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REVIEW

Functionalization of Implantable Systems for Controlled Drug Delivery and Beyond

Alfonso F. Blanco[1,2] · José Crecente-Campo[1,2] · María José Alonso[1,2]

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Abstract
The functionalization of implantable systems through polymer coatings offers a promising strategy to enhance the therapeutic performance and longevity of medical devices. These coatings serve as versatile platforms for delivering therapeutic agents directly at the site of implantation, addressing specific clinical needs while minimizing systemic side effects. This review examines key polymer coating techniques, including dip coating, spray coating, spin coating, and chemical vapor deposition, which enable precise control over coating thickness, composition, and drug release profiles. Such control allows for tailored therapeutic outcomes, optimizing the interaction between the implant and surrounding tissues. The functionalities provided by these coatings include biocompatibility, which ensures minimal immune response; anti-fouling properties that prevent unwanted protein and cell adhesion; and the reduction of corrosion, friction, and wear, which improves the durability of implants. A particular focus is placed on drug delivery and the controlled release of anti-inflammatory agents, which can significantly modulate local inflammation, reduce adverse immune responses, and promote better integration of the implant with host tissues. By exploring both the current challenges and future directions in the field, this review underscores the potential of polymer coatings to revolutionize implantable drug delivery systems, paving the way for more effective and safer therapeutic options.

Lay Summary The development of medical implants requires research into material properties like biomechanics and biocompatibility to ensure effective function, seamless tissue integration, and reduced immune responses. As implants evolve, polymer coatings play a crucial role in enhancing performance and safety. This review explores how polymer coatings can enhance implant functionality by analyzing common synthesis methods and their intended functionality when applied to implantable devices. Additionally, it provides a thorough analysis of their use in delivering therapeutic agents, with a focus on managing foreign body reactions and recent advancements in releasing anti-inflammatory drugs to improve implant integration, functionality, and longevity.

Keywords Implants · Drug delivery · Polymer coating · Anti-inflammatory · FBR

Future Work Future work should focus on overcoming challenges in controlling multi-drug release from polymer coatings, ensuring precise dosing, and achieving varied release kinetics. Approaches like stimuli-responsive polymers and layer-by-layer systems could enable tailored drug delivery. Additionally, combining computational modeling with experimental methods may streamline the development of advanced, patient-specific coatings.

✉ María José Alonso
mariaj.alonso@usc.es

1 Center for Research in Molecular Medicine and Chronic Diseases (Cimus), University of Santiago de Compostela, 15782 Santiago de Compostela, Spain

2 Department of Pharmacology, Pharmacy and Pharmaceutical Technology, School of Pharmacy, University of Santiago de Compostela, 15782 Santiago de Compostela, Spain

Introduction

Integrating biomaterials into modern medicine has revolutionized the approach to treating a wide array of medical conditions, particularly through implants and advanced polymer technologies. Biomaterials have become indispensable in various biomedical applications due to their versatility, biocompatibility, and ability to be engineered for specific functions. The development of medical implants involves extensive research into materials properties such as biomechanics and biocompatibility to ensure that they perform their intended functions effectively and integrate seamlessly with the body's tissues, minimize the risk of immune response, and reduce the likelihood of complications. As

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a result, medical implants continue to evolve, incorporating advanced materials and technologies to enhance their performance, longevity, and patient safety [1]. Two types of implants are currently being used: biodegradable implants, designed to gradually break down and be absorbed by the body, thus eliminating the need for surgical removal after they have served their purpose, and non-biodegradable implants, intended to remain in the body permanently or for extended periods, providing long-term functionality [2]. Some of the most used implants, materials, and required properties are summarized in Table 1.

In this context, polymer films have emerged as promising coatings for medical devices due to their ability to enhance both functionality and biocompatibility. While previous reviews have focused on specific polymers for particular implants, such as polyesters for bioceramic scaffolds [3], there is a need for a broader evaluation that spans different polymer coatings and their applications across various medical devices.

A significant area of research in this field is the development of polymer films, with micro- or nanoscale thickness, for the controlled release of therapeutic agents from medical devices, enabling implants to exhibit bioactive properties and interact with surrounding tissues actively. Recently, many studies have explored specific devices—such as cardiovascular stents, balloons, or titanium implants [4, 5]—or have focused on the release of different therapeutics from these coatings [6].

On the other hand, a critical issue to be confronted when developing implants is their interaction with the immune system, which often triggers complex biological reactions like inflammation and fibrous encapsulation [7–9]. An approach to deal with this issue has been the formation of protective films covering the implants and releasing anti-inflammatory drugs [10–12]. Despite advances in this area, the long-term effects of localized drug release on tissue compatibility and the optimization of release kinetics remain underexplored. While Welch, Winkler, and Thissen [13] reviewed valuable insights into antifibrotic strategies for implants and prostheses, gaps persist in understanding how drug-releasing polymer coatings can more effectively mitigate this challenge.

Therefore, there is a need for a more in-depth evaluation of the broad application of polymer coatings across various implant and prosthesis compositions, synthesis methods, and functions. Specifically, this review addresses the gaps in knowledge regarding the synthesis strategies, the most promising tasks of these coatings, and their capacity to release anti-inflammatory agents to modulate the immune response and reduce adverse post-implantation effects.

Table 1 Summary of the main types of implants, their composing materials, and the essential properties required for their effective performance

Implant	Material	Needed properties	References
Dental	Metals and alloys (Ti, Ti alloys) Ceramics (Al_2O_3, Si_3N_4) Polymers (PEEK)	Biocompatible Corrosion resistance Wear resistance High elastic modulus	[68]
Cardiovascular (Stent)	Metals and alloys (Stainless steel, NiTi, CoCr, Zn, Mg) Polymers (PLA, PLLA, PCL, PGA)	Biocompatible Bioresorbable (6 months–2 years) No long-term inflammation Enable endothelial regeneration Maintain mechanical properties No restenosis	[69, 70]
Neural (Cochlear)	Metals and alloys (Pt, Ti) Polymer (PDMS) Ceramics	Biocompatible Maintain function of electrical components Flexibility and long-term stability No increased risk of bacterial infection No FBR	[71, 72]
Orthopedic	Metals and alloys (Ti, Al, stainless steel, Co-Cr–Mo) Polymers (PTFE, PMMA, PCU, PU, UHMWPe) Ceramics (Al_2O_3, ZrO_2)	Biocompatible Light weight Adaptable mechanical properties Corrosion resistance Wear resistance Reduce need of revision surgery Limited FBR	[73–75]

Abbreviations: *Ti* titanium, Al_2O_3 aluminum oxide (Alumina), Si_3N_4 silicon nitride, *PEEK* polyetheretherketone, *NiTi* nickel-titanium alloy (Nitinol), *CoCr* cobalt-chromium, *Zn* zinc, *Mg* magnesium, *PLA* poly(lactic acid), *PLLA* poly(L-lactic acid), *PCL* poly(caprolactone), *PGA* poly(glycolic acid), *Pt* platinum, *PDMS* polydimethylsiloxane, *FBR* foreign body reaction, *Al* aluminum, *Co-Cr–Mo* cobalt-chromium-molybdenum, *PTFE* polytetrafluoroethylene, *PMMA* polymethyl methacrylate, *PCU* polycarbonate urethane, *PU* polyurethane, *UHMWPe* ultra-high-molecular-weight polyethylene, ZrO_2 zirconium dioxide (Zirconia)

This review will first describe the properties of polymers used as functional coatings and then examine the various types of medical implants and prostheses, their functional requirements, and current limitations. It will also present synthesis methods and applications of polymer coatings on specific implantable devices, emphasizing their contribution to improving prostheses' functionality and advancing implant technology. Finally, a comprehensive analysis of their use in drug delivery, focusing on anti-inflammatory drugs, will be presented. The review will also discuss the evolution towards multi-drug release systems designed better to meet the complex biological demands of the body. Lastly, future directions in the field will be outlined.

Key Characteristics of Polymers Used for Functionalization of Implants

Biopolymers used for functionalization of implants must exhibit key properties such as biodegradability, mechanical strength, flexibility, and biocompatibility [14–16]. Interestingly, as detailed in the "Functionality of Polymer Coatings" section, polymer coatings can provide additional functionalities to the bulk material without compromising its inherent mechanical properties. Biodegradable polymers can fulfill their intended function and subsequently be eliminated from the body through excretion or resorption, eliminating the need for surgical removal [15]. When designing biodegradable biomaterials, several critical properties must be considered. These materials should minimize the risk of prolonged inflammatory responses and degrade at a rate that matches their intended purpose and is suitable for their specific application. Additionally, they should produce non-toxic degradation byproducts that the body can readily absorb or excrete while providing the necessary permeability and processability for their intended use [17].

The mechanical strength of polymers is critical because it determines the material's ability to withstand physiological forces and stresses without failing. For instance, orthopedic implants require sufficient mechanical integrity to support tissues and maintain their structure in the body. Thus, the polymer coatings synthesized over them will require similar mechanical properties to better adapt to their target location. The mechanical properties of tissues in the body vary significantly depending on the tissue type. For example, bone typically has an elastic modulus in the range of 5 to 30 GPa, depending on whether it is trabecular or cortical bone [18–20], while softer tissues such as skin and muscle have much lower stiffness within the kilopascal to megapascal range [21–23]. Importantly, thin polymer coatings can enhance and improve the implant's functionality without altering the bulk mechanical properties of the base material, bridging the mechanical mismatch between implants and tissues. For example, chitosan/polyvinyl alcohol–based polymer composite coatings have been shown to enhance the performance of titanium implants, favoring a better match of mechanical properties with native tissue and promoting better integration with bone [24]. In particular, chitosan has been described to promote the mechanical stability of titanium implants for dental applications [25]. Mechanical strength also influences the durability and longevity of medical devices. For example, very promising polymers such as collagen have been limited by their poor mechanical strength compared to their natural state in the body [26]. However, alternatives such as chemical, physical, or enzymatic crosslinkers have allowed their application in fields such as skin wound repair [27], corneal diseases [28], bone defects [29], or tendon damage [30], among others.

Regarding flexibility, it is a significant factor in biomedical polymers. Flexibility in polymers is often quantified by metrics such as the polymer's elongation at break and ultimate strain [31]. When the degree of internal rotational freedom within a polymer is sufficiently high, the molecular chains can change their conformation, resulting in enhanced flexibility [32]. Flexibility enables these materials to closely replicate the mechanical behavior of organs and tissues, making them well-suited for use in heart valves, implants, prosthetics and polymer coatings, and tissue engineering scaffolds. Polymers such as polydimethylsiloxane (PDMS) and poly(ε-caprolactone) (PCL) have been extensively used because of their flexibility [33]. For example, the flexibility of R-GO/P(VDF-TrFe) copolymer coating was explored for the fabrication of transparent and highly responsive temperature sensors, seamlessly integrating with flexible substrates for advanced field-effect transistors (FETs) [34]. The ability of these polymers to adapt and conform to various shapes promotes seamless integration in the body, minimizing the risk of damage or rejection. This adaptability enhances patient outcomes and expands the potential applications of these polymers in regenerative medicine and other advanced medical technologies [35, 36].

Finally, biocompatibility is crucial because it ensures that the material does not elicit an adverse immune response when in contact with body tissues. This property helps prevent inflammation, toxicity, or rejection by the body, enabling the polymer to function effectively within the biological environment. Biocompatibility can be assessed through in vitro studies, such as cytotoxicity assays (e.g., MTT, live/dead staining, or ELISA for inflammatory markers), as well as in vivo implantation studies evaluating the immune response, fibrosis, or integration of the implanted material with host tissue [37–39]. Key metrics of success include low cytotoxicity, minimal inflammatory response, and stable long-term integration with the surrounding tissues. Biocompatible polymers are currently used safely in a wide range of medical devices, implants, and drug delivery systems, interacting closely with biological tissues without causing harm or disruption to physiological processes. For instance, polymeric materials in direct contact with human blood must effectively manage protein adsorption and blood cell adhesion. These interactions are critical as they can trigger the body's defense mechanisms, potentially leading to complications such as clot formation or immune responses. Therefore, ensuring that these materials can handle these processes without adverse effects is essential for their safe and effective use in medical applications [40]. Biocompatible polymers can be classified based on their source into natural polymers, which are generally biocompatible, such as chitosan and cellulose, and synthetic polymers, including polylactic-co-glycolic acid (PLGA), PCL, polylactic acid (PLA), poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV), poly(trimethylene carbonate) (PTMC), and polyethylene glycol (PEG) [40, 41].

Technological Approaches for the Functionalization of Implants with Polymer Coatings

As explained above, implants, from artificial joints to cardiovascular stents, are gaining importance as world populations tend to live longer (Table 1). However, the interaction between these foreign materials and the host's biological environment can pose challenges. These difficulties include the risk of infection, inflammation, and, finally, implant rejection. Revision surgeries cost millions and are detrimental to countries' public health [42, 43]. Moreover, the recurrence of revision surgeries significantly affects patients' quality of life [44–46]. Therefore, different processing methods and surface modification of implants, such as roughness modification (i.e., sandblasting [47, 48], acid-etching [49, 50], laser-based [51, 52] processing), chemical modifications (i.e., anodization [53], plasma treatment [54–56]), inorganic coatings (i.e., silver coating [57], hydroxyapatite [58, 59]), grafting (i.e., graft polymerization [60]), and polymer coatings (i.e., polydopamine [61–63] and polyester [3, 64–67]), have been developed to mitigate infection risk, reduce inflammation, or improve biocompatibility, thereby enhancing implant integration and longevity.

Among these modifications, polymer coatings are essential because they provide a versatile and adaptable solution due to the vast array of commercially available and well-described polymers. By effectively modifying the surface properties of implants, polymer coatings can enhance implant performance and longevity; promote tissue integration and biocompatibility; minimize the risk of adverse reactions, wear, or infections; and provide controlled drug release, all of which contribute to the success and safety of implantable medical devices. This underscores the significance of polymer coatings in optimizing the performance of implants.

Methodology for the Coating of Implants

As previously outlined, various techniques for synthesizing polymer coatings have been reported, often without a specific focus on drug release or limited to particular implant materials [76, 77]. In this section, we describe some of the most common methodologies for coating implants, irrespective of the implant's composition, focusing on approaches designed for controlled drug release. The preparation of polymer coatings on implants can be achieved through different methods, mainly utilizing liquid or gas-phase techniques (Fig. 1):

Dip Coating

Dip coating is a widely used technique known for its adaptability, affordability, simplicity, and ability to be scaled up [78]. The process involves immersing an implant into a polymer solution or suspension and then withdrawing it to form a polymeric coating. The versatility of this method stems from its ability to accommodate a range of variables, such as polymer concentration, solution volume, and viscosity. Consequently, this technique can coat various morphologies and complex shapes, as it does not depend on the object's geometry [79–82]. This technique has been used in commercially available products such as ZoMaxx (Abbott Vascular, USA) stent, which releases zotarolimus using phosphorylcholine coating to prevent restenosis of the metallic stent [83]. Limitations of this process include the processing time, the volume of material needed for the coating process, and the use of organic solvents [84–86].

Spray Coating

Spray coating is known for its ease of use, scalability, and speed [87, 88]. This technique creates films with a granular texture due to the pressurized atomization of the solution droplets [89]. One of the advantages of this method is that it can coat surfaces regardless of their shape. However, a significant drawback is that material waste is often not utilized during the coating process. To address this, variations like ultrasonic spray (US) have been developed to enhance material utilization and manufacturing efficiency [90–92]. In particular, US combines ultrasonic atomization and spray deposition, using high-frequency vibrations to break liquid into micron-sized droplets, which are carried by inert gas to coat a substrate uniformly [93].

Additionally, films produced by spray coating are typically less durable and exhibit inferior mechanical properties due to defects associated with the granular topology

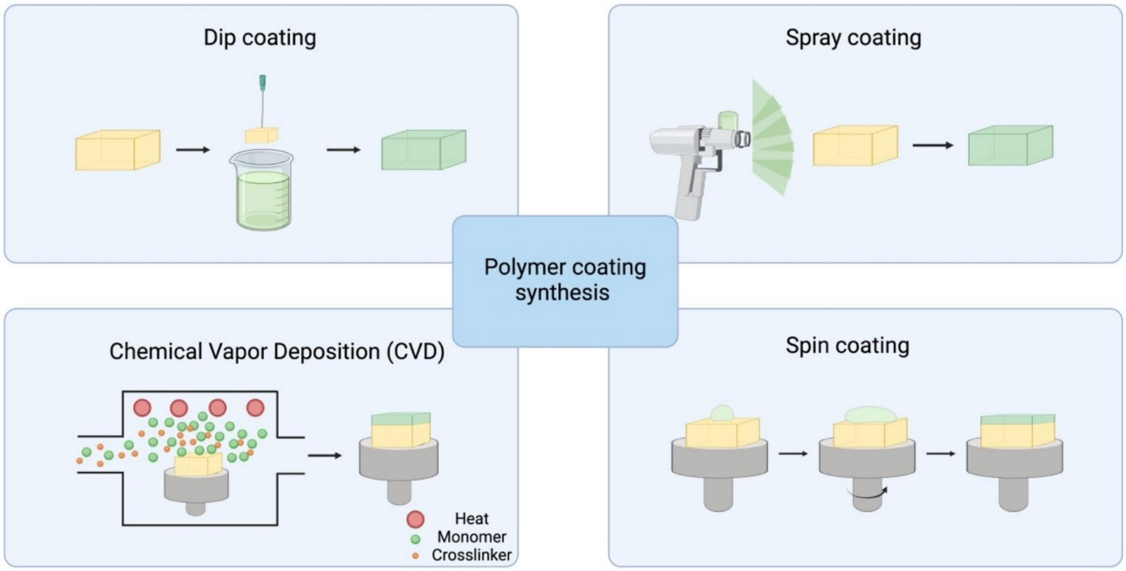

Fig. 1 Representative methods for the synthesis of polymer coatings over implantable devices and prostheses

characteristic of this coating process and inhomogeneous thickness [89]. Another limitation is the viscosity of the spraying solution; more viscous solutions such as those containing high molecular weight polymers or high concentration polymer-drug solutions, can struggle to pass through the airbrush and atomize effectively. This challenge has led to the development of alternative spraying methods, such as airless systems, to handle higher-viscosity solutions [88]. Spray coating has been used to create the polymer coating over CoCr stents, such as in XIENCE V (Abbott Vascular, USA) stents, which release the immunosuppressive agent everolimus from PBMA and PVDF-HFP coating to prevent restenosis and improve long-term safety [83, 94].

Chemical Vapor Deposition

Chemical vapor deposition (CVD) polymerization consists of the delivery of monomers in a vapor-phase state to synthesize well-defined polymer films directly on the surface of substrates [95, 96]. In this case, polymerization occurs without solvents in an all-dry process. The ability to provide uniform coating is a distinctive feature that sets CVD polymerization apart from solution methods of non-planar substrates, which may experience issues related to non-wetting, formation of aggregates, and surface tension effects [95, 97, 98]. This technique allows for modulation of the film thickness, enabling the control of tens of nanometers. It has been increasingly used in the field of drug delivery to tune the release kinetics of some drugs from a drug-loaded substrate coated by these films [99–102]. Among the drawbacks of this technique are its complexity and material requirements for film formation.

Spin Coating

Spin coating is a deposition technique used to achieve homogeneous, uniform, and thin film, commonly used in the laboratory. The process involves dispensing a liquid solution onto the center of a spinning substrate and then rapidly spinning the substrate to spread the solution uniformly across its surface through the centrifugal force. This centrifugal force not only ensures an even distribution of the polymer solution but also aids in the rapid evaporation of the solvent. Spin-coated films are used in various biomedical applications, such as wound dressings, drug delivery, and biosensing [103]. Some drawbacks of this technique include challenges in scaling up production and limitations related to substrate geometry. Moreover, complex geometries pose difficulties in achieving effective coatings [104].

Functionality of Polymer Coatings

Reduction of Corrosion

Implants, especially metal-based prostheses, may suffer corrosion during their time implanted. Depending on their location, they may suffer structural damage because of the action of body fluids, in particular, pH variations, temperature, and electrolytes [105–109]. Polymer coatings should have good chemical inertness and stability to avoid degradation or corrosion by the surrounding environment (Fig. 2A). Some polymers with good chemical resistance are PTFE [110] and PEEK [111], among others. Also, polyesters have been described as candidates for implant coating to protect these devices against biocorrosion [112].

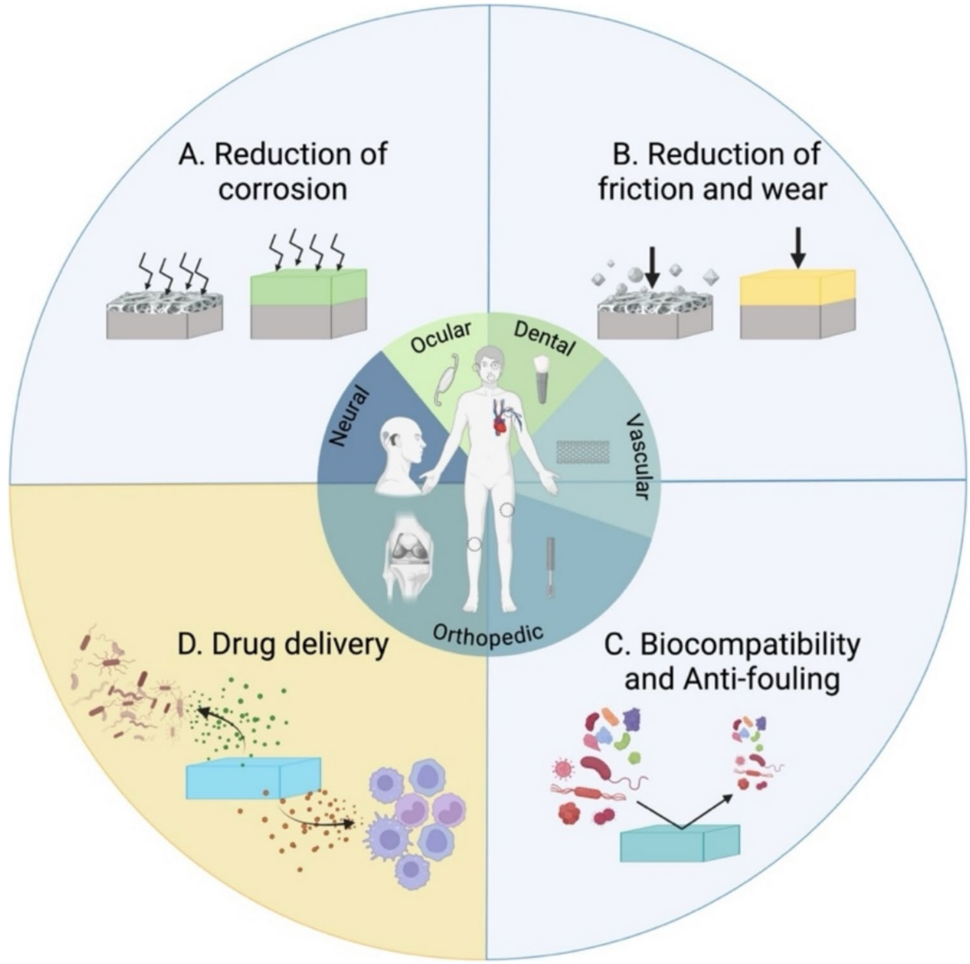

Fig. 2 Main types of prostheses and implantable devices functionalized with polymer coatings and the most characteristic functions of these polymer coatings: Reduction of corrosion (**A**), reduction of friction and wear (**B**), biocompatibility and anti-fouling (**C**), and drug delivery (**D**)

Reduction of Friction and Wear

Based on the final purpose and location of the implant, the modulation of friction and wear can be a determining factor. Zones, where high mechanical stresses can be expected, would require the implant to succeed upon demanding conditions that can damage the device's integrity. This is the case with orthopedic implants, which are particularly important in joint replacements where the movement of the implant against the bone and other tissues should be as smooth as possible. Here, polymer coatings can be used to reduce friction and wear (Fig. 2B). For example, titanium alloys, such as those used for hip and other joint replacements, present intrinsic properties such as high corrosion resistance. However, these implants are associated with wear, pitting, cracks, and failure, which could be avoided by limiting micromotion using polymer coatings. The presence of polymer coatings that limit micromotion would be beneficial in reducing these implants' wear and prolonging the lifespan of these implants [113]. Reducing wear is particularly needed because wear debris can result in an undesired inflammatory reaction that compromises the action of the implant [114]. Among the properties that improve wear resistance appear mechanical properties such as high tensile strength, high Young's modulus, hardness, stiffness, plasticity to bear the mechanical load and prevent excessive wear (i.e., PAI, PI, and PEEK), and low friction coefficient to reduce energy loss and heat generation during sliding (i.e., UHMWPE, POM, PTFE, and PAI) [115, 116].

Improvement of Biocompatibility and Anti-fouling

Human physiology tends to react against artificial objects implanted in the body. Consequently, biocompatible polymer coatings can be created to minimize the risk of immunological reactions or rejections to build a barrier between the surface implant material and surrounding tissues (Fig. 2C). Among the polymers used to improve biocompatibility, polynucleotides [117–119], polysaccharides [120–122], polypeptides [123, 124]), and synthetic polymers (such as PLA, PEG, and PVA) [125–128] stand up. The upgrade in biocompatibility can be based on the properties of the polymer itself or the modulation of the implant surroundings by releasing molecules. Hydrophobic surfaces are often associated with high protein adsorption and subsequent attraction of immune cells that react against the foreign object. If this degradation proves unsuccessful, fibroblasts will surround the implant and form a fibrous capsule, isolating it from the neighboring microenvironment. This phenomenon is known as the foreign body reaction (FBR) and results detrimental to the implanted device (Fig. 3) [129–131]. Increasing the surface hydrophilicity of the implants using, for example, PEG [132] or PVA [133] enhances the overall performance of the implant by reducing non-specific protein adsorption responsible for immune rejection. The design of polymer coatings based on zwitterions, or with anti-coagulant and anti-inflammatory properties, has allowed for the modulation of inflammation, which significantly diminishes implant function [134–136].

Another point to consider is that most implants are intended to stay in place for extended periods. Even when the materials chosen for these prostheses exhibit good biocompatibility with host cells, they may also provide a suitable environment for bacterial adhesion and growth, leading to peri-implant infections. Implant-related infection has a huge socio-economic impact that supposes billions of expenses to healthcare systems worldwide [137, 138]. These infections can occur anytime, but the first 4 weeks for dental implants are particularly critical [137, 139]. Biofilm formation on implant surfaces can severely compromise their function [140]. Recent advancements have focused on reducing bacterial adhesion and preventing biofilm formation through antibacterial modifications of implant surfaces, such as using chimeric peptides [141]. Some polymer coatings act as barriers to reduce the risk of infection associated with implants or even incorporate antimicrobial agents. Furthermore, the in situ release of antimicrobials by diffusion and polymer degradation overcomes hurdles that can result from the systemic administration of antibiotics, such as systemic side effects and the growing multidrug resistance of bacteria [142–144]. Thus, polymer coatings can inhibit the growth of bacteria on the implant's surface and help prevent post-operative infections while keeping their antimicrobial effect localized.

Drug Delivery

The incorporation of drug delivery technologies in prostheses and implants is becoming increasingly important to achieve a site-specific effect of the delivered molecules.

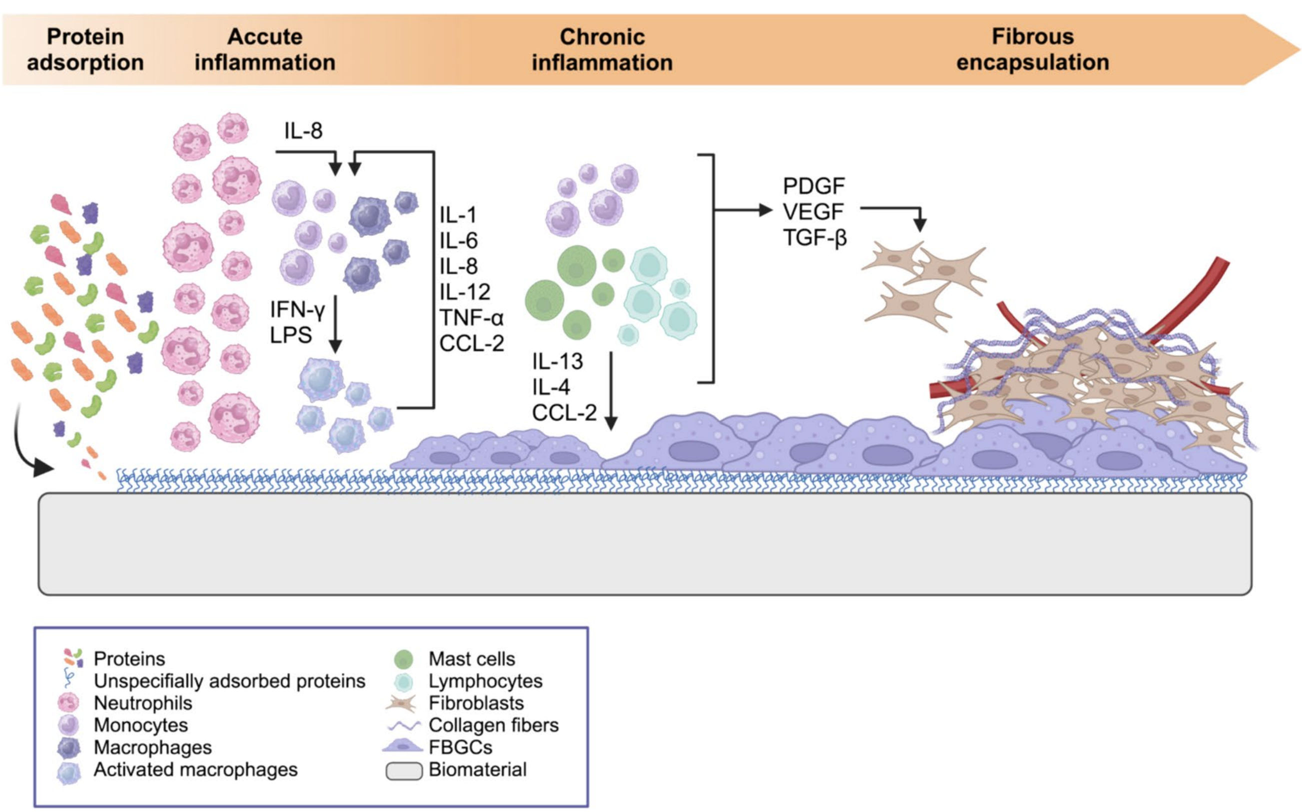

Fig. 3 Schematic representation of the FBR upon implantation of a biomaterial in the body. Abbreviations: *IL* interleukin, *IFN* interferon, *LPS* lipopolysaccharide, *TNF* tumor necrosis factor, *CCL* C–C motif chemokine ligand, *PDGF* platelet-derived growth factor, *VEGF* vascular endothelial growth factor, *TGF* transforming growth factor

Controlled drug release may help manage pain, reduce the inflammatory response and fibrosis, promote biocompatibility and cell adhesion, differentiation, and proliferation, and fight bacterial infections (Fig. 2D) [7, 82, 145–150]. Antibiotics, growth factors, anti-osteoporosis, anti-neoplastic, anti-thrombosis, and anti-inflammatory drugs are the most commonly used for these purposes [6]. Additionally, polymeric matrices can protect these molecules from enzymatic degradation within the body. Furthermore, certain polymer coatings do not release drugs directly from their matrices via diffusion or degradation; instead, they regulate the release of molecules from the implant surface as the polymer degrades [151].

The choice of polymer material and the coating design depend on the type of implant, its intended function, and the specific medical application. This selection is crucial in fields where precise sensing, drug dosing, and timing are essential. For example, porous drug-releasing polyurethane (PU) coatings over glucose sensors have been developed to mitigate local inflammation by the release of Dexamethasone (DEX) [152]. Also, rifampicin (RIMP) loaded in PLGA films has been recently used to coat Ti dental implants to prevent peri-implant bacterial contamination [153]. Factors such as polymer type, expected degradation time, drug formulation, polymer-to-drug interaction, and coating design significantly influence drug release rates, treatment duration, and the compatibility of the coating with both the implant and surrounding tissues. Thus, drug-eluting implants undergo rigorous evaluation by regulatory authorities such as the FDA to ensure they meet strict safety and efficacy standards before being approved for clinical use [154–156].

Delivery of Anti-inflammatory Drugs from Polymer-Coated Prostheses The release of anti-inflammatory drugs from implants is crucial, regardless of the implant type, location, or whether it is in soft or hard tissue [6]. The local administration of anti-inflammatory drugs at the site of action can avoid the two main limiting hurdles of oral administration: lack of adequate local concentrations and side effects due to long-term systemic administration.

The release of anti-inflammatory drugs is significant for mitigating foreign body reaction (FBR) and fibrosis, which can limit the survival and function of implantable devices. For example, in fields such as neural electrodes, FBR can severely affect implant performance, leading to complications like glial scar tissue formation and implant loosening due to macrophages' reaction to implant debris. To address this, the release of anti-inflammatory drugs has been explored to improve implant integration and reduce these inflammatory responses [6].

As illustrated in Fig. 3, FBR progresses through multiple stages, occurring over a period ranging from minutes to months. Immediately after implantation, an acute inflammatory response is triggered by the adsorption of proteins onto the biomaterial's surface. In this initial phase, neutrophils rapidly migrate to the site, releasing factors and chemical signals that recruit monocytes. These monocytes then differentiate into M1 macrophages within the first few days post-implantation. If this acute response does not degrade the biomaterial, the process transitions into chronic inflammation. This second stage is marked by mononuclear cells, including lymphocytes and monocytes. Macrophages undergo a phenotypic switch from the pro-inflammatory M1 to the anti-inflammatory M2 phenotype, playing a crucial role in forming a fibroblast- and extracellular matrix (ECM)–rich capsule that encapsulates and isolates the implant.

Additionally, macrophages may fuse into multinucleated foreign body giant cells (FBGCs). Ultimately, this process leads to a chronic fibrotic response, where the implant is encapsulated in fibrous tissue and isolated from the surrounding environment. This encapsulation often results in the loss of implant function and increases the likelihood of revision surgery to remove the device. While the cellular processes of FBR are well understood, the main features and determinants of the foreign body reaction are not fully elucidated. Therefore, implants must be designed to accommodate some degree of FBR, ensuring its severity is manageable [131, 157].

Many anti-inflammatory drugs have been investigated for their release from polymer-coated prostheses. Cyclosporin A (CsA), an immunosuppressant, has primarily been used in ocular applications. For example, spin-coated PLGA loaded with CsA has been applied to intraocular lenses (IOLs) to mitigate posterior capsular opacification (PCO). This coating has effectively modified IOLs by inhibiting cell proliferation, promoting cell death in vitro, and preventing PCO in vivo in rabbits [158]. Additionally, using ultrasonic spray technology that allowed precise spray position control, NSAIDs like Bromfenac have been loaded into PLGA to coat IOLs, providing intraocular anti-inflammatory effects. The system showed controlled release of Bromfenac for 14 days and the complete degradation of the PLGA coating after 2 months. This method has successfully prevented PCO by inhibiting TGF-β2-induced cell migration and the epithelial-mesenchymal transition (EMT) of residual lens epithelial cells (LECs) via the ERK/GSK-3β/Snail signaling pathway while also demonstrating biocompatibility in vivo in a rabbit model [159].

Other NSAIDs, such as aspirin, have been used to modify blood-contacting implants. For example, Chen et al. created a coating through thermal-initiated radical copolymerization of methacrylate esterified heparin (MA-heparin) with methyl methacrylate (MMA) and n-butyl acrylate (nBA). After this process, reactive oxygen species (ROS)–responsive polyoxalate containing vanillyl alcohol (PVAX) was anchored onto the coating via esterification, and Aspirin was dissolved in the MMA and nBA solution and encapsulated in the coating during copolymerization. This coating, which could be synthesized on surfaces of any size and geometry, effectively mitigates acute inflammation mediated by PVAX and addresses chronic inflammation with aspirin. In preclinical trials, this technology has shown promise in rabbits by being applied to PU-based indwelling needle cannulas and central venous catheters, where it demonstrated a significant reduction in inflammation and prevention of thrombosis. This indicates its potential for improving the performance and safety of blood-contacting medical devices [160].

Among the anti-inflammatory drugs, DEX is considered the gold standard for reducing fibrous encapsulation and modulating inflammation following implantation. Recently, DEX has been incorporated into various polymer matrices for diverse biomedical applications. For instance, it has been explored in intracochlear applications using biodegradable implants made from PLGA or PEG-PLGA [161]. For bone regeneration, DEX has been incorporated into a hybrid layer composed of PEO, PCL, and a 3D-printed PG-NH-DEX scaffold, synthesized on a biodegradable Mg implant substrate. The osteogenic differentiation of these cells was promoted through the upregulation of mitogen-activated protein kinase phosphatase-1 (MKP-1), which stimulated the expression of RUNX2 and other osteogenic proteins [162].

In vascular applications, DEX has been applied to PDA-modified PLA stents using a membrane-mimicking copolymer, MA(PCLA), synthesized by dip coating, which serves a dual function by acting as both an antifouling and anti-inflammatory coating. This coating inhibits coagulation and inflammation during the early stages of implantation. Given the relationship between high concentrations of ROS and excessive inflammatory responses, a ROS-responsive molecular prodrug of thioketal-bearing DEX, known as PEI-Tk-DEX, was incorporated into the coating to promote self-regulation of inflammation and tissue healing on demand under high ROS conditions. Its effectiveness in preventing intimal hyperplasia, enhancing endothelial coverage, and modulating inflammatory responses was demonstrated in vivo in rabbits following abdominal aortic stent implantation [163]. Additional examples of anti-inflammatory drug release from polymer coatings are summarized in Table 2.

The localized and sustained release of drugs from polymer coatings on medical implants addresses inflammation at multiple levels while minimizing the side effects of long-term systemic drug administration. Delivery systems that can co-deliver different drugs with distinct kinetics would be particularly beneficial in managing the inflammatory microenvironment at various stages post-implantation. For example, a polyelectrolyte multilayer coating system has been designed for the fast delivery of heparin, combined with the long-term benefits of naproxen to mitigate cell adhesion and inflammatory cascades. In particular, this technology, in which naproxen was released from nanoparticles in the polymer coating, efficiently reduced the formation of foreign body giant cells after 15 days [178]. In applications such as osteoarthritis (OA) [179], our lab is exploring polymer coatings that could combine corticosteroids for rapid post-operative inflammation control with NSAIDs to manage pain and long-term inflammation, thereby enhancing the synergistic effects of individual drugs and improving overall therapeutic outcomes. However, several considerations remain regarding the release of anti-inflammatory drugs from polymer coatings. For instance, in the context of preventing fibrotic encapsulation, it is crucial to determine the optimal duration of drug release to reduce or prevent fibrosis effectively [9]. Moreover, in this regard, a critical issue would be that the erosion of the polymer coating does not contribute to the inflammation process.

Future Perspectives and Conclusions

Since the introduction of the first drug-eluting implant in 1937, advancements in polymer coating technology, like those described above, have reinforced the growing trend of developing smart systems for more precise and controlled drug release. These innovations highlight the need for stimuli-responsive or modulated drug-delivery systems that provide temporal release profiles to achieve optimal therapeutic effects [6]. In the context of anti-inflammatory activity, post-implantation inflammation, a complex and multi-factorial process, can sometimes lead to the isolation of the implant, rendering it ineffective and necessitating removal—resulting in significant socioeconomic costs. The development of systems capable of releasing multiple drugs to mitigate inflammation at both acute and chronic stages has become increasingly important. Lastly, in terms of pain management and the complications associated with long-term systemic administration of anti-inflammatory drugs, emerging technologies like re-loadable hydrogels offer valuable inspiration for designing polymer coatings that can be replenished with additional anti-inflammatory drugs after implantation once the initial dose has been fully released [180]. These questions and outlooks underscore the need for continued exploration of polymer coatings for implants to enhance the quality of life for the growing number of individuals undergoing implantation surgeries worldwide.

In recent decades, significant advances in polymer chemistry and coating methodologies have driven the development of polymer coatings for drug delivery in implantable devices. Despite these advances, essential challenges and unmet clinical needs persist, particularly in controlling the release of multiple drugs from a single system. Precise dosing and achieving varied release kinetics remain difficult,

Table 2 Relevant examples of recently developed polymer coatings over implants designed to release anti-inflammatory drugs

Implant type	Material implant	Polymer coating	Polymer coating technology	Drug released and function	Reference
Cochlear implant	Electrode (Silicone)	PLGA	Film casted by dip coating	DSP, Ara-C, NAD Reduce growth of connective tissue and increase neuroprotection	[164]
	Electrode (not specified)	HA crosslinked with BDDE	Hydrogel coating casted by extrusion coating	DEX Promote anti-inflammatory effects in the cochlea and protect against auditory hair cells (HCs) apoptosis	[165]
	Electrode (Silicone)	PLLA	PLLA layer synthesized by spray-coating over O_2 plasma and GOPS treated silicone	DEX (from silicone implant) and DCF (from PLLA coating) Reduce the formation of fibrous tissue isolating implant	[166, 167]
Tissue engineering scaffold	Substrate independent	DEX-PEG-(PDDA/PSS)$_9$	PDDA and PSS layer-by-layer film coating	DEX Decreasing collagen deposition, promoting partial regeneration of skin appendages and mitigating post-implantation tissue fibrosis	[168]
Implantable device	Substrate independent, i.e., PU glucose biosensor	PLGA/PVA	Composites of PLGA microspheres/PVA hydrogels coating synthesized by freeze–thaw cycles	DEX Control immunogenic response, negative tissue responses and guarantee device performance	[169, 170]
Vascular stent	-	C-HA-Cys	Catechol HA and Cys hydrogel synthesized by spin-coating	Allicin Cross-linked network responsive to redox changes caused by inflammation and oxidative stress, smartly releasing allicin to improve biocompatibility, and to regulate atherosclerosis	[171]
	PLA	Ox-HA and PEI	Layer-by-layer system of PEI-Tpl, EGCG and RIVA-Ox-HA nanogel	Thrombin-triggered RIVA (anticoagulant) release, and Tpl and EGCG (anti-inflammatory) Limit stent failure and restenosis	[172]
Non-biodegradable metallic implants	Ti-6Al-4 V	PLGA	PLGA coating synthesized by depositing the polymer solution (drop coating)	Asp Release from surface of the implant to immunoregulate macrophages, enhancing M2 and depressing M1 genes and proteins, improving osseointegration	[173]
	AISI 316LVM	CMC, β-CD	Multilayer bioactive system using CMC and DEX solubilized with β-CD	DEX Promote anti-inflammatory activity and osteogenesis in orthopedic application	[174]
	Ti-SLA	CS	Drug-loaded chitosan microparticles coating PDA-modified Ti-SLA by Schiff-base reaction	Asp and Amo Modulate cell proliferation, decrease inflammation, and reduce bacterial activities	[175]

Table 2 (continued)

Implant type	Material implant	Polymer coating	Polymer coating technology	Drug released and function	Reference
Biodegradable orthopedic implants	Zn	CMC/Gelatin	Organometallic hydrogel composite created by dip-coating	Asp and Zn^{2+} Modulation of inflammation, osteogenesis, and antibacterial performance	[176]
Patches for wound healing	Polymer	PCL/HAp, PGA, and PLL	Multilayer polymer film by combinations of solvent casting and dip coating	Small molecule model drugs Promote a model system to address wound healing by the release of the different drugs with different release kinetics	[177]

Abbreviations: *PLGA* poly(lactic-co-glycolic) acid, *DSP* dexamethasone sodium phosphate (DSP), *Ara-C* cytosine arabinoside hydrochloride, *NAD* nicotinamide adenine dinucleotide, *HA* hyaluronic acid, *BDDE* 1,4-butanediol diglycidyl ether, *DEX* dexamethasone, *GOPS* (3-glycidyloxypropyl) trimethoxysilane, *DCF* diclofenac, *PEG* poly(ethylene glycol), *PDDA* poly-diallyl dimethylammonium, *PSS* poly-styrene sulfonate, *PU* polyurethane, *PVA* polyvinyl alcohol, *C-HA* catechol modification of hyaluronic acid, *Cys* cystamine, *PLA* poly(L-lactide), *Ti-6Al-4 V* titanium alloy, *Asp* aspirin, *Ox-HA* oxidized hyaluronic acid, *PEI* polyethylenimine, *RIVA* rivaroxaban, *Tpl* tempol, *EGCG* epigallocatechin gallate, *Hap* hydroxyapatite, *AISI 316LVM* medical grade stainless steel, *CMC* carboxymethyl cellulose, *β-CD* β-cyclodextrin, *Ti-SLA* sandblasted and acid-etched titanium, *CS* chitosan, *PDA* polydopamine, *Amo* amoxicillin, *Zn* zinc, *PCL/HAp* poly(caprolactone) reinforced with hydroxyapatite nanoparticles, *PGA* poly(glutamic acid), *PLL* poly-L-lysine

often requiring trial-and-error methods and extensive screening to optimize the release rates of different molecules [181].

The functionalization of medical devices has become crucial in enhancing their performance, especially by developing polymer coatings. These coatings have significantly improved corrosion resistance and reduced friction and wear, both essential for ensuring durability and functionality. Additionally, creating antifouling and biocompatible surfaces has prevented the adhesion of undesirable proteins or cells, reducing the risk of bacterial infection and maintaining device functionality. Beyond structural improvements, polymer coatings have enabled the development of localized and controlled drug delivery systems, offering precise modulation of the surrounding biological environment. In particular, the release of anti-inflammatory and immunomodulatory drugs has become a cutting-edge strategy, effectively preventing complex and progressive responses such as foreign body reaction (FBR), enhancing device longevity and functionality, minimizing the need for revision surgeries, alleviating pain, and improving patient compliance. Designing polymer systems that release therapeutic agents, such as anti-inflammatory or immunomodulatory drugs, in a site- and time-specific manner can reduce complications and minimize the side effects associated with systemic drug administration.

Moreover, many fields would benefit from combining these technologies. For example, in knee osteoarthritis (OA), which is strongly influenced by inflammation and meniscus injury, considerable efforts have been directed toward either replacing injured menisci with meniscus orthopedic prostheses or scaffolds [182, 183] or delivering anti-inflammatory drugs to prevent the onset of OA [184, 185]. Thus, combining meniscus prostheses with surface functionalization using polymer coatings for inflammation management is expected to become a significant area of research [186, 187]. To date, the only reported example is a silk/graphene oxide-based meniscus scaffold coated with tannic acid/$Sr^{2}+$, which has demonstrated the ability to protect cartilage and delay osteoarthritis progression due to its anti-inflammatory and anti-ROS properties [188].

Finally, the polymer coating field is moving towards developing advanced polymer systems that incorporate stimuli-responsive degradation by responding to changes in the tissue environment, such as pH variations or temperature fluctuations [189]. Additionally, polymer systems that respond to exogenous stimuli, such as light, ultrasound, or magnetic fields, are being explored for on-demand drug release, enabling more precise time and site-specific control over therapeutic delivery [190, 191]. Furthermore, systems incorporating multiple polymers, such as layer-by-layer (LbL) coatings, enable precise control over the release of biomolecules and drugs with different functions to better address post-implantation needs, such as preventing bacterial infection, reducing inflammation, promoting tissue regeneration, or a combination of these outcomes [192–195]. Early efforts are also oriented to the design of hydrogels that enable drug reloading post-implantation [196]. This could lead to re-loadable hydrogels coating different medical implants. This capability could significantly enhance the longevity and efficacy of implantable devices by allowing for on-demand refilling of drugs tailored to the patient's evolving needs while minimizing invasive procedures or systemic drug administration. In addition, integrating computational biology, which can simulate biological responses without invasive procedures, and design of experiments (DoE), which optimizes formulation variables, could transform the approach to polymer coating design. These methodologies would enable precise predictions of biological responses across various tissue types and individual patients. This would enhance the development of smarter, more rational coatings tailored to specific clinical needs in the coming years. Together, these innovations promise to overcome current limitations and expand the potential of polymer-based drug delivery systems to tackle a wide range of medical conditions.

Looking forward, continued advances in polymer coatings with advanced drug delivery capabilities hold immense potential to transform implantable device technologies. By addressing challenges in drug release kinetics and immune modulation, these innovations could significantly improve the efficacy, safety, and affordability of medical treatments, ultimately enhancing the quality of life for patients undergoing implantation surgeries.

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Declarations

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