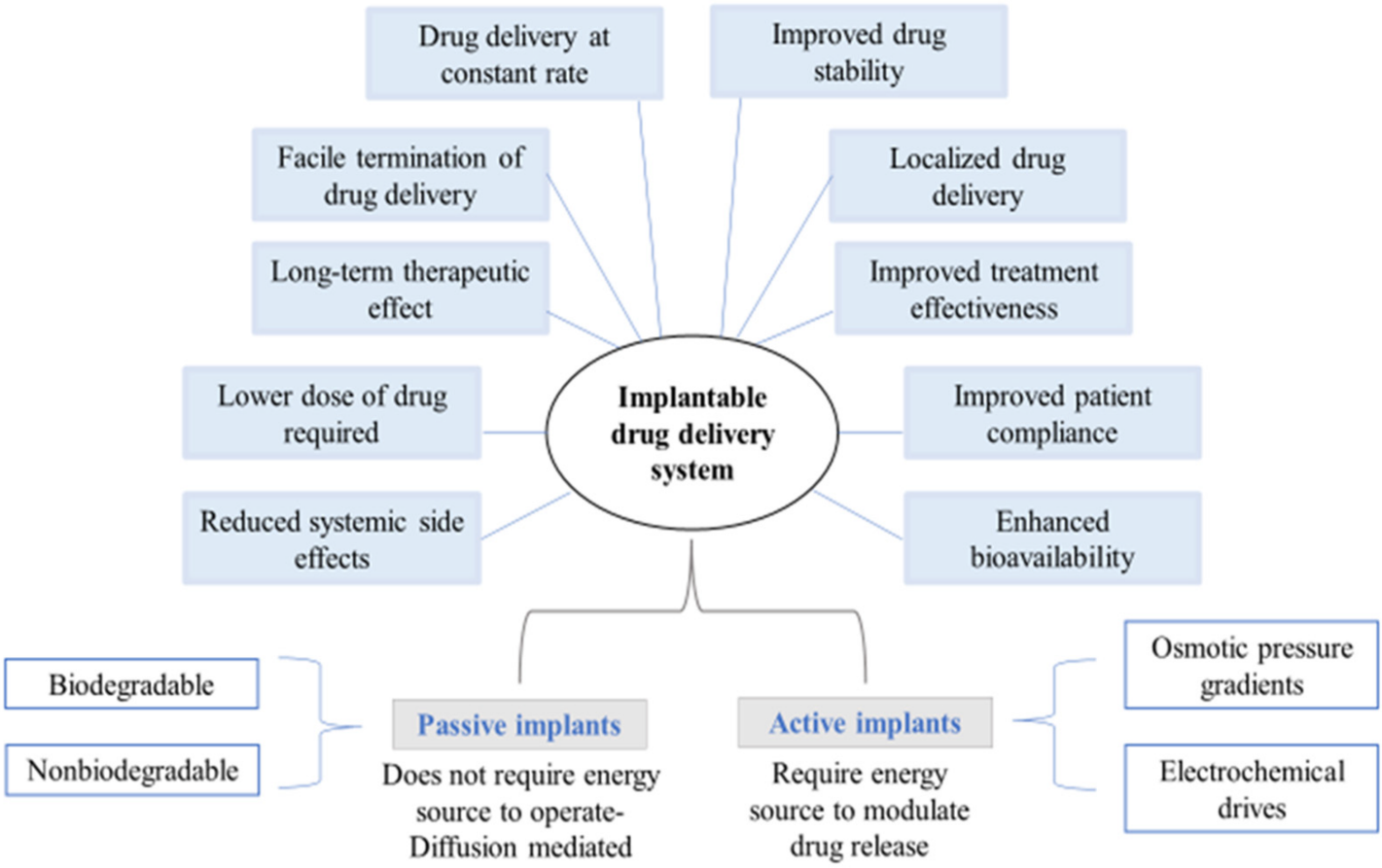

Figure 2. Drug delivery and biomedical applications of polysaccharides.

Polysaccharides belong to a diverse group of biopolymers comprising repetitive mono- or disaccharide units that are connected through enzyme-hydrolysable glycosidic linkages. These are widely used as controlled release drug carriers that impart remarkable physiological and physicochemical properties such as biocompatibility, biodegradability, and low immunogenicity [6]. Polysaccharide-based biopolymers are classified based on the source of their origin (**Table 1**).

Table 1. Classification of polysaccharide-biopolymers [5].

Origin	Polysaccharides
Plant/algal	Starch (amylose/amylopectin), cellulose, agar, alginate, carrageenan, pectin, konjac, guar gum
Animal	Chitin/chitosan, hyaluronic acid
Bacterial	Xanthan, dextran, gellan, levan, curdlan, polygalactosamine
Fungal	Pullulan, elsinan, yeast glucans

Moreover, advanced drug delivery systems based on polysaccharides can also improve the drug's bioavailability due to their capacity to entrap the drug molecules in its interspaces, biocompatibility, and ability to provide a controlled release of the drug molecules [6]. All these characteristics make them ideal for use in

References

implantable drug delivery. **Figure 3** dictates the prime attributes of polysaccharides, making them ideal for the development of implants.

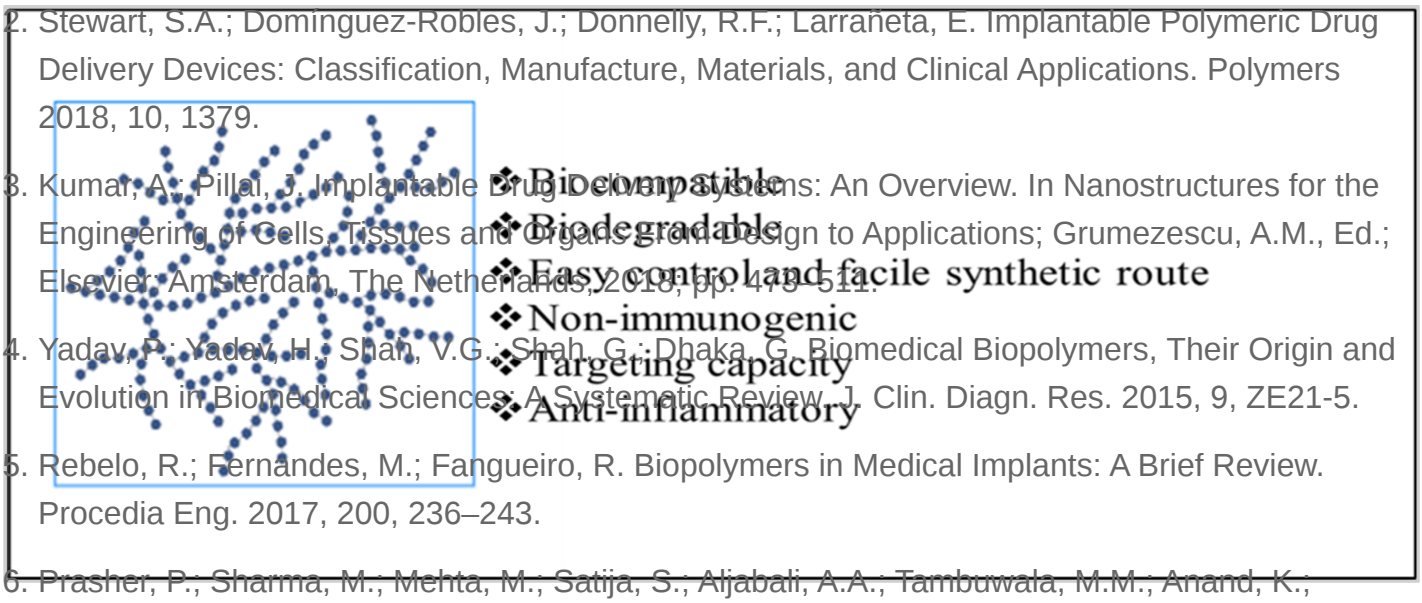

Figure 3. Unique characteristic of polysaccharides suitable for drug delivery and biomedical applications.

3. Strategies to Employ Polysaccharides in Implant Formulation

Implants can either be entirely made up of polysaccharides, contain polysaccharides as a part of the polymeric blend [7] or be coated with polysaccharides depending upon the therapeutic action required [8][9][10]. **Figure 4** displays the representation of these strategies for developing polysaccharide-based implants.

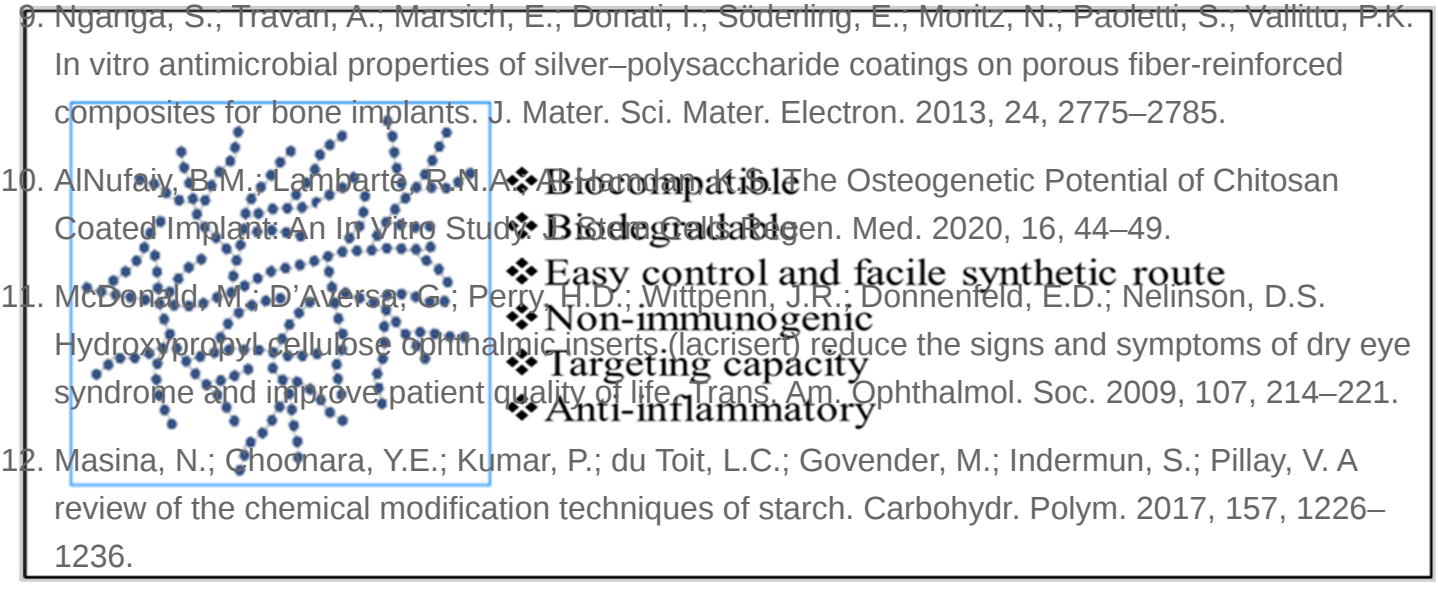

Figure 4. Schematic representation of strategies employed to develop polysaccharide-based implants.

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Further, the type of release pattern required governs the choice of polysaccharide or combination of polysaccharides. For instance, Lacrisert is a marketed ocular insert to be placed in the inferior cul-de-sac of the inferior eyelid and is indicated for the treatment of dry eye disease. The insert is entirely made up of hydroxypropyl cellulose (HPC), a cellulose-based polysaccharide, and dissolves gradually in the tear fluid [11]. The drug release from implants can also be modified by combining the matrix polymer with a secondary material, like a pore former, depending on the material properties of the implant. Certain polysaccharides are employed for their specific functions, e.g., water soluble cellulose-based polymers such as MC and HPMC are incorporated in the implants as pore formers.

4. Polysaccharide Based Polymers

4.1. Starch

Chemical modification of the surface-active hydroxyl functional groups in starch confers controlled release characteristics to it that aids in the efficient delivery of therapeutic molecules to the target site. The widely used methods of modification include esterification, etherification, oxidation, cross-linking, and cationization, that ultimately lead to alteration in the physicochemical properties of starch. Each glucose unit in starch consists of three free hydroxyl groups that, in the presence of oxidizing agents, under controlled temperature and pH conditions, yield carbonyl or carboxyl derivatives of reduced viscosity, high clarity, improved swellability, and better stability. Oxidation alters the surface morphology of the starch matrix, resulting in controlled biodegradation of the polymer and sustained release of the active agent over a specific period of time [12]. Etherification involves the alkali-catalyzed interaction of starch and alkyl oxides to yield hydroxyalkyl starches that promote disruption of internal bonds and enhance the freedom of motion in the amorphous region of starch granules. The weakening of bonds between starch chains depends on the degree of hydroxypropyl group substitution, which in turn enhances the solubility, ease of hydration, swelling power, and enzyme digestibility. On subjection to freeze-thaw cycling, hydroxypropyl groups, being hydrophilic in nature, prevent the separation of water through syneresis, thus enhancing the freeze-thaw stability [13]. Acetylated starch is an example of ester modification, where the substitution by acyl groups confers hydrophobicity to the starch molecule and enhances the thermoplastic characteristics. Hydrogen bond disintegration induced by acetylation in native starch results in retardation of crystallization and a lowering of pasting temperature that in turn enhances its swelling power [14]. The introduction of ammonium, phosphonium, imino, or sulfonium groups confers a positive ionic charge on starche and this process is referred to as cationization. The modification method can be either dry or wet. Dry cationization involves spraying the cationic molecules on dried starch in the absence of a liquid medium, whereas wet cationization involves a liquid medium mediated reaction between starch and the cationic molecules. The characteristic properties exhibited by cationic starches include improved dispersibility, solubility, and stability [15]. Cross-linking of starch is facilitated by the use of polyfunctional reagents such as sodium trimetaphosphate, phosphorus oxychloride, genipin, and epichlorohydrin that form covalent bonds with the starch granules, making the ordering of the internal granules denser than its native counterparts. Cross-linking improves the tolerance of starch towards processes involving high shear and extreme pH [16].

4.2. Cellulose

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Owing to its mechanical strength and biocompatibility, it is widely used in tissue engineering. Even though both plant-based as well as bacteria-based cellulose are natural, considerable differences have been observed between them with respect to purity and macromolecular characteristics. In comparison to plant-based cellulose, bacterial cellulose has a high value of Young's modulus [17][18][19], a high-water absorption capacity, and a high aspect ratio in its fibers [20]. Cellulose degradability can be induced by oxidation, which is a very effective approach. Many different oxidizing agents, including $NaClO_2$, CCl_4, nitrogen oxides, and free nitroxyl radicals, can be used to create oxidized cellulose [21][22]. The remarkable properties such as high absorbability, antiviral and antibacterial effect, non-toxicity, and anti-adhesive qualities have made oxidized cellulose a popular choice for use as a wound healing material [23][24][25].

4.3. Alginate

Extraction of alginate from seaweed is a multistage procedure. First, the dried raw material is treated with dilute mineral acid. Once the alginic acid becomes pure, it is converted into its water-soluble sodium salt in the presence of calcium carbonate, which is then transformed back into acid [26]. Alginate has great potential as a biomaterial for numerous biomedical applications, particularly in drug delivery, wound healing, and tissue engineering. Characteristics like biocompatibility, mild gelation conditions, and simple modifications for preparing alginate derivatives with new properties make it suitable for these possible applications. Alginates undergo acid-mediated hydrolytic cleavage [26]. The reaction consists of three stages: (a) protonation of the oxygen atom at a glycosidic bond; (b) hydrolysis of the conjugate to generate the carboxonium ion and the non-reducing terminus; and (c) fast addition of water molecules onto the carboxonium ion, resulting in the formation of a reducing end. Sodium alginate can be stored as a dry powder at room temperature for several months without undergoing degradation [27].

4.4. Chitosan

The low aqueous solubility and poor acid stability of chitosan limit its use in pharmaceutical products. Various structural modifications are performed at various functional groups for solubility enhancement of chitosan. Modifications at amino, hydroxyl or both amino and hydroxyl group forms N-modified, O-modified or N, O-modified chitosan derivatives. Incorporation of carboxymethyl groups at the C6-hydroxyl group or at the NH_2 functional group is an important method for enhancing chitosan's solubility [28][29].

4.5. Pullulan

Pullulan is a linear, unbranched, neutral exopolysaccharide obtained from the fungus *Aureobasidium pullulans* that is composed of maltotriose units interconnected by α-D-(1,6) glycosidic bonds. The three glucose units present in each maltotriose unit are in turn connected by α-D-(1,4) glycosidic bonds [30]. The distinctive linkage pattern of pullulan confers unique physicochemical properties to the biopolymer, including oxygen impermeability, adhesiveness, water solubility, and structural flexibility. Based on the strain and fermentation parameters, the molecular weight of pullulan ranges from 45 to 600 kDa, offering polymers of varying viscosities that play a crucial role in controlling the release of the active agent [31]. Mechanical stability of the pullulan matrix can be enhanced by interchain cross-linking. In practice, the concentration of cross-linkers should be well optimized to obtain the

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desirable release kinetics, water-absorption capacity depends on the degree of cross-linking. Pullulan is soluble in water, partially soluble in dimethyl formamide and dimethyl sulfoxide, and insoluble in other organic solvents. Imparting hydrophobicity to pullulan by chemical modification is highly desirable for its use in drug delivery applications. Grafting is one such method that involves either the free-radical mediated covalent attachment of hydrophobic monomers onto a polymeric backbone or the incorporation of pre-synthesized grafts to the polymeric chain charged with complementary functional groups [32].

4.6. Carrageenan

Carrageenan is a marine polysaccharide isolated from certain species of red seaweed belonging to the class Rhodophyceae. It is a linear, anionic, sulfated polysaccharide composed of alternative units of D-galactose and 3,6-anhydro-galactose interconnected by alternate α-(1,3) and β-(1,4) glycosidic bonds. The average molecular weight is above 110 KDa, in which the ester-sulfate content contributes to around 15 to 40% of the total content [33]. Gelation of carrageenan occurs on cooling in the presence of cations like Na+ and K+. Based on the number of ester-sulfate groups, its relative position, and the subsequent differences in solubility, carrageenan can be categorized into three main classes, namely, kappa (κ), iota (ι), and lambda (λ). The respective ester-sulfate content of κ, ι, and λ was found to be 20%, 33%, and 40%, which is prone to variations attributable to the differences in the species of the seaweed. Carrageenan with a higher ester content is characterized by low solubility temperature and gel strength [34]. In order to achieve control over the gelation properties and to overcome the challenges associated with the degradation of the polysaccharide on exposure to physiological conditions, various physical and chemical modification approaches have been investigated. Cross-linking between the charged polymer and counterions through the formation of physical bonds results in brittleness of the matrix. Hence, chemical cross-linking is mostly employed in drug delivery and tissue engineering applications, owing to its ability to form stable covalent bonds. Methacrylation of carrageenan has received wide attention as it confers the ability to be photocrosslinked. Silvia et al. in the presence of ultraviolet light and a chemical photo initiator, developed photocrosslinkable hydrogels of κ-carrageenan by varying the degree of methacrylation that enabled easy tailoring of properties such as viscosity, swelling ratio, elastic moduli, and pore size distribution [35]. However, in order to overcome the drawbacks associated with UV-crosslinking, photoinitiators that can be activated by visible light, such as Eosin Y and triethanolamine, have been investigated. Other modification approaches include de-esterification, carboxymethylation, thiolation, acetylation, and phosphorylation. Besides its biocompatibility and biodegradability, carrageenan possesses unique immunomodulatory properties that enable it to exert protective action against viral infections. The anti-viral activity is related to the degree of sulphation, location of the sulfate groups and molecular weight, and it has been identified that λ-carrageenan exhibited a greater inhibitory effect against drug-resistant viruses. Carrageenan also exhibits antimicrobial effects against foodborne pathogenic bacteria such as Staphylococcus aureus. The sulfate groups in carrageenan facilitate its binding to biologically active proteins that are responsible for its anticoagulant activity [36]. Prolonged drug release from the carrageenan matrix can be achieved as a result of gradient hydration on exposure to an aqueous environment that causes the matrix to swell, forming a gel or viscous outer layer. This layer acts as a polymeric shell to control the dissolution and diffusion of the loaded drug. The release rate is affected by the type of carrageenan used, and it has been found that κ-carrageenan exhibits a faster release rate. Its adhesiveness to mucosal and epithelial tissues serves as an added

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advantage for prolonging the drug release. Hence, carrageenan can be widely used in drug delivery applications due to its conformational versatile characteristics [37].

4.7. Dextran

Dextran possesses various important properties that make it a useful biopolymer for the development of implantable systems. It is a non-immunogenic, biocompatible, and biodegradable polymer with excellent solubility characteristics. It is generally not degraded when acted upon by the enzymes present in the upper gastrointestinal tract. The activity of dextranase enzymes located in the lumen of the large intestine, liver, kidney, and spleen is responsible for its degradation [38][39]. The molecular weight and branching of dextran dictate its rheological properties. Dextran, having a molecular weight in the range of 40,000 to 2 million, behaves like a Newtonian system up to a concentration of 10% [40]. High molecular weight Dextran shows pseudoplastic behavior. This can be explained by the fact that the forces generated during the application of shear would have broken the structural interaction between α-glucan chains in solution [41].

4.8. Hyaluronic Acid (HA)

HA is a weak polyelectrolyte, and therefore, its rheological properties in aqueous solution are affected by varying conditions of pH, ionic strength, and temperature. The change in pH of the aqueous buffered HA solution significantly affects its stability. HA degradation occurs at acidic (pH < 4) and alkaline (pH > 11) conditions [42]. At very high concentration, the HA solution has a very high viscosity, but on application of pressure, it flows easily. This shear-thinning behavior is due to the breakdown of intermolecular H-bonds and hydrophobic interactions under increasing shear rates [43][44][45].

4.9. Agar

Agarose is a neutral gel-forming molecule. Due to a similarity in their backbone structures, agaropectin and agarose are closely linked. The bacterial species do not enzymatically breakdown agar. Agarose and agaropectin consist of chemical structure alternating between 1,3-linked-B-D-galactopyranose, and 1,4-linked-3,6-anhydro-L-galactopyranose which can be masked to variable degrees by various sugar residues. Agarose is the component with the highest gelling tendency. Agar gels can withstand temperatures of up to 65 °C, but molten agar cannot gel until cooled to roughly 40 °C. Gels made of agar are very transparent [46]. Agar's exceptional ability to gel is solely due to hydrogen bonds created between its galactan chains, which offer high reversibility in gelling and melting points that differ by roughly about 45 °C. Agar was broken down by enzymes and acid to produce agarobiose and neoagarobiose, respectively, which shows that 1, 3-linked-β-D-galactopyranose and 1, 4-linked-3, 6-anhydro-α-L-galactopyranose alternate with agarobiose repeating disaccharide units to make up agarose. Agaropectin has a substantial number of acid groups, such as sulphate, pyruvate, and glucuronate groups, despite having what seems to be the same structural backbone as agarose.

4.10. Pectin

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Pectic acids are poly(α-D-galactopyranosyluronic acids) galacturonoglycans that lack or have a very low concentration of methyl ester groups. There are several levels of neutralization for pectic acids. Pectates are the name for the salts of pectic acids [47]. Pectin is a high-value functional food component that is frequently used as a stabilizer and gelling agent. Additionally, it is a plentiful, common, and multipurpose component of all terrestrial plant's cell walls. Pectin defines a family of oligosaccharides and polysaccharides that share similar properties, yet are exceedingly different in their fine structures [48].

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4.11. Gellan Gum

Gellam gum (GG) is a linear, negatively charged exopolysaccharide, also called as S-60 [49]. A bacterial polysaccharide called GG was initially made commercially by Kelco (now Monsanto PLC) using the bacterium Sphingomonas elodea. The de-esterification produces a stiff, brittle gel, while the native polysaccharide generates a weak, elastic gel [50]. At high temperatures, gellan molecules appear as random coils, but at low temperatures, they appear as double helices. GG can withstand acid and heat stress when being manufactured. It is ductile, non-toxic, biocompatible, biodegradable, and thermoresponsive. GG possesses mucoadhesive qualities. Due to its negative charge, this polysaccharide can create polyelectrolytes with polymers that have the opposite charge, such as chitosan. GG is regarded as a pseudoplastic at high shear rates. GG is not destroyed by an acidic environment and is resistant to enzymatic activity. The GG beads expand at high pH levels and remain stable at low pH levels. Additionally, it possesses a broad range of mechanical, acceptable rheological, and high processability qualities. The finest qualities of GG are its high efficiency, malleability, and gelling ability [49].

5. Biomedical Applications of Polysaccharide-Based Implantable Devices

5.1. Implants for Oral Cavity

HA is widely studied for its osteoinductive and osseointegration properties [51]. Surface treatment of HA on titanium (Ti) dental implants enhances migration, proliferation, adhesion, and differentiation of progenitor cells by enhancing the interaction between the bone and the implant (**Figure 5**a). This facilitates fixation of dental prosthesis precisely in the early loading phase, thus improving patient compliance [52]. Similarly, chitosan has also been reported to have osseointegration capacity. The Ti implants were coated with lactose-modified-chitosan (Chitlac) and this Chitilac-Ti implant was reported to have anti-inflammatory and anti-infective activity [53] (**Figure 5**b).

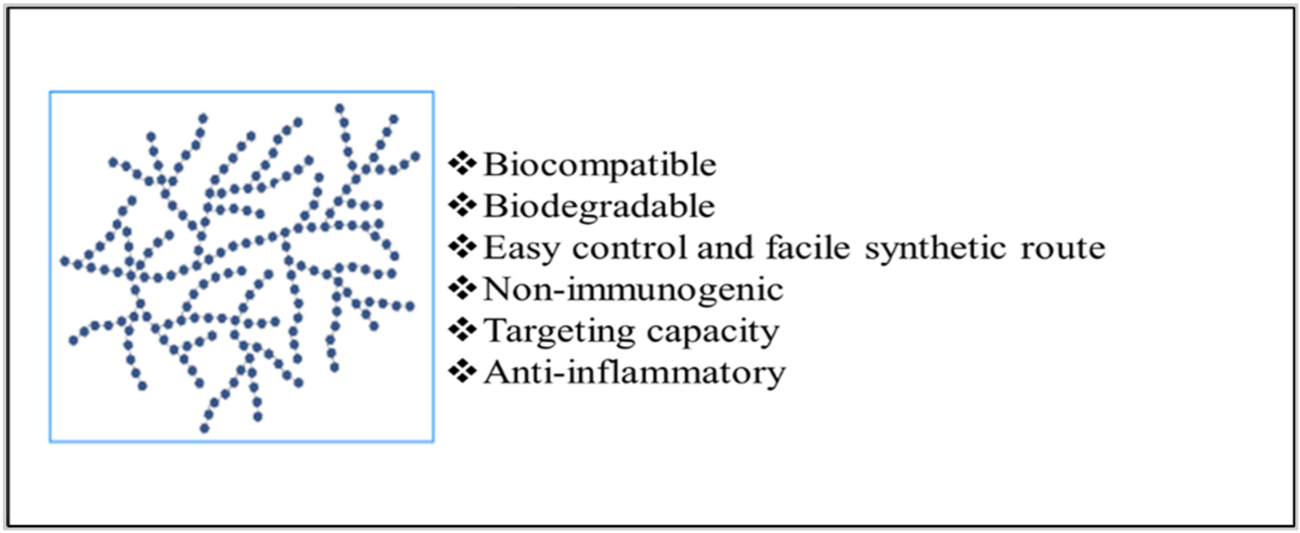

Figure 5. Schematic representation of: (**a**) Hyaluronic acid coated titanium implant; (**b**) Titanium implants coated with chitilac (lactose modified chitosan).

5.2. Implants for Nasal Cavity

Nasal implants are widely used for correction of internal and external nasal valve collapse, in combination also known as lateral wall insufficiency (LWI), leading to nasal obstruction, and also for the treatment of chronic rhinosinusitis (CRS) [54]. The ideal implant for the nasal cavity should be economical, non-toxic, inert, non-carcinogenic, easily available, and should be able to provide mechanical support [55][56]. Various nasal implants have been approved by the FDA, namely, Propel™ implant, Relieva Stratus™ MicroFlow spacer, the Sinu-Foam™ spacer, and many more. “Propel” is a mometasone-releasing PLGA based biodegradable implant approved for the treatment of CRS [57].

Silicon (Si) tubes are generally used as an implant for the treatment of the obstruction of nasolacrimal duct, but these implants are found to be associated with side effects such as allergic reactions and bacterial infection, which lead to failure of surgery. In order to overcome these limitations, Park et al. performed hydrophilic polysaccharide based multilayer nanofilm coating on Si-tubes, which has the capability to load as well as release antibacterial and anti-inflammatory agents, i.e., levofloxacin and prednisolone-21-acetate, respectively. They utilized chitosan (CHI) and carboxymethylcellulose (CMC) for the preparation of multilayer films for coating. They observed that CHI/CMC coated Si-tubes exhibited significant antibacterial activity by preventing the attachment of bacteria to them [58].

5.3. Bone Implants

Osteointegration between the implanted biomaterial and the surrounding bone is critical for the acceptance of implants by the human body as it eliminates the outgrowth of fibrous tissue at the bone-implant interface [59]. Polysaccharide-based biomaterials offer good potential in the treatment of critical-sized bone defects due to their tailorable chemical and biological properties. Chitosan based scaffolds are widely researched for tissue engineering purposes. Lyophilization of chitosan acetate solution results in the formation of porous interconnected structures that are ideal for cell seeding, cell migration, and nutrient supply that facilitate bone regeneration.

Electrospinning, particle aggregation, and solvent-exchange phase separation are other methods employed in the generation of chitosan scaffolds (**Figure 6**) [60].

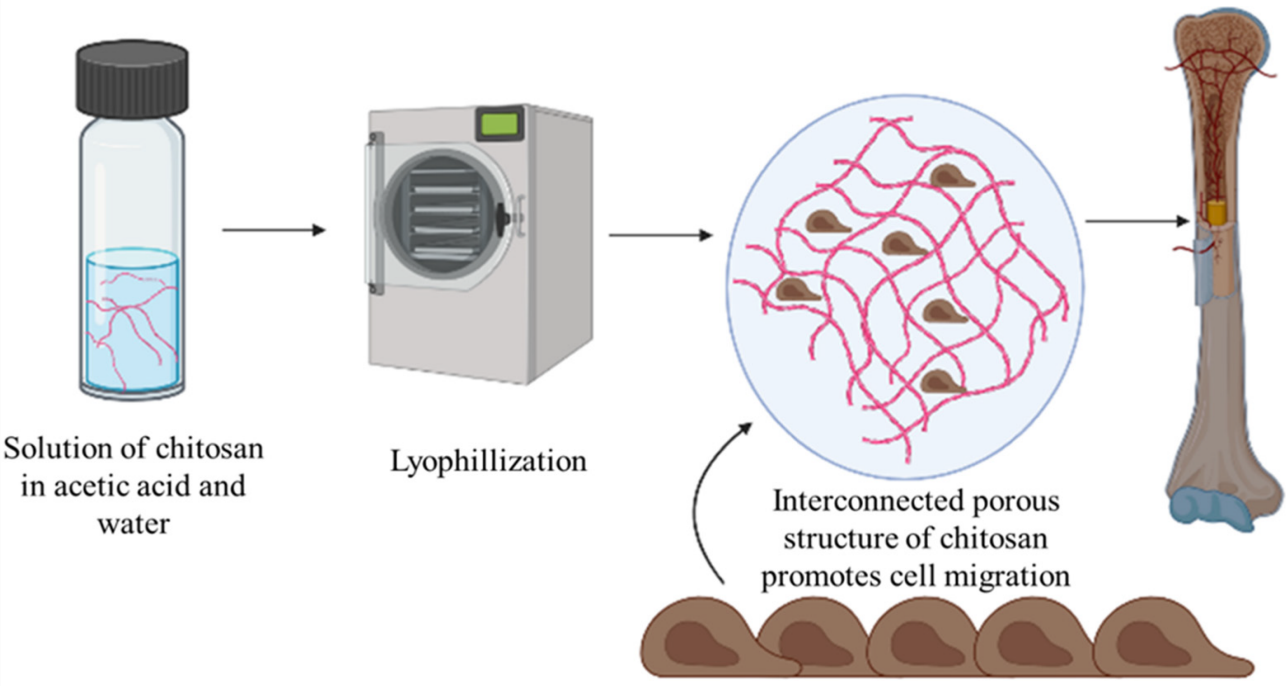

Figure 6. Diagrammatic representation of chitosan based implantable scaffold for bone regeneration.

Promotion of bone regeneration can be achieved by the delivery of therapeutic agents such as growth factors via implantable biomaterials. Lee et al. developed a chitosan–silica hybrid membrane for the delivery of bone morphogenetic protein-2 (BMP-2) and evaluated the bone healing capacity using in vivo and in vitro studies. BMP-2 exhibited excellent affinity towards the hybrid membrane due to its mesoporous structure. The efficacy of the membrane to act as a carrier was established by evaluating the induction of BMP-2 mediated cellular responses such as proliferation and differentiation in cell-culture studies. In vivo studies also indicated that a short-term implantation of the hybrid membrane for about 2 weeks accelerated the healing of bone defects [61].

Tissue engineering of non-load bearing bones, such as the trabecular, maxillofacial, or craniofacial bones, involves the use of bio-polymeric scaffolds owing to their definite microarchitecture and the ability to alter the spatio-temporal distribution of therapeutic molecules at the injury site. Agarwal et al. designed a novel alginate bead-based 3D implant using metronidazole as the model drug against bone infections caused by *E. coli*. Hexagonal close packed layers of calcium alginate beads were stacked to produce a patterned array of interconnecting octahedral and tetrahedral pores. The respective average diameter of the pores was found to be 262.9 and 142.9 µm. A 2.7-fold increase in the compressive modulus was observed on incubation of the implant in simulated body fluid. The increase in the rigidity of the implant with time could be attributed to the progressive ionotropic gelation of the alginate molecules. The osteoconductive nature of the implant was confirmed through in vitro studies, in which increased expression of differentiation markers such as runx2, alkaline phosphatase, and collage type 1 was observed in human mesenchymal stem cells [62].

The extrusion-based 3D printing technology is widely used in the fabrication of artificial bone graft substitutes that overcome the donor site complications inherently associated with autologous grafts. Bhattacharjee et al. developed a Zn^{2+} functionalized hydroxyapatite-starch composite for orthopedic applications. The poor mechanical strength of starch was hypothesized to be overcome by the formation of a zinc–starch complex. Experimental results revealed that a four-fold increase in compressive strength was achieved upon Zn^{2+} functionalization. The functionalized grafts maintained mechanical integrity throughout the 6-week dissolution study in simulated body fluid, whereas the non-functionalized HA-starch grafts were found to degrade within a week [63].

5.4. Implant for Ocular Use

Proteins and polysaccharides appear as ideal candidates for biodegradable drug delivery due to their biocompatibility, biodegradability, low immunogenicity, and pH stability under physiological conditions. Polysaccharides such as cellulose, hyaluronic acid, gelatin, collagen, xanthan gum, alginic acid, and chitosan have been successfully explored in drug delivery for eye diseases. These polysaccharides are extensively used as additives for improvements in permeability, contact time, and ocular absorption. Chitosan is the most widely explored polymer for ocular drug delivery due to its mucoadhesive property and inertness [64]. Manna et al. prepared intravitreal chitosan and polylactic acid-based methotrexate micro-implants to treat primary intraocular lymphoma. The results indicate that uncoated chitosan methotrexate implants administer drug approximately for 1 day, and after coating with polylactic acid, the implants show drug release for 50 days with a release rate of 0.2–2.0 µg/day [65]. In further continuation of their previous work, to improve the methotrexate release profile, Manna et al. utilized different combinations of PLGA-PLA coating. They observed two findings after the increase in the PLA content in PLGA: (a) the initial burst release effect gets reduced, and (b) delayed swelling and biodegradation of the micro implants. After coating with different ratios of PLA-PLGA, they observed drug release of 0.2–2.0 µg/day of methotrexate for an extended period of ~3–5 months [66].

5.5. Implants for Antiviral Therapy

The major limitation associated with antiretroviral therapy is its longer duration of treatment, leading to nonadherence to the medication [67]. In order to overcome these limitations, long-acting antiviral drug-loaded biodegradable implants have been developed which can offer sustained release of the antiretroviral drug for a considerable period of time, ranging from several weeks to months [68]. Though, the utilization of polysaccharide based coated implants for antiretroviral therapy is not yet established in the literature, various polysaccharides including heparin, galactan, fucoidan, glucan, cellulose, dextran, or dextrin have been reported to possess antiviral properties, that can be explored in the future for prevention of viral infections [69]. The layer-by-layer coating of polysaccharides on the implant surface can be used as a potential approach to prevent viral growth on implants [70]. The ability of sulfated polysaccharides to mimic the glycosaminoglycans present in the cell membrane confers it with distinct antiviral properties. Sulfated polysaccharides are known to interfere with the steps involved in the lifecycle of a virus such as adsorption, invasion, transcription, and replication and thus lead to an enhanced host immune response by accelerating the viral clearance rate. Hence, they offer a potential for further scientific and clinical research on implantable systems [71].

6. Conclusions

The use of polysaccharide-based implantable devices in the treatment of various diseases is becoming increasingly important. Polysaccharides are used in the development of implantable devices to improve its biodegradability and biocompatibility. In addition, polysaccharides also confer certain unique properties to the composites such as mechanical strength, which favors the tissue reconstruction process. Though only a few commercial products, as discussed in the previous sections, have been successfully developed, the scope of this field is emerging vastly and holds a promising potential to create a niche market. In recent times, a considerable number of efforts have been devoted towards the development of biodegradable polysaccharide implants by various researchers and it can be expected in the near future that these innovative composites can undergo scale-up and commercialization. This would serve as a breakthrough achievement in the field of biomedical sciences, thus expanding the scope of tissue engineering applications. Polysaccharide-based implanted devices or coated implants outperform synthetic or semi-synthetic polymers. Polysaccharide-based devices are now being studied/explored for their physicochemical features, which include surface morphology, in-vitro characterization, and in-vitro evaluation. However, once implanted as a medical intervention, the implants begin to integrate the unique interaction with human body elements such as cells, tissue, organs, or the endocrine system. As a result, it is critical to comprehend such a potential interaction and research the side effects of those implantable devices. Because polysaccharides are widely used in biomedical and pharmaceutical applications, further examination is required due to safety concerns. Polysaccharide-based materials are now regarded safe in terms of biocompatibility, biodegradability, and non-toxicity, although additional research should be conducted. Once, the safety of these devices is well-established, it will in turn enhance the patient acceptability. Further, the degradation rate and the mechanism of degradation has to be well-studied for each polysaccharide. The erosion rate can significantly affect the drug release. Quick degradation in the physiological environment and result in excessive release of the drug (burst release) and may also result in premature loss of strength of the polysaccharide. Thus, the degradation mechanism of each polysaccharide needs to be validated and must be well controlled so that a better idea can be obtained regarding its in-vivo behavior.