RESEARCH PAPER

Polysaccharide-Based Implantable Drug Delivery Systems for Long-Term Therapy

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ABSTRACT

The emergence of implantable drug delivery systems has created an opportunity for innovative new therapies for treating chronic health problems such as diabetes, cancer, chronic pain, neurological disorders and autoimmune disorders. With traditional methods of administering medication to systemic circulation, patients are often treated with an 'up and down' fluctuation of drug concentrations in their blood. These fluctuations can be experienced as off-target or unwanted side effects and poor patient compliance. The implantable drug delivery systems will allow for consistent delivery (over several weeks to months) of medication with a lower potential for systemic adverse effects and improved overall efficacy of treatment. Some polysaccharides, such as chitosan, alginate, hyaluronic acid, dextran, cellulose derivatives and pullulan, have been the most extensively studied of the biomaterials considered for use in implantable drug delivery systems. They have been investigated for their beneficial properties including biocompatibility, biodegradability, tunable crosslinking chemistry and low immunogenicity. Use of polysaccharide-based hydrogels, in situ forming depots, microspheres, nanofibrous scaffolds and composite implants will allow for the potential for programmable (controlled) delivery of drugs either through diffusion, degradation or via a stimulus of some type. Despite these initial studies showing promise in pre-clinical models of drug delivery using implantable systems, there are still significant challenges that must be addressed before these advanced drug-delivery devices can be successfully introduced into clinical practice. These challenges include long-term stability and biomechanical integrity, foreign body reaction, sterilization compatibility, and ability to be produced and manufactured at commercial scale in accordance with the established regulatory framework. This review examines the principles of design and engineering materials, therapeutic applications, translational roadblocks, and innovations in polysaccharide-based implantable drug delivery systems. Additionally, this review will identify the current research gaps that exist to develop predictive mathematical models describing degradation kinetics, modulating the immune response, and predicting the in-vivo performance of polysaccharide-based implants. Lastly, this review will offer future perspectives related to "smart" bioresponsive implants, hybrid/combined systems, and incorporation of precision medicine in the development of new, long-term therapeutic delivery systems.

Keywords: Polysaccharides; Implantable drug delivery; Long-term therapy; Biodegradable implants; Controlled release

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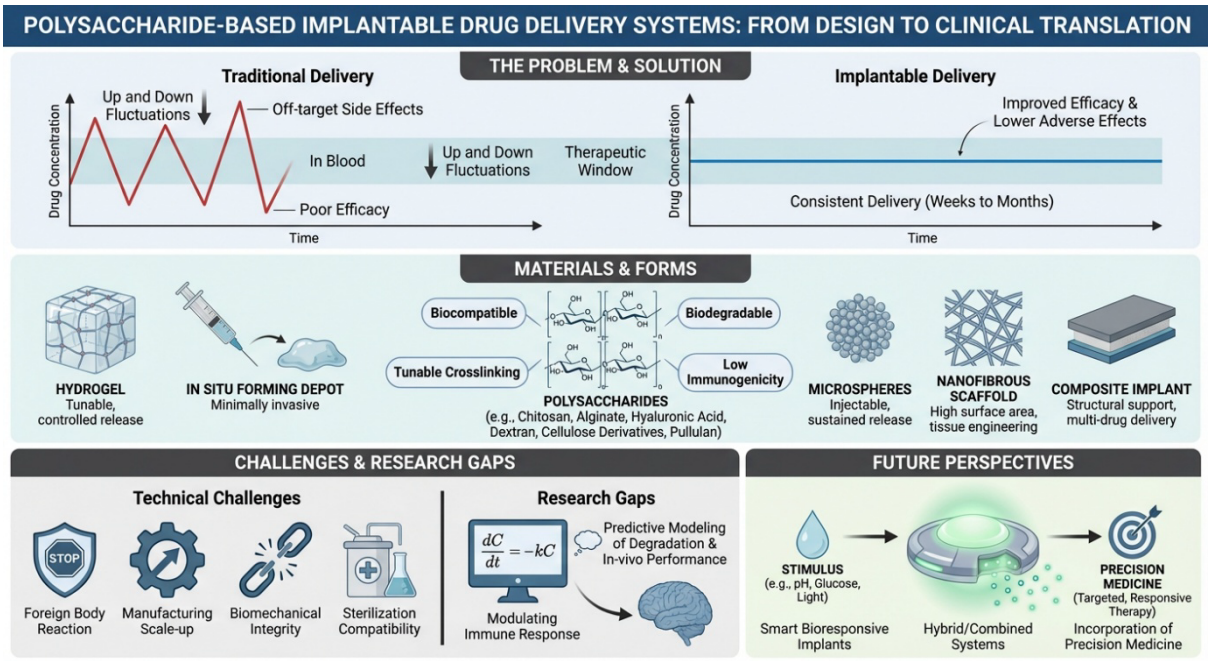

Highlights

- Implants made of polysaccharide can provide long-term drug delivery over periods up to several months.
- Matrices made from materials that are biodegradable minimize the need for surgical removal after implantation.
- Degradation and drug release kinetics are dependant on crosslinking density.
- Foreign body response will continue to be a translational problem.
- The future of implant material innovation is represented by smart, bioresponsive implants.

1. Introduction

Sustainable long-term treatment of chronic illnesses typically necessitates sustained therapeutic levels of drugs in the body over an extended duration of time--from weeks to years. Due to issues related to conventional oral or parenteral methods of administration, there exist quite significant fluctuations in blood plasma levels of drugs, lack of patient compliance, systemic toxicity and reduced effectiveness of drugs. Thus, implantable drug delivery systems have developed to provide local, long-term, controlled and consistent delivery of drugs straight to either the intended target site or into the general circulation(1).

Implantable systems have demonstrated their effectiveness in a variety of disease states (e.g., cancer, chronic pain, diabetes, hormonal disorders, diseases of the eye, neurologic disorders, etc) where long-term, consistent exposure to drugs at effective levels plays a pivotal role in successful treatment. Different types of drug delivery systems include, but are not limited to, biodegradable depots, injectable in situ-forming gels, microspheres, and nanofibrous scaffolds. The predictable nature of drug delivery through implantable drug delivery platforms promotes patients' compliance by delivering therapeutic level drugs on a sustained and regular basis while minimizing the systemic side effects of drugs(2).

Polysaccharides are one of the most attractive classes of biomaterial used for development and application in implantable drug delivery systems because they are derived from natural sources, exhibiting very good biocompatibility, being biodegradable, and exhibiting structural versatility. The polysaccharide chitosan, which is derived from chitin, has cationic charge and bioadhesion characteristics; while alginate, which is an extract from brown seaweed, forms ionically crosslinked hydrogels that can be designed with a range of mechanical strengths. Hyaluronic acid, which is a naturally occurring polysaccharide, has excellent compatibility with tissue and exhibits very good affinity with cell surface receptors. For additional structural stability, dextran, cellulose derivatives, and pullulan can easily be modified chemically. The large quantities of functional groups (–OH, –COOH, –NH2) in these polymers permit development of various types of chemical reactions to create more desirable characteristics in the material, such as

alteration to the manner in which the drug is delivered based upon rates of degradation from the implantable material(3).

Through three different mechanisms--diffusion-controlled, polymer degradation, and swelling-mediated--polysaccharide-based implantable drug delivery systems depend upon diffusion as a means to deliver drugs to the general circulation or at the intended target site. The density of the crosslinking network has a considerable impact on the mesh size as well as how quickly drugs will diffuse out of the implantable system. While the use of chemical crosslinkers offers the potential for long-term stability of implantable systems, ionic crosslinking offers more flexibility by creating reversible and stimulatory-response behaviors in implantable drug delivery systems(4). By using injectable in situ-forming polysaccharide gels, a physician can implant these types of systems with little invasiveness while providing long-term local drug delivery by forming depots upon interaction with physiological conditions(5).

While progress has been made to utilize polysaccharide-based implantable drug delivery systems, many challenges still exist that present barriers to permitting their routine clinical practice. In general, there is much complexity when one attempts to predict the long-term degradation kinetics of polysaccharide implants when placed within the body (due to a variety of different factors such as pH levels, levels of enzymatic activity, and the patient's immune response). The potential for foreign body reactions (FBR) to form fibrotic encapsulation about implantable systems significantly alters the kinetics of drug release and, as such, can greatly reduce their therapeutic effect(6). The need to achieve a balance between mechanical strength and structural stability while at the same time permitting the degradation of the implantable system will help avoid premature structural failure or incomplete degradation of the system. Additionally, the process used to sterilize the implant (e.g., ethylene oxide, gamma irradiation) can significantly affect the molecular integrity and the stability of both the polysaccharide polymer and the drug contained(7).

In addition to the challenges noted above, significant challenges to translating polysaccharide systems to the clinical environment are associated with the capability of producing sufficient product quantities in order to demonstrate regulatory compliance with Good Manufacturing Practices (GMP). The manufacturing process must be designed to minimize the risk of significant batch-to-batch variations in product produced with polysaccharides, including residual impurities and reproducibly formed crosslinks. Furthermore, the approval process for products classified as combination products, which include biodegradable implants, will require extensive evaluation of biocompatibility and safety(8).

Efforts have focused upon utilizing newer innovations such as hybrid composite materials, development of nanostructured scaffolding, and systems that are responsive to various stimuli (e.g., pH, temperature) to develop more effective methods of achieving adaptive release of drugs from implantable systems. In addition, the integration of predictive modeling tools and computer-based modeling platforms will help to enhance the overall understanding of the various mechanisms resulting in the degradation of polysaccharide implants and the release of drugs from the implants(9).

This review discusses the various aspects of the material design strategies, the therapeutic applications, the challenges and barriers associated with the translation of polysaccharide materials into clinical applications, and future directions related to polysaccharide-based implantable drug delivery systems for use in long-term patient therapies(10). The importance of developing a comprehensive collaborative strategy to bridge the materials science discipline into the clinical practices and regulatory processes associated with implementing polysaccharide-based implantable drug delivery into the practice of medicine has been emphasized(11).

Table 1. Common Polysaccharides Used in Implantable Drug Delivery Systems

Polysaccharide	Key Functional Groups	Implant Format	Therapeutic Application	Limitation	Reference
Chitosan	$–NH_2$	Injectable hydrogel	Cancer, pain management	Variable solubility	(12)
Alginate	$–COO^-$	Ionically crosslinked depot	Diabetes, protein delivery	Weak mechanical strength	(13)

Hyaluronic Acid	–COOH	Injectable gel	Ophthalmic therapy	Rapid enzymatic degradation	(14)
Dextran	–OH	Microspheres	Hormone therapy	Limited targeting	(15)
Cellulose derivatives	–OH	Solid implants	Long-term release systems	Slow degradation	(16)
Pullulan	–OH	Crosslinked scaffold	Tissue engineering	Moderate mechanical strength	(17)

2. Material Engineering and Crosslinking Strategies for Long-Term Implant Stability

Material engineering parameters primarily affect the performance of polysaccharide-based implantable drug delivery systems, with crosslinking strategy, network architecture, mechanical integrity, and degradation kinetics being the four most significant parameters. Implants that will be supported by long-term (weeks/months) therapy must maintain structural stability over the same period while allowing for predictable and controlled drug release(18). Achieving these competing properties is still a main obstacle to be overcome in the design of polysaccharide implants(19).

Crosslinking will have a significant impact on the mechanical strength of the implant, its swelling characteristics, mesh structure, and rate of degradation. Ionic crosslinking, which is used in most alginate-based systems with the use of divalent cations such as calcium, forms reversible networks that are biocompatible and do not negatively impact the processing conditions; however, these ionically crosslinked networks will undergo gradual ion exchange with the surrounding biological environment once implanted, thus decreasing their mechanical integrity and increasing the rate of degradation. Therefore, long-term ionic systems may require some form of secondary stabilization via covalent reinforcement(20).

Covalent crosslinking produces an increase in structural integrity, and improved integrity of the implanted material over time. Chemical crosslinkers (e.g. genipin, glutaraldehyde (use caution), carbodiimide-mediated coupling, and photo-crosslinkable methacrylate modifications) have been used to enhance the strength of various matrices (e.g. chitosan, hyaluronic acid, and dextran). Because of the ability to fine-tune crosslink density (common to both ionic and covalent crosslinking) with covalent networks, both diffusion coefficients and drug release kinetics can be precisely controlled(21). HoweverThe creation of hybrid polymer systems involves two steps, which include ionic bonding and then covalently bonded networks, with the ionic bonding allowing for rapid transformation of the polymer to a gel followed by creating a stable gel via covalent bond formation. The use of ionic and covalent crosslinking allows for creating different structure types of crosslinked polymer gels with known degradation rates(22).

In addition to the crosslinking method, they will also be impacted by the overall architecture of the polymer network. For example, high molecular weight polysaccharides create a dense polymer network that is composed of closely packed polymer chains with small mesh size and slow drug diffusion; therefore, the rate of drug release will be reduced(23). There is a potential impact because of increased density on the efficiency of drug loading and will potentially result in incomplete degradation of the implant. When you are looking to do both, use the same level of polymer concentration and the same level of substitution for both processes(24).

Degradation kinetics are one of the most important things to look at when evaluating how a material will perform long-term. Factors influencing the degradation of polysaccharides are hydrolysis, enzymatic activity, and oxidative breakdown, and many in vivo factors will affect the polysaccharide degradation rate, including local enzymatic activity, local pH, inflammation in the surrounding area, and the location of the implants. Because of the variation in biological microenvironments, it is extremely difficult to predict how fast the material will degrade. Most pre-clinical polysaccharide degradation testing is done in vitro; however, many in vitro degradation methods do not accurately represent in vivo degradation of polysaccharides(25). It will be extremely important to establish physiologically relevant models for polysaccharide degradation in order to accurately

anticipate how the drug will perform clinically and become commercially viable(26).

For load-bearing implants or those designed to provide structural support, concerns will be the mechanical strength of materials used in such. The addition of reinforcing materials (nanocellulose fibers, graphene oxide, and biodegradable synthetics such as polycaprolactone) to the breast of a polysaccharide will enhance the mechanical properties of the material. Composite systems can provide sufficient tensile strength and degradation rates along with potential additional regulatory challenges for product approval(27).

Injectable in situ forming implants provide another engineering concept. Both pH-responsive and thermosensitive polysaccharides have been investigated for their ability to convert from liquid to gel when injected, providing for local depot status of drugs(28). An example of an injectable thermosetting polymer system that has been evaluated for its ability to provide a thermosetting product is chitosan with β-glycerol phosphate. Care must be taken to ensure that gelation, mechanical integrity of the polysaccharide, and the use of this technology in a clinical setting are controlled(29).

Engineering decisions regarding material manufacture will be influenced by the sterilization compatibility of the candidate material. Any of the various sterilization techniques such as gamma radiation, ethylene oxide, and steam sterilization can significantly affect the molecular weight and/or crosslink integrity of the polymer. Therefore, a sterilization technique that preserves stability of the drug and mechanical properties of the polymer is required(30).

Current research and technology advances; however, there are still research gaps in development of medical devices using PCM. The long-term mechanical integrity of PCM developed and implanted into a living organism is not well established. No devices exist that use a standard method of modeling degradation with regards to designing medical devices composed of polysaccharides(31). Additionally, multiple areas of future research exist concerning the crosslinking density, type of inflammatory response of the tissue, and time(32).

To advance engineering efforts concerning the development of durable drug-delivery implants, an emphasis should be placed on utilizing biodegradable crosslinks with known degradation rates, the use of composite polymer systems having good mechanical properties and developing mathematical modeling with empirical testing to model and predict degradation and diffusion properties of polysaccharide-based gels when utilized in vivo(33).

In summary, the engineering of materials is possible through the use of crosslinking strategies and by utilizing appropriate polymer network architecture and degradation kinetics and mechanical properties of the implant. Success is based on the effective use of systematic approaches to control polysaccharide network architecture, degradation rate of an implant, and mechanical performance of the implant to improve the efficiency and accuracy of the use of chronic therapies(34).

Table 2. Crosslinking and Engineering Strategies in Polysaccharide-Based Implants

Strategy	Crosslink Type	Effect on Stability	Therapeutic Relevance	Limitation	Reference
Ionic crosslinking (Ca^{2+}-alginate)	Reversible ionic bonds	Moderate mechanical strength	Injectable depots	Ion exchange instability	(35)
Covalent crosslinking (genipin)	Stable chemical bonds	High mechanical stability	Long-term implants	Residual crosslink toxicity	(36)
Methacrylate photo-crosslinking	UV-induced network formation	Controlled density	Customizable implants	UV exposure limitations	(37)
Dual crosslinking	Ionic + covalent	Enhanced durability	Extended release therapy	Complex synthesis	(38)
Nanofiller reinforcement	Composite formation	Improved tensile strength	Load-bearing implants	Regulatory complexity	(39)

Thermoresponsive gelation	Physical transition	Minimally invasive placement	Local depot formation	Gelation variability	(40)

3. Drug Release Mechanisms and Long-Term Kinetics Modeling

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Table 3. Drug Release Mechanisms in Polysaccharide-Based Implantable Systems

Release Mechanism	Governing Factor	Kinetic Model	Advantage	Limitation	Reference
Diffusion-controlled	Mesh size, drug MW	Higuchi model	Predictable for stable matrices	Limited in degrading systems	(37)
Degradation-controlled	Polymer breakdown rate	First-order/Mechanistic models	Sustained release	Variable in vivo conditions	(40)
Swelling-mediated	Hydration kinetics	Korsmeyer–Peppas	Controlled expansion	Initial burst risk	(43)
Stimuli-responsive	pH/enzymatic triggers	Custom mechanistic models	Targeted release	Environmental variability	(46)
Zero-order release	Balanced diffusion/degradation	Zero-order model	Constant drug levels	Difficult to maintain	(49)
Multi-phase release	Combined mechanisms	FEM-based modeling	Realistic prediction	Complex computation	(6)

4. Therapeutic Applications of Polysaccharide-Based Implantable Systems

Polysaccharides have emerged as a promising option for delivering drugs over long periods of time in chronic disease management, due to their ability to provide prolonged, localized delivery of drugs and naive systemic administration for patients who experience negative systemic effects of drugs distributed throughout the body(7).

For example, there is potential to use polysaccharide-implantable drug delivery systems for treatment of cancer through the placement of polysaccharide matrices containing chemotherapeutic agents (such as doxorubicin or

paclitaxel) directly at the site of the resected tumor, thus allowing for sustained release of chemotherapeutic agents from the matrix with limited exposure of the agents to other parts of the body. This may result in greater therapeutic efficacy and lower toxicity due to decreased distribution to other tissues via the systemic circulation. Similarly, polysaccharide hydrogels that release immune-modulating agents may have some effect on changing the cancer microenvironment; however, variations in vascularization and the immune response to tumors may impede the effectiveness of drug distribution to the intended site, as well as the consistency of delivery(10).

For patients with diabetes, studies have evaluated the use of microencapsulated insulin or pancreatic islet cells (using alginate) as an approach to achieve long-term serum glucose control, and to protect the encapsulated islet cells from destruction by the immune system. Alginate microcapsules have shown success in vitro with releasing insulin, but the clinical application of the microcapsules has been hampered due to their long-term stability and to prevent formation of fibrotic encapsulations(12).

Finally, chitosan and cellulose may also be beneficial in managing chronic pain with implantable drug delivery systems, as both polymers can provide a depot system that releases an analgesic agent (opioids or local anesthetics), to provide the patient with a continued supply of analgesia without the risk of developing an addiction or experiencing any of the other systemic side effects associated with these types of systems. Additionally, hydrogels capable of forming after injection may provide a means for delivering drugs near nerves using minimally invasive procedures.Control of burst release is a substantial consideration for safety in controlling possible overdose or unintentional overdose(15).

Polysaccharide-based implants for sustained delivery of anti-VEGF agents or corticosteroids into the eye have been explored in ophthalmology for use in conditions such as AMD or DR. Hyaluronic acid (HA)-based hydrogels have demonstrated excellent biocompatibility with respect to ocular tissue. Long-term eye implants need to maintain optical clarity and structural integrity and to avoid an inflammatory response(20).

Neurologic disorders, especially Parkinson's Disease and epilepsy, may benefit from implantable devices that can provide local delivery of neurotransmitters or neuroprotective medications. Matrix materials such as dextran or chitosan that are implanted intracerebrally provide sustained release and reduced systemic exposure. Biocompatibility and neuroinflammation must be evaluated rigorously for all CNS implantations(22).

Hormonal therapies providing birth control have been delivered via implants as examples of established clinical applications for polymeric systems. Synthetic polymers have typically been used as the basis for currently marketed polymer-based implants; however, polysaccharide-based biodegradable alternatives are being studied for future applications to eliminate the need for surgical removal of implants. Predictable degradation of a polymeric implant without the formation of an inflammatory capsule is particularly applicable to hormone therapies(25).

Despite much promise from preclinical studies of biodegradable polysaccharide-based implants, there are still substantial gaps in the research. To date, limited long-term clinical data have been produced for biodegradable polysaccharide implants in humans. Additionally, the foreign body response (FBR) to a polymeric implant may produce a fibrotic capsule that can alter the diffusion of drug and potentially decrease the effectiveness of the implant. Furthermore, differences in the degradation rate of a polymeric implant at the implantation site may complicate the predictability of dosing(27).

Combination therapy implants that combine several drugs into a single device and employ staggered release kinetics represent a potential area for new innovative developments in drug delivery. Combination therapy implants will likely provide substantial benefits in the treatment of cancer and chronic inflammatory diseases. However, increased complexity in release modeling and regulatory approval will be a challenge for the development of multifunction combination therapy systems(29).

Future innovations in the area of drug delivery will focus on developing smart implants, which have the ability to sense and respond to physiological conditions (e.g. a glucose-responsive insulin-delivering implant or an inflammation-responsive anti-inflammatory implant). Integration of a biosensor into an implantable drug delivery system may lead to the creation of closed-loop drug delivery systems(30).

In summary, polysaccharide-based drug-delivery implants have the potential for use in many areas of medicine (cancer, metabolic disorders, pain

management, ophthalmology, neurologic disorders, and hormonal therapy and will require further research to demonstrate long-term stability, immune compatibility, and predictable release modeling in order to expand their utilization in medical practice(32).

Table 4. Therapeutic Applications of Polysaccharide-Based Implantable Drug Delivery Systems

Therapeutic Area	Polymer Used	Drug Delivered	Clinical Goal	Key Advantage	Limitation	Reference
Oncology	Chitosan hydrogel	Doxorubicin	Local tumor control	Reduced systemic toxicity	Tumor heterogeneity	(34)
Diabetes	Alginate microcapsule	Insulin/Islet cells	Glycemic regulation	Immune shielding	Fibrotic encapsulation	(36)
Chronic Pain	Chitosan depot	Local anesthetics	Sustained analgesia	Reduced dosing frequency	Burst release risk	(38)
Ophthalmology	HA hydrogel	Anti-VEGF agents	Long-term retinal therapy	Biocompatibility	Ocular inflammation risk	(40)
Neurology	Dextran scaffold	Neuroprotective agents	Local brain delivery	Targeted release	Neuroinflammatory response	(44)
Hormonal therapy	Cellulose-based implant	Hormones	Long-term contraception	Biodegradable alternative	Degradation variability	(46)

5. Research Gaps, Foreign Body Response, and Translational Barriers

Polysaccharide-based drug delivery systems in terms of long-term implantation face several translational hurdles, notwithstanding the promising therapeutic uses they may present. The most significant barrier to these systems is the Foreign Body Response (FBR), an intricate immunological response to implanted biomaterials. Although polysaccharides have reasonable biocompatibility, long-term implantation will inevitably lead to protein adsorption, macrophage recruitment, and fibrotic capsule formation after the implant has been placed. These events may adversely impact the drug release kinetics and functionality of the polysaccharide-based drug delivery implant(48).

The FBR is preceded by the rapid adsorption of plasma proteins on the implant surface and forms a provisional matrix, which will influence the subsequent cellular response. Adhered macrophages may eventually fuse to form FBGCs, producing pro-inflammatory cytokines and reactive oxygen species. Chronic inflammation may result in fibrous encapsulation that creates a barrier of collagen surrounding the implant, resulting in inhibiting drug diffusion. As a result, fibrous encapsulation may significantly alter pharmacokinetics of polysaccharide drug delivery implants by providing increased diffusion resistance or increasing the rate of implant degradation through the action of inflammatory enzymes(50).

The chemistry of polysaccharides will cause them to interact with the cells of the immune system differently. For example, chitosan will provide a cationic charge, which will promote cell adhesion but will also stimulate the activation of macrophages. The purity of alginate and its endotoxin content will influence the degree of inflammatory free response following implantation. Differences in molecular weight, the degree of substitution, and other polysaccharides will further complicate the prediction of how individual polysaccharides will have predictable immune responses(6). Thus, it is imperative that standards for purification of polysaccharides are established to limit adverse immune responses(8).

FinallyPolysaccharides usually convert to low-toxicity sugars and oligosaccharides. However, polysaccharides can create an unexpected response when they become impacted by accumulation of the polysaccharide or changes in the metabolism of the polysaccharide at a particular implant site. Therefore, long-term biocompatibility studies are needed for the use of implants for long periods of time (months to years)(10).

Another translational issue related to sterilization compatibility is that gamma irradiation may create chain scission, which may impact the mechanical strength and kinetics of degradation of the implant; further, there may be cytotoxic effect due to the presence of ethylene oxide residues, if not completely removed. Thus, it is important to validate an effective method of sterilization verification that will not compromise the properties of the implant(13).

Due to an increase in inflammation caused by the lack of mechanical properties of the implant that are similar to the tissue surrounding the implant, and/or due to the increase in chronic irritation due to higher rigidity of the implant than that of surrounding tissue, developing implants with mechanical properties similar to those of the target tissue will decrease the amount of foreign body response (FBR) and increase the integration of the implant into the body(15).

There is also a lack of information and data predictive models for in vivo performance for transformation of mechanical properties to the implant. Most other degradation and release studies have been conducted in analytical/in vitro conditions, which do not represent actual dynamic (moving) in vivo conditions such as stress and immune response. Thus, developing advanced in vitro models that demonstrate the effect of using immune cells along with flowing liquids would translate much closer to in vivo(17).

Substantial obstacles exist on the regulatory side of the translation. Generally, implantable devices are combination products that require rigorous evaluations of biocompatibility, degradation, pharmacokinetics, and performance of the device prior to obtaining regulatory approval; therefore, regulatory approval will not be granted until complete toxicological evaluations (i.e. genotoxic, immunotoxic, and long-term cancer evaluation) are conducted, as well as validation of reproducibility of products from batch to batch and good manufacturing process (GMP) compliant manufacturing processes(20).

The translation of polysaccharides as implantable drug delivery systems is influenced by the scalability and economic feasibility of polysaccharide extraction and purification methods to be at a minimum at the grade of pharmaceuticals. The cross-linking reaction must also occur reproducibly without residual toxic chemicals. Composite implants synthesized with nanomaterials or hybrid polymers will likely receive more scrutiny(23).

Future research must focus on developing anti-fibrotic surface modifications (e.g. zwitterionic coatings or immunomodulatory agents) in order to inhibit the FBR to improve long-term use of the implant; and/or there should be research to develop computational models to better predict fibrosis incidence, these models would simulate the interaction between polysaccharides and the immune system(25).

In conclusion, FBR, long-term degradation safety, sterilization compatibility, and the complexity of regulatory processes are the key translational/clinical examples that present a significant translational barrier for polysaccharide-based implantable drug delivery systems. Biomaterials engineering, immune modification strategies, and predictive modeling will play a key role in overcoming the above-mentioned translational barriers for polysaccharide-based drug delivery systems over time(27).

Table 5. Key Research Gaps and Translational Challenges in Polysaccharide-Based Implantable Systems

Gap	Impact on Clinical Performance	Required Advancement	Reference
Foreign body response	Fibrotic encapsulation, altered release	Anti-fibrotic surface modification	(29)
Degradation variability	Unpredictable long-term kinetics	Physiologically relevant degradation models	(32)
Sterilization effects	Polymer chain alteration	Validated sterilization protocols	(34)
Mechanical mismatch	Chronic inflammation	Tissue-matched mechanical engineering	(36)
Limited long-term clinical data	Regulatory hesitation	Extended in vivo studies	(38)
Manufacturing reproducibility	Batch variability	GMP-standardized production	(40)

6. Future Perspectives: Smart, Bioresponsive, and Hybrid Implantable Systems

Future polysaccharide-based implantable systems should progress from releasing a constant amount of medication to releasing medication based on patient need. As treatment of chronic diseases becomes more focused on precision medicine and tailored therapies, there is a need for these implantable systems to be able to adapt and programmed to release medications as needed, while still providing long-term biocompatibility. Bioresponsive implants are an exciting new direction in implantable system development. Polysaccharide meshes modified with linkage structures respond to various stimuli, such as pH, glucose levels, enzyme activity, and inflammatory markers. For instance, glucose-sensitive alginate-based implants with phenylboronic acid-linked, self- regulating insulin-release systems will allow diabetic patients to have some control over their insulin delivery. Similarly, chitosan-based hydrogels containing ROS-cleavable linkers that release anti-inflammatory medications when there are flare-ups may not release any anti-inflammatory agents during the non-flare-up times. Adaptive systems reduce over-treatment and under-treatment and decrease side effects in patients when compared to fixed-release implantable systems. Hybrid composite implants are innovative forms of implantable delivery systems. Biodegradable synthetic polymers will be incorporated into polysaccharide meshes to enhance the mechanical strength of and structural integrity of the implant while still being biodegradable. The mechanical properties and diffusion pathways of hybrid implantable systems using reinforcements (such as nanocellulose, graphene oxide, and silica nanoparticles) can be improved; however, care must be taken to design these systems in a way that balances mechanical reinforcement with predictable degradation times and considers the regulatory requirements for each of these systems. The integration of biosensors intoImplantable devices with builtin sensors that monitor glucose, inflammation, and/or drug concentrations could rapidly alter their drug delivery to patients via on-demand release. While many challenges exist to integrating microelectronics into polysaccharide-based hydrogels, they hold great promise for revolutionizing the future of chronic disease management(41).

There are many additional applications (such as 3D printing and additive manufacturing) that will play a role in changing the design of medical devices. Implant manufacturers are anticipated to produce patient-specific implant designs based upon individual anatomical and pharmacokinetic requirements; this should be done by utilizing bioinks derived from polysaccharides(43).

By ing the use controlled pore structure and definitive drug location within 3D printed implants, drug release can be programmed. Developing reproducible, sterile, and mechanically consistent 3D-printed implants will be major research areas where success is still needed(44).

Surface modification for immunomodulation is another emerging area for research to foster development of drug delivery technology. Application of zwitterionic polymers, anti-inflammatory peptides, and extracellular matrix (ECM) mimetic onto the surfaces of implants has been shown to reduce the tissue's foreign body reaction, which in turn reduces the fibrotic capsule. Additionally, chemically modifying polysaccharide structure to reduce macrophage attachment to the implant will help increase the integration of the implant into the surrounding tissue(46).

Advanced computational modelling, including digital twins will assist researchers in forecasting how implants will perform in the body long term under dynamic physiologic conditions. Combining degradation and pharmacokinetic models will also provide researchers with methods to develop personalized drug dosing regimens that correspond to each patient's metabolism and immune system(47).

Future research must also focus more on translating innovative research into practical devices. As multifunctional devices become increasingly complex, their regulatory and manufacturing burden becomes larger. Long-term safety and efficacy of smart implants will require extensive clinical and preclinical studies(49).

Integration of electronics to biodegradable matrices is a highly complex challenge that needs to be addressed. The use of remote-controlled or sensor-based, implanted devices will also require regulatory scrutiny regarding; privacy of data, security of the device, and long-term reliability(4).

The future requires researchers to simplify multifunction hinges into one mechanism while continuing to scale up production of drug delivery implants utilizing responsive biodegradable cross-linkers that have preprogrammed cleavage kinetics and minimal inflammatory response. To achieve

success, collaboration between bioengineers, clinical practitioners, biomaterial scientists, and regulatory personnel is essential; this will accelerate the transition from lab to use for patients(8).

In conclusion, the future is bright for polysaccharide-based implantable drug delivery; adaptive and individualized therapy will guide future designs for smart, bioresponsive hybrid platforms. The ultimate transition will be made possible via; advanced material development, sensor technology, and computational modelling of future generations' implantable devices that have revolutionized the management of chronic diseases(12).

Table 6. Emerging Innovations in Polysaccharide-Based Implantable Drug Delivery Systems

Innovation	Mechanistic Advancement	Clinical Benefit	Limitation	Reference
Glucose-responsive implants	Boronic acid–glucose interaction	Self-regulated insulin release	Sensitivity optimization required	(15)
ROS-responsive hydrogels	Oxidative-triggered degradation	Inflammation-adaptive therapy	Biomarker variability	(18)
Hybrid polymer composites	Mechanical reinforcement	Improved durability	Regulatory complexity	(20)
Sensor-integrated implants	Real-time monitoring	Closed-loop drug control	Electronic integration challenges	(22)
3D-printed personalized implants	Custom geometry & release	Patient-specific therapy	Sterility validation	(24)
Anti-fibrotic surface modification	Reduced macrophage adhesion	Improved long-term integration	Coating stability concerns	(30)

7. Conclusion

Long-term therapeutic management of a wide range of chronic diseases is made possible through the novel use of polysaccharide-based implantable drug delivery systems, as these systems provide a highly versatile platform with unique advantages. These advantages include inherent biodegradability, biocompatibility, chemical tunability, and low systemic toxicity, making polysaccharide-based implantable drug delivery systems attractive alternatives to traditional synthetic-polymers used for implantation. By enabling sustained, localized release of drug, polysaccharide-based drug delivery systems will help to address some of the primary limitations associated with repeated systemic administration, including fluctuations in plasma drug levels, reduced patient compliance, and systemic side effects.

Material engineering strategies for the successful development of polysaccharide-based drug delivery systems (e.g. controlling cross-linking, reinforcing with composites, optimizing network architecture) will be essential in achieving mechanical stability and predictable long-term release kinetics. For instance, diffusion-controlled, degradation-mediated, and stimuli-responsive release mechanisms support a more customized therapeutic profile. Nonetheless, significant factors in determining an implant's long-term and clinical success include the complexity of the in vivo degradation environment and the immune response to the implant, which highlight the need for physiologically relevant modeling techniques and predictive frameworks

The wide range of possible applications for polysaccharide-based drug delivery systems encompasses oncology, diabetes, chronic pain relief, ophthalmology, neurology, as well as hormonal therapy. The various clinical applications of localized chemotherapy depots, insulin-releasing alginates, long-term pain-relieving implants, and intraocular hydrogels, exemplify the significant clinical potential for polysaccharide-based drug delivery systems. However, the lower level of long-term clinical validation (in comparison to synthetic polymer-based systems) exemplifies the need for further practical translation to clinical use.

One of the primary barriers to the successful long-term use of polysaccharide-based drug delivery systems is the foreign body response (FBR) to commonly implanted materials or devices, and the resulting fibrotic encapsulation of the implant, which affects the rate of drug diffusion from the implanted material. There are several factors contributing to the severity of macrophage activation, the extent of tissue integration, and the FBR itself, and the major variables associated with these factors include: material purity, surface

chemistry, and mechanical compatibility. Engineering solutions to reduce macrophage activation and promote tissue integration will be key to achieving various engineering goals necessary for successful long-term use. Furthermore, researchers must develop standardized in vitro models that replicate the dynamic and physiological characteristics of in vivo environments in order to improve the predictive power of any in vivo studies conducted with the polysaccharide-based drug delivery systems.

Manufacturing capacity and regulatory compliance of polysaccharide-based drug delivery systems continue to be consideration and barriers to successful use. The variance in naturally-derived polysaccharide sources means that implementing appropriate quality control will require adherence to Good Manufacturing Practices (GMP). Additionally, the sterilization technique(s) must maintain the integrity of the chemical structure of the polymer and the stability of the drug which is released by the polymer. To meet regulatory criteria, biodegradable drug delivery systems will continue to undergo biocompatibility, degradation product, pharmacokinetics, and long-term safety assessments prior to receiving regulatory approval.

Future directions for implantable drug delivery systems will need to focus on the development of smart and bioresponsive hybrid drug delivery systems capable of adjusting drug release in response to physiological stimuli. The integration of sensor technology and digital monitoring and/or control systems will create the possibility for closed-loop therapeutic control. Further, 3-D printing techniques and patient-specific implant fabrication will extend the range of possibilities for tailored therapy. However, continued innovation in this field must remain consistent with compliance to applicable regulatory framework and design for manufacturability.

In conclusion, polysaccharide-based implantable drug delivery systems have the potential to transform long-term therapeutic administration through sustained, localized, and adjustable drug delivery. Future research will need to address the gaps in knowledge concerning polypacket drug delivery systems with respect to biocompatibility, modeling the degradation process, and standardized methods for long-term evaluation, prior to being able to translate them into clinical use. By continuing to further collaborate across disciplines and develop sound engineering principles, polysaccharide-based implantable drug delivery systems could radically alter the future of chronic disease management and advance the practice of precision medicine.

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