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Localized, on-demand, sustained drug delivery from biopolymer-based materials

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Abstract

Introduction: Local drug delivery supports high concentrations of drug molecules at or near the treatment site to enhance treatment efficiency and reduce drug toxicity and other systemic side effects. However, local drug delivery systems face challenges in terms of encapsulation, delivery, and controlled release of therapeutics.

Areas covered: We provide an overview of naturally derived biopolymer-based drug delivery systems for localized, sustained, and on-demand treatment. We introduce the advantages and limitations of these systems for drug encapsulation, delivery, and local release, as well as recent applications.

Expert opinion: Naturally derived biopolymers like cellulose, silk fibroin, chitosan, alginate, hyaluronic acid, and gelatin are good candidates for localized drug delivery because they are readily chemically modified, biocompatible, biodegradable with the generation of metabolically compatible degradation products, non-toxic, and can be processed in aqueous and ambient environments to maintain the bioactivity of peptides, proteins, and other therapeutics. The drug release mechanisms can be diffusion-based, degradation-controlled, and on-demand, triggered release. The tradeoff between the effective treatment dosage and the response by local healthy tissue should be balanced during the design of these delivery systems. Future directions will be focused on strategies to design tunable and controlled biodegradation rates, as well as to explore commercial utility in substituting biopolymer-based systems for currently utilized synthetic polymers for implants for drug delivery.

Keywords

biopolymer; biodegradation; hydrogel; localized drug delivery; medical implant; on-demand release; sustained release

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Declaration of interest

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1. Introduction

The field of medicine depends on therapeutics to treat or cure diseases. In 2020, it was estimated that $1.3 trillion was spent globally on prescription drugs (1). As more therapeutics are developed, there is an opportunity for refined modes of delivery to increase safety and efficacy. With any mode of drug delivery, the active pharmaceutical ingredient (API) should be delivered at a concentration that reaches the therapeutic index, which describes the dose range where a medication is effective without causing adverse effects (2). This concentration can be challenging to achieve due to unpredictable drug release rates, the inability to precisely target the desired tissues, renal/hepatic clearance of the delivered drugs, and unreliable stability of the therapeutic (3). As a result, when therapeutics are delivered systemically, they often must be delivered at much higher concentrations than the target requirements to achieve an effective dose (Figure 1), leading to adverse side effects or harm to other organs.

Local delivery permits the release of medications at or near the target site, which can reduce drug toxicity associated with systemic delivery. Local delivery is applicable to many disease models, such as pediatric cancers like neuroblastoma, where systemic effects of chemotherapy agents can be devastating in children. Local delivery is also effective for the treatment of glioblastoma, where tumor recurrence is inevitable due to drug resistance and realistically impractical surgical removal of all cancer cells, followed by systemic chemotherapy (4–6). The local delivery of antibiotics and pain medications can significantly enhance local infection treatment efficiency as well as improve local pain management. In contrast, when these classes of APIs are taken systemically, adverse gastrointestinal events, addiction, and bacterial resistance can occur (7–9). Local delivery of hormones has been explored to avoid the adverse effects that systemically delivered hormones have on neurohormonal regulatory pathways.

Naturally-derived biopolymers have been increasingly investigated for drug delivery implants due to their tunability, biocompatibility, degradability, ability to achieve controlled and sustained release, and API-friendly material processing conditions (10). Unlike biodegradable synthetic polymers that can release acidic byproducts during their degradation which may result in inflammatory responses for surrounding tissues, naturally-derived biopolymers such as alginate, cellulose, silk fibroin, chitosan, gelatin, and hyaluronic acid release non-toxic and non-inflammatory degradation products. Furthermore, naturally derived biopolymers are advantageous in terms of aqueous solution-based processing and drug loading methods, with a wide range of options for material format to match the local environment.

In this review, we first introduce several diseases that could significantly benefit from local drug delivery (Figure 1) and cover the applicable methods for loading APIs into naturally derived biopolymer-based implants. We then discuss materials fabrication and how different APIs are released from biopolymer-based implants, including passive and stimuli responsive release. Finally, we introduce degradation mechanisms for biopolymer-based implants and associated tissue responses from these implants.

1.1. Diseases

1.1.1. Cancer—In 2020, cancer was responsible for almost 10 million deaths, with an estimated 19.3 million new cancer cases worldwide(11). Surgery is the common approach for the treatment of most solid tumors. Not all tumors are operable, however, and even if they are, not all cancer cells are removed, resulting in tumor relapse and metastasis. Surgery is typically followed by rigorous chemotherapy and radiotherapy to eliminate residual cancer cells, which are not always successful as cancer cells can become resistant to the therapies, and often leads to harsh side effects for patients (12).

1.1.1.1 Glioblastoma: Gliomas are cancers where tumor relapse and drug resistance are common and comprise 80% of all malignant central nervous system tumors. The most malignant form is glioblastoma multiforme (GBM), with a survival rate of 12–18 months post-diagnosis (13). The current standard of care for GBM includes maximal surgical resection followed by temozolomide chemotherapy and radiation. Surgery, however, is not always possible due to risks associated with surgical intervention if the tumor is in a challenging area in the brain. Additionally, the presence of heterogenous subclones may drive relapse, drug resistance, and recurrence in GBM, even after tumor resection and treatment (4–6).

Nearly 80% of GBM recurrence occurs inside or at the edge of the radiation field, and degree of resection significantly impacts survival. Thus, the area of resection is an important region to focus on to prevent recurrence (14). Additionally, since the brain is isolated by the blood-brain barrier (BBB), local delivery provides more aggressive chemotherapy treatment while limiting toxicity to the rest of the body (14). Overall, within the central nervous system the tissue and tumor responses to various drugs can be modulated by novel delivery systems to reduce morbidity to surrounding neural tissues. In the future, delivery systems may move beyond just reducing the damage, to improving drug delivery and bioavailability using novel biopolymer carriers. Local drug delivery for the treatment of GBM has the potential to deliver high doses of therapeutics without adverse side effects, with many current phase I and II clinical trials that demonstrate the potential of the technology.

1.1.1.2 Pediatric Cancer

Neuroblastoma –: Neuroblastoma is the most common extracranial solid tumor in children under the age of 5. Noted for its complex heterogeneity, it accounts for nearly 15% of all pediatric cancer related deaths (15). Patients undergo combinations of intense chemotherapy, surgical resection, and radiotherapy; however, many patients cannot be operated on due to tumor location. Chemotherapy is delivered intravenously, thus, systemic toxicity results in significant patient morbidities such as cardiotoxicity, myelosuppression, renal toxicity, endocrinopathy, and growth failure (16, 17). In a study of nearly 11,000 childhood cancer survivors, including neuroblastoma patients, the cumulative incidence of chronic health conditions 30 years after primary diagnosis was approximately 73%, with an estimated incidence of about 42% being severe, disabling, and/or life-threatening conditions (15). As a result, systemic chemotherapy side-effects on developing children remain unaddressed, which is problematic as the pathways that contribute to the higher prevalence of chronic

health conditions are also poorly understood. Local chemotherapy delivery systems have the potential to improve these outcomes, especially in children.

1.1.2. Infections—Local delivery systems for antibiotics are increasingly common for the treatment of localized infections, especially osteomyelitis and periodontitis. The motivation for exploring local antibiotic delivery systems is the ability to reach high local concentrations of antibiotics without systemic toxicity. The infected wound region often has areas of avascularity, preventing sufficient concentrations of systemically delivered antibiotics from accessing the target site (18). Periodontitis is an infection-instigated inflammatory disease in tooth-supporting tissues, primarily caused by dental plaque accumulation (19). Failure to pursue treatment can result in the loss of bone tissue, periodontal pocket formation, and bleeding from gums (20, 21). Since scaling and root debridement cannot eliminate all bacteria residing in inaccessible regions of the periodontal pocket, and invasive procedures to treat the interior of the teeth and gums result in morbidity to the surrounding tissue, antibiotics have been used to manage periodontitis. Repeated use of antibiotics can, however, contribute to the development of resistant bacterial strains, secondary infections, and lack of patient compliance (8, 21). A significant challenge in treating periodontitis is the poor specificity of oral antibiotics for bacteria in the mouth, necessitating the use of larger doses that can lead to nausea, vomiting, gastrointestinal distress, overdoses, and allergic reactions, while also contributing to global antibiotic resistance and residuals entering the environment (e.g. wastewater) (21). Additionally, high doses of metronidazole, tetracycline and chlorhexidine, drugs commonly used in non-surgical treatments of periodontitis, can damage the gums and periodontal ligaments (22). As periodontitis is a localized disease, an injectable biopolymer that localizes antibiotics to the teeth and gums while promoting the activity and bioavailability of the drug has the potential to revolutionize the treatment of periodontitis and other dental conditions, while minimizing damage to sensitive oral tissues. Recent advances with silk (23) and chitosan (24) films suggest such approaches are feasible, creating another practical method for localized oral application. As the ability to deliver drugs *via* films is improved, their potential applications should expand significantly.

Orthopedic wounds also have a high prevalence of potentially life-threatening infections. Lower extremity fracture infection rates are as high as 52% for all detected fractures (25). For acute osteomyelitis or prosthetic joint infections, the current standard of care is proper irrigation, debridement and prolonged (4–6-weeks) use of systemic antibiotics (25). Approximately one in six patients treated with systemic antibiotics for chronic osteomyelitis experiences adverse reactions to the drugs (26). Accordingly, there is increased interest in local antibiotic delivery to reduce their systemic use for orthopedic infections (27).

1.1.3. Pain/Injury—Over 80% of patients who undergo surgery report acute postoperative pain. The current standard of care is oral pain medication that patients take as needed, requiring patients to determine dosing (28). Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and aspirin are widely used to relieve pain, fever, and other inflammatory processes (9). The main mechanism behind NSAIDS is the inhibition of the enzyme cyclooxygenase (COX). There are two types of COX isoenzymes: COX1

and COX2. Most NSAIDs do not distinguish between the two; COX1 is important for maintaining gastrointestinal mucosa, kidney function, and platelet aggregation, while COX2 is expressed during inflammatory responses. As a result, when patients take NSAIDs, adverse gastric and renal events are common (9). Additionally, the use of prescription opioids for pain management doubled between 2001 and 2013, significantly contributing to ongoing opioid misuse (7). To address these issues and decrease adverse events related to systemic delivery of APIs for pain management, implantable, biodegradable, and biocompatible local drug delivery systems at or near the target site can be useful.

Of special interest is research on drug and encapsulated cell delivery to the spinal cord to mitigate inflammation during acute injury, and to enhance regeneration and repair during the prolonged healing phase (29–31). Therapeutics targeting spinal cord injuries have poor efficacy when administered globally, but local administration has proved challenging. BBB permeability is also a concern with some drugs used to treat spinal cord injuries, necessitating carriers that can either bypass the BBB or be injected into the spinal column without eliciting an immune response. Future applications of natural biopolymers may target local delivery of pain medication to the lower back, where systemic administration of medications can have off-target effects and decreased availability of the drug at the desired site (32).

1.1.4. Hormone-related—Nearly 80% of women from high income countries have reported using oral hormonal contraceptive pills (33). These hormones include androgens, estrogens, and/or progesterone. Combination pills that include both estrogen and progestin are associated with breakthrough bleeding, a 2-fold risk of myocardial infraction and stroke and a 37 times higher risk of venous thrombosis (33, 34). Additionally, contraceptive pills must be taken daily, leading to decreased patient compliance and drug effectiveness if the user forgets to take or misplaces the pills. Subdermal implants that achieve sustained, long-term systemic release of contraceptives were created to address these issues (35). Nexplanon is an etonogestrel-releasing ethylene vinylacetate copolymer rod-shaped implant inserted sub-dermally in the arm, and can be left in place for 3 years via surgical incision (36). If the patient sustains injuries near the implant site, however, the implant could be damaged and requires surgical removal (37). Additional side effects associated with systemic subdermal contraceptives include menstrual disturbances, acne, headache, abdominal pain, hair loss, weight gain, and follicular cysts (35). Currently, the most popular local contraceptive delivery systems are intrauterine devices (IUDs), which are used by more than 168 million women worldwide. However, IUDs also have complications such as infections, pelvic inflammatory disease, uterine perforation, and menstrual disturbances (38, 39).

Overall, with current systemic and local contraceptives causing adverse side effects and issues with patient compliance, there is a need to investigate additional delivery platforms that limit systemic exposure and that patients feel comfortable using. Although degradable biopolymers could be useful in addressing these issues, few local contraceptive biopolymer-based drug delivery platforms have been tested.

1.2. Biopolymer based implants

In the discussion above, we highlighted several examples demonstrating opportunities for local drug delivery, but this is not an all-inclusive list of applications which can benefit from local treatments. Materials including metals, ceramics, and synthetics are widely used as drug implants for local treatment. However, many problems remain unsolved when using these materials. For example, because metals and ceramics are not biodegradable, secondary surgery for implant removal is required. While synthetic polymers can be biodegradable, their degradation is often the result of hydrolysis, with acidic degradation products that lower the local pH, which leads to cell and tissue necrosis, and inflammatory responses (10). In addition, loading drugs into synthetic polymers is challenging, especially for biologics where organic solvents can be detrimental.

Biopolymers represent a new generation of drug delivery implants with many unique properties, as they are readily chemically modifiable, biocompatible, biodegradable with metabolically compatible degradation products, non-toxic, and can be processed in aqueous and ambient environments (40). Biopolymers have a molecular backbone of repeating units of saccharides or amino acids, with additional chemical side chains that provide functionality as well as accessible chemical handles for facile modifications. In addition, alternating crystalline and amorphous domains can be used to control drug release by tuning the crystallinity of the biopolymer (41), or through the use of nanoparticle/microparticle formats (42, 43). Biopolymers tend to be hydrophilic due to the presence of functional groups such as carboxylic acids or amines, leading to enhanced loading efficiency with hydrophilic biologics. Silk fibroin has been shown to stabilize biologics during formulation, storage, and delivery. Biopolymer processing is often based on aqueous solutions, enabling facile formulation for biologics that are otherwise sensitive to organic solvents (44). Many biopolymers like HA, gelatin, or silk enable one step hydrogel formation in water without compromising bioavailability of the biologic. In Table 1, we summarize currently available natural biopolymer-based local delivery systems as solutions to the above-mentioned diseases. In Table 2, the characteristics of natural biopolymers are summarized with the emphasize of their individual advantages as local delivery materials. Taken together, biopolymer-based implants show potential for local disease treatment. More research is warranted to expand the uses of biopolymer-based drug delivery systems into areas where more research and development is needed, such as contraceptives and cancer treatment.

2. Biopolymer based drug loaded implants

In this section, we first discuss the methods that can be used to load drugs (small molecules, nucleic acids, protein/peptides and living cells) into biopolymer systems, alongside loading challenges. In Table 3, we summarize the methods and challenges of locally delivering small molecules, genes, proteins/peptides and live cells, and how biopolymers are beneficial for drug loading and delivery (66). We then summarize the methods of generating various material formats such as hydrogels, micro/nanoparticles, films, microneedles, and dense material-based implants.

2.1. Drug loading and delivery of therapeutics

Loading drugs into medical implants is achieved via two main avenues (Figure 2): solvent-based and solvent-free powder-based methods. Solvent-based methods include adsorption, solvent evaporation, diffusion, supercritical fluid technology, spray drying and covalent grafting. When drug loading is completed before material fabrication, the loading efficiency is mainly dependent on the solubility and stability of the drug in the solvents used. For methods where drug loading is completed through diffusion and adsorption after material fabrication, drug loading efficiency depends on the interactions between the biopolymer and drug molecules, the solubility of the drug, and the porosity of the materials. Solvent-based methods are applicable to most therapeutics, including small molecules, protein/peptides, antibodies, and genes (nucleic acids). The bioavailability of APIs can, however, be compromised by the choice of solvents or mechanical disruption during material fabrication, further impacting drug loading efficiency.

Solvent free methods include physical powder mixing, melting, co-milling, and making reservoirs, where the solid formats of drug and biopolymers are used. The solubility of the drug is irrelevant for these methods; thus, the loading efficiency is not limited by the solubility of the drug. The material integrity still depends on the mixing ratio of drug and biopolymers, but the utilization of solvent free methods also means the bioavailability of the drug molecules is not affected by solvents The mechanical mixing or elevated temperature required for some methods, however, can reduce the stability of the therapeutic.

2.2. Materials fabrication

One of the advantages of using biopolymers for drug delivery implants is the range of available methods for materials fabrication (Figure 2B,C). For local drug delivery, the selection of the material formats depends on many factors, including matching mechanical properties with local tissues, desired release kinetics, preferred implantation/injection methods, treatment areas (the size of the wound area), and required penetration depths into the local tissues.

2.2.1. Solvent-based methods

2.2.1.1 Hydrogels: Most biopolymer-based hydrogels can be produced in aqueous solution by chemical, physical or biochemical (enzymatic) crosslinking. Chemical crosslinking provides more stable structures because the polymeric chains are covalently bonded through the crosslinking agent. However, crosslinking methods can impact biocompatibility. Physically crosslinked hydrogels are formed *via* non-covalent interactions, and therefore, are more dynamic and have reversible sol-gel transition properties. Biochemical crosslinking (78) refers to enzyme mediated crosslinking of polymers, where the enzymes facilitate the interpolation of reactive species, forming covalent bonds between the biopolymer chains. Designs of biopolymer-based hydrogels were recently reviewed, including polysaccharides, glycosaminoglycans, and polypeptides by Li et al (79).

For local delivery, hydrogels are injected into the treatment area where they undergo a sol-gel transition at the injection site (67). As shown in Figure 2D, the biopolymer solution, crosslinking reagent, and loaded drug molecules are mixed in a syringe, with crosslinking

occurring during or after injection with a sol-gel transition. The hydrogel material format offers advantages including mechanical properties matching soft tissue, injectability, and is less invasive compared to other material formats, with reversible dissolution following drug release.

2.2.1.2 Nano/microparticles: Nanoparticles and microparticles have been investigated for local delivery in applications such as cancer. Nanoparticles can be exploited to enhance the permeation and retention effect (EPR), where leaky vasculature of solid tumors and weak lymphatic drainage synergistically encourages particle accumulation in the target cells (80). Biopolymer-based nanoparticles and microparticles are typically prepared *via* water-in-oil or oil-in-water emulsions, spray drying, salting out, and nanoprecipitation(81–83). Nanoprecipitation is the most popular technique due to its overall simplicity (81). Nanoprecipitation, otherwise known as the solvent displacement method, involves two miscible solutions, where the first solvent contains the polymer (the solvent), and the second solvent does not (non-solvent). This method involves rapid dissolution of the polymer, which induces precipitation of nanoparticles when the polymer solution is added to the nonsolvent (84). This occurs due to the Marangoni effect, where the interfacial turbulences between the solvent and the nonsolvent govern the formation of particles (85). Once formed, the remaining non-solvent can either be evaporated (if acetone or ethanol) or ultracentrifuged out. APIs may be solubilized in the solvent solution, or preformed nanoparticles may be soaked in a drug solution for absorption of insoluble APIs.

2.2.1.3 Films/foams/sponges: Biopolymer-based films or minifoams can be prepared by drop-casting. In this method, a drug-loaded biopolymer solution is dried under ambient conditions or in a humidity chamber. The resulting films or minifoams can be used to for local implantation. Since most biopolymers are water-soluble, this method is straightforward for loading biologics that are organic solvent sensitive. Various methods can be used to crosslink the film or minifoams to make them insoluble *in vivo* for long-term implantation and sustained drug release. These crosslinking methods can also be used to tune the release kinetics of the films/minifoams. Layer-by-layer (LBL) assembly of nanofilms can also be used for drug delivery implants (86).

2.2.1.4 Dense materials: Dense materials can also be prepared using solvent-based methods. For example, silk microneedles (87) are produced through vacuum drying in polydimethylsiloxane (PDMS) microneedle molds followed by water annealing to enhance insolubility. Silk orthopedic devices are also produced with high mechanical strength (88, 89). Antibiotics like gentamicin or growth factors like bone morphogenetic protein 2 (BMP2) can be dissolved in the silk solution before water evaporation to make functional orthopedic devices for long-term drug release during bone repair.

2.2.2. Solvent-free methods

2.2.2.1 Co-milling: Milling is a top-down approach for producing fine particles. While milling has been used in the pharmaceutical industry to enhance the solubility of drug molecules by changing the drug crystal shape, surface area, or size (90), co-milling can be used to mix drug powders with biopolymer excipients to achieve solid state drug loading

(91, 92). This method has been used for inhaler formulations and offers new opportunities for solid state mixing before thermoplastic molding, melt extrusion or pressing to prepare drug delivery implants.

2.2.2.2 Thermoplastic molding: Thermoplastic molding is applicable to silk-based biopolymer systems (93). Protein molecules like protease enzymes can be co-milled with amorphous silk particles to form dense solid materials with elevated processing pressures and temperatures without losing bioavailability (93). This enables easy manufacturing of precisely shaped drug implants with high mechanical strength and tunable release kinetics. This approach also allows encapsulation of therapeutics in the solid state, expanding the range of drugs for implants by avoiding limitations of drug solubility or bioavailability. With thermoplastic molding, staged or sequential release of multiple drugs can be achieved by controlling the locations of the drugs and establishing selective diffusion barriers. These methods can also be applied to other biopolymers like cellulose and cellulose derivatives (94), chitosan (95), and gelatin (96).

2.2.2.3 Melting: Hot melt extrusion can be used to load drugs into biopolymer systems by pumping drug powder with a rotating screw above the glass transition or melting temperature of the polymer, to achieve molecular level mixing. This approach facilitates homogeneity and ease of scale up, with a solvent-free manufacturing process. Melt extrusion can be used to produce a variety of delivery formats like granules, pellets, tablets, suppositories, and implants (97–99). Recently, hot melt extrusion for encapsulating small molecules and protein formulations has been demonstrated (100). However, for biopolymers that do not have a clear glass transition or melting temperature, this method is challenging to apply (41).

2.2.2.4 Reservoirs: Reservoir-based implants can be produced by embedding solid drug powder in implants through a trilayer of biopolymers. Each layer of biopolymer wafer is prepared and a cavity is established in the middle layer where the drug is deposited. The system is sealed using high pressure. Silk-based systems loaded with cisplatin (48) and prepared using this method have shown sustained cisplatin release from the reservoir. Reservoir based methods are especially useful for insoluble therapeutics. The amount of drug loading can be varied to control the dose, and release kinetics can be influenced by both biopolymer thickness and degree of crosslinking.

3. Drug release

Drug release from biopolymer-based implants can be divided into passive diffusion/degradation-based release and on-demand stimuli responsive release. The rate of passive release depends on solubility of the drug, interactions between the drug and the polymer matrix, and the characteristics of the material (e.g., chemistry, porosity, density). The rate can be tuned through crosslinking, chemical modifications, and/or surface coatings; while control of the kinetics is often limited to the properties of the materials and the therapeutic. To achieve more controlled delivery, stimuli-responsive release and degradation release can be used. Below, we review stimuli-responsive release from biopolymer-based materials.

We provide insight on how to control degradation, as well as design both staged and degradation-based release.

3.1. Stimuli-responsive release

On-demand, stimuli responsive, release refers to releasing drugs by programming the carrier material to respond to spatiotemporal stimuli. This occurs *via* noninvasive and externally applied cues including light, ultrasonic waves, or electric and magnetic fields. Alternatively, for carriers and devices requiring transit to a destination, specific environmental signals such as pH, redox, and tissue/organelle specific proteases can be utilized to release drugs on arrival. Upon the application of one or a combination of these cues, the material may be designed to undergo sol-gel transitions, changes in hydrophobicity/hydrophilicity, swelling or shrinking, shifts in conformation, or degradation (101).

In many cases, the biomaterial chosen for the application has a natural stimuli-responsive behavior, for example chitosan is pH-sensitive. The glucosamine units (pK_a 6.2–7) are protonated and positively charged at acidic pH, making the polymer insoluble at neutral pH (102). Carboxymethylcellulose (CMC) exhibits the inverse trend: gels begin to swell above pH 4 where the carboxyl groups become protonated (103). Alginate crosslinks through chelation with calcium ions and resolubilizes upon removal of these divalent cations (104). Gelatin and collagen are degradable by proteases upregulated in tumor tissues (105). In the absence of a native stimulus response, labile crosslinking schemes or the incorporation of other responsive materials may be required. Acid sensitive acylhydrazone bonds (106, 107), redox-sensitive disulfide bonds (107, 108), and specific protease recognition sites create preprogramed triggers for solvation or degradation of gels and coatings. In photothermal therapy (PTT), near infrared (NIR) dyes and nanomaterials are used to provide spatiotemporal hyperthermia to ablate surrounding cancerous tissue or infectious microbes (109, 110). Magnetic particles can also be integrated within a material composite, where alternating magnetic fields can generate heat (111–113). These types of signals can be used in conjunction with heat responsive polymers to release drugs for combined therapeutic impacts (110, 113).

3.1.1. Exogenous stimuli—Light is capable of providing spatiotemporal control of reaction chemistries with micron-level resolution, where the extent of activation can be tuned by the light intensity (114). Although there are many photolabile or photoswitchable chemical linkers available for hydrogels, most of these require UV radiation, which has limited tissue penetration. Unlike NIR wavelengths which are more suitable for deeper penetration (115), making, NIR upconverting nanoparticles a necessity for UV-sensitive linkers (116). For local delivery to the joint cavity in an osteoarthritis application, photothermal NIR-responsive molybdenum disulfide nanosheets coated with chitosan provided tight control over the release of the anti-inflammatory dexamethasone, conentrating the drug release was almost completely within the joint cavity (110).

Ultrasound is another safe applied stimulus that penetrates tissues with millimeter precision, and can provide localized hyperthermia as well as mechanical effects (117). Acoustic cavitation can be used to enhance the degradation of implanted silk fibroin based scaffolds

(118). Ultrasound stimulation can also be used to temporarily disrupt ionic crosslinks within alginate hydrogels (104). Magnetic fields can provide spatiotemporal control over carrier localization as well as initiate drug release. Remote control of the trajectory of magnetic microswimmers was achieved using rotating magnetics fields (105). Alternating magnetic fields created tight control of doxorubicin (DOX) release from alginate-chitosan microspheres, where the internal temperature gradient supported enhanced diffusion of drugs (112).

Precise stimulus application can also be achieved by integrating films and implants with conductive polymers, allowing for on-demand, electrically stimulated drug release. Silk films imbedded with an interpenetrating network of the conductive polymer pyrrole and 3-amino-4-hydroxybenzenesulfonic acid, provided both electrochemical loading and release of Texas-red-labeled gentamicin (119). In an injectable hydrogel consisting of chitosan, oxidized dextran, and conductive polyaniline, the release kinetics of ibuprofen and amoxicillin were tuned by the applied voltage (120).

3.1.2. Endogenous stimuli—Endogenous environmental signals should be specific to the destination tissue or disease state to prevent premature release during carrier transit. Many pH discrepancies are associated with disease states. In cancer, the intertumoral environment is acidic (pH 6–6.5) due to the hypoxic conditions in the growth mass (121, 122). Injectable cellulose-based, doxorubicin-loaded hydrogels were programmed with acylhydrazone linkages and were sensitive to pH 6.2. Intertumoral injection of the DOX-gel significantly inhibited tumor growth compared to free DOX (121). Dopamine-conjugated alginate hydrogels formed a pH-sensitive reversible covalent bond to boronic acid groups on Bortezomib (122). The boronate ester was a stable covalent linkage at neutral pH, but upon exposure to tumor physiologic pH, the drug was chemically released. Tumor environments also upregulate matrix-metalloproteases, which can be utilized to degrade carriers and release cargo (105, 123). Gelatin nanoparticles delivered the NIR dye indocyanine green, a signal transducer, and activator of transcription 3 (STAT3) inhibitors into tumors for a combined immune and photothermal therapy approach, which improved treatment efficacy in a head and neck carcinoma mouse model.

For nanoparticles targeting cancer cells for intracellular delivery, release is programmed to take place upon entry into the late endosome or lysosome where the pH significantly drops to 4.5–5.5. The redox environment inside cells is also highly reducing compared to the extracellular space due to a three-fold higher glutathione (GSH) content (108). A combination of pH sensitive and redox sensitive cues has been used in conjunction (107, 108). Hydrophilic cytarabine and hydrophobic methotrexate were co-encapsulated into a dual pH and redox responsive platform. Staged release of each drug was achieved through an acid-labile oxidized CMC and chitosan hydrogel containing mesoporous silica nanoparticles coated with disulfide crosslinked HA (107).

In oral administration of drugs, targeting the colon, nano or microparticle carriers need an inverse pH switch to avoid premature release in the gastric environment (pH 1–1.5), as well as the slightly acidic environment in the intestine (pH 6.8) but must release at the neutral colon (pH of 7.4) (124). Carboxymethyl cellulose-grafted graphene nanoparticles showed

minimal release of methotrexate (MTX) in simulated gastric and intestine environments, and rapid release within simulated colon (124). For co-delivery of aspirin and methotrexate, two pH switches were incorporated into CMC and alginate hydrogels where aspirin was targeted to the small intestine and MTX to the colon (125).

For topical applications, healthy skin is acidic (pH 4–6), while inflamed skin (pH 7.3–7.4) and wounds (pH up to 8.9) are more basic (126, 127). Alginate dressings loaded with alkaline responsive silica nanoparticles delivered an antiseptic in response to *E. coli* and *S. aureus* infected artificial wounds (127). Delivery of topical steroids through hair follicles can take advantage of increasing pH with increasing depth into the hair follicle up to 7.5 (126). Cellulose acetate phthalate (CAP) and hydroxypropyl methyl cellulose phthalate (HPMCP) nanoparticles were able to swell and release dexamethasone at alkaline conditions.

3.2. Staged release

The release profile for passive release systems is often predetermined with no control over the spatial distribution of the drugs over time. Precise control of the timing, duration, and dosage of drug release for local treatment allows better regulation of release profiles, helps reduce systematic toxicity, and ensures high efficacy for local treatment (128).

On-demand, or engineered, staged release systems are useful for chronic diseases or tumor treatments where multiple cycles of drug combinations are often used (129). Advantages include extended drug release timeline, improved patient compliance due to reduced dosage frequency and side effects, and dose administration timed (or synched) with circadian rhythms or disease stage. Many strategies have been adopted to achieve staged, on demand, or pulsatile release (129–131) (Figure 3). Figure 3A is a typical case when the loaded drug releases from a biopolymer matrix through passive diffusion or controlled degradation. Figure 3B shows the incorporation of stimuli-triggered reversible crosslinking for the staged release of the therapeutics, where stimuli including light, temperature, and pH can be used to switch the release. Another approach to design staged release is through the control of diffusion or degradation. As shown in Figure 3C, multiple layers of polymeric coating can be introduced to the implant system, serving as barriers to control drug release.

The design strategies for multiple drug systems are summarized in Figure 3D. When mixing two drugs in the implant, the release kinetics of each drug depend on the passive diffusion of the drug in the biopolymer matrix. To allow two drugs to release at different stages, the release of the later drug can be managed by the spatial distribution of the two therapeutics, nanoparticle encapsulation, and polymeric coatings.

3.3. Degradation and degradation-based release

3.3.1. Advantages of biodegradable medical implants—The *in vivo* degradation of synthetic polymer-based drug implants can be problematic, as often these materials are not degradable; or in the case of polyesters, the degradation products are acidic, leading to higher risk of inflammatory responses (132). Second (Figure 4A), synthetic polymer degradation is based on chemical hydrolysis with bulk degradation, which limits the use

of larger implants due to premature implant collapse (133) and subsequent unwanted rapid release of the drug (134).

Compared with synthetic polymers, biopolymer-based implant degradation is more controlled. The degradation mechanisms are enzymatic mediated (Figure 4A), meaning the erosion starts from the surface (134), often resulting in slower rates of degradation and avoiding the loss of structural integrity. The biodegradation products from biopolymer based implants are usually biocompatible and can be metabolized *via* normal physiological pathways (135).

3.3.2. Challenges for biopolymer-based implant *in vivo* degradation— Although biopolymer-based implants are advantageous, surface degradation means that the degradation rate is often slow. For example, silk based scaffolds can take up to a year to degrade completely *in vivo* (136). Drug implants with controllable rates of degradation or triggered degradation are therefore needed.

Figure 4B includes a method to embed enzymes inside the implant to create an inside-out approach for biodegradation (93). Instead of surface erosion with enzymes in body fluids, the enzymes can be introduced into the implants and are activated by water and small molecule diffusion, leading to bulk degradation. Biopolymers like cellulose are not biodegradable in humans due to the lack of cellulase enzymes, but by introducing the enzyme into the implant, cellulose biopolymer-based implants can be designed to degrade. When introducing enzymes to drug delivery systems, the toxicity of the enzyme to normal tissues must be considered. The ideal situation is that the implant can perform its function with a sustained release profile, without losing structural integrity, until after the function is completed, at which point rapid degradation can be triggered (Figure 4B,). These stimuli responsive enzymes can be added to bridge the gap between device degradation and device function.

3.4.3. Factors impacting degradation—The rate of biodegradation of an implant is impacted by several factors other than enzymes (Figure 4C). Relevant factors include polymer hydrophobicity, molecular weight, degree of crosslinking, crystallinity, implant density and porosity, size, and surface morphology. Crystallinity of the biopolymer plays a major role in degradation: higher crystallinity results in slower degradation. By tuning the crystallinity of the material, the degradation rate can be altered to fit the clinical need (137). Hydrophobicity of the biopolymer affects water and ion diffusion into the implant, indirectly affecting the activity of the degrading enzymes. Further, the external local treatment environment can impact implant degradation, as the infected area could have a different pH, temperature, or ionic environment to influence the rate of degradation.

3.4.4. Degradation controlled drug release—Besides diffusion-mediated control, sustained drug release from biopolymer-based implants can be controlled by the degradation rate. In some cases, release of the drug is purely degradation based; this occurs when the degradation rate is significantly higher than the rate of diffusion and release.In some cases, degradation controlled drug release could lead to two-stage release, where diffusion based

release happens for the first period, then residual tightly bound molecules are released during a second stage that is degradation controlled (138).

4. Tissue response to local drug delivery

Much of the existing work in local drug delivery using biodegradable polymers has focused on poly(lactic co-glycolic acid) (PLGA) and polyethylene glycol (PEG). Results of studies using PLGA and PEG can be extended to new approaches using natural biopolymers, with the goal of minimizing inflammatory responses and cytotoxicity. Driving the pursuit of naturally derived biopolymers for drug delivery is the potential to mitigate or eliminate unwanted responses from healthy tissues to a greater degree than can be achieved with the synthetic polymers like PLGA, PEG, and others. This section examines some of the natural polymers that have been used for local drug delivery or have potential for use in drug delivery applications.

4.1. Foreign body response and tissue toxicity

Two critical factors impact responses of healthy tissue to local drug delivery: the material used in the delivery system and the drug itself. Tissue responses to the material are crucial determinants of the system to be used, due to the possibility of foreign body response (FBR). FBR is an inflammatory reaction to the implant, even if the materials are biocompatible or cytocompatible in the traditional sense (139). FBR has been reviewed elsewhere (140–142). Briefly, FBR is characterized by an acute inflammatory phase, followed by encapsulation of the implant in collagen (scar formation), and possible damage to both the material and the surrounding tissue. The fibrous collagen capsule formed around an implant is detrimental to drug release, as it disrupts the interaction between the delivery system and the tissue (143, 144). FBR is a main factor in the lack of commercially available polymer-encapsulated cell delivery systems, as cell-loaded constructs have fared relatively poorly due to fibrous capsule formation *in vivo* (139). Several strategies have been used to facilitate local drug delivery without eliciting a strong FBR, mainly by modifying the delivery material (141, 145) or by including anti-inflammatory drugs in the delivery. These strategies include adjustments to the physical properties of the implanted biomaterials, combining anti-inflammatory drugs or biological agents to suppress the inflammatory response, and modifying bioactive elements on the surface of implanted biomaterials (139).

Biopolymer-based materials have occasionally fared better compared to synthetic polymers when FBR mitigation is the goal (101, 146). Notably, natural biopolymer-derived nanoparticles may have decreased cytotoxicity compared to nanoparticles derived from polymers such as PEG, PLGA, and polycaprolactone (PCL), further establishing them as advantageous systems for the delivery of therapeutics (147). Despite increased usage and study of biopolymer-based delivery systems, maintaining a balance between cytotoxicity and effective treatment concentrations of therapeutics is an ongoing challenge. The cytotoxicity of highly toxic agents, such as platinum-based anti-cancer therapeutics (i.e., cisplatin), which have significant and irreparable off-target effects, can be mitigated by appropriate polymeric delivery (148, 149).

4.2. Strategies for mitigating FBR

To mitigate the FBR, a significant advantage of biopolymers is that many of their parameters can be adjusted. One example is controlling the thickness of the delivery system so that it remains small (<100 μm); thicker materials (>100 μm) result in a worse FBR, while materials 100 μm or less integrate into surrounding tissue more effectively and with less inflammation (150, 151). The impact of thickness on FBR underscores why biopolymer films have such potential for local drug delivery. While small sized implants can be achieved with polymers such as PLGA, biopolymer films also solve the issue of acidic byproducts even in larger implant structures due to the avoidance of a buildup of hydrolytic acidic degradation products. If a thicker drug delivery system is necessary, however, FBR and tissue toxicity can also be mitigated by altering the shape of the biopolymer (152). Fiber-shaped hydrogels can be used with little to no host response even at sizes up to 1 mm, compared to hydrogels of random shapes (153).

In addition to thickness and overall delivery system size and shape, the alignment and orientation of the materials can be tuned to reduce FBR. Nanofibrous scaffolds with aligned fiber orientations minimized FBR compared to randomly oriented fibers in control scaffolds (154). The topological features of the delivery systems, which broadly encompass aligned scaffolds, including sponges and films, as well as micro- and nanopatterning of materials, remain underexplored as tools for controlling FBR in biopolymer-based drug delivery systems.

The mechanical properties of the delivery system also impact FBR. Macrophage activation phenotypes can be modulated by substrate stiffness for some types of materials, including collagen (155), polyacrylamide (156), and agarose (157). Stiffness can be regulated in many natural biopolymers, including collagen, silk, alginate, and cellulose hydrogels. Finally, to minimize toxicity from breakdown products, the degradation rate of natural biopolymers can be tuned, as with silk sponges and implants, which can resist breakdown for months or years (158, 159). However, a disadvantage of some biopolymers is the relatively rapid breakdown time, resulting in acute rather than sustained drug release profiles.

The formulation of the delivered therapeutic and the use of accompanying anti-inflammatories or anti-fibrotic drugs can also be optimized to avoid FBR. Crystallized drug formulations, combined with long-term controlled-release strategy, can prevent inflammatory responses and fibrosis in rodents and non-human primates for 1.3 years and 6 months, respectively (160). Anti-inflammatories are another viable approach for enhancing the feasibility of cell delivery *via* alginate microspheres. Delivery of cells and therapeutics *via* alginate microcarriers is a promising method for locally treating disorders, though toxicity to local tissues remains a challenge (161).

Effectively delivering therapeutics alongside treated cells may enhance clinical feasibility of local drug delivery. Small-interfering RNA (siRNA) delivery has been shown to reduce fibrosis by downregulating collagen expression (162, 163). Another consideration is blocking protein adsorption using drugs, rather than materials. While anti-protein adsorption materials have been used successfully in medical implants, they are less effective in small drug-delivery polymer systems. Using a drug to block protein adsorption and prevent

capsule formation could delay or prevent FBR. Such a drug could be delivered alongside anti-inflammatory substances and the desired therapeutic, however, protein adsorption has also been shown to be necessary for preventing non-specific cellular uptake of nanocarriers (164). More work is needed to understand how to control protein adsorption with positive therapeutic outcomes during local drug delivery.

Taken together, several materials, drug formulations, and accompanying drug strategies can be combined to mitigate FBR, optimize drug release, and minimize byproduct toxicity in natural biopolymer delivery systems. The biopolymers highlighted in this review have the potential to address these criteria, although novel combinations are needed to advance the field.

5. Conclusions

Systemic delivery of therapeutics at effective doses often leads to adverse effects. Local drug delivery implants help solve this issue by providing effective dosages to the local disease area with low or non-toxic effects to other organs and tissues. Many conditions including tumors, local infections, local pain/injury, and hormone imbalances can significantly benefit from local treatments. Biopolymer based local drug delivery systems, such as silk fibroin, cellulose and cellulose derivatives, chitosan, HA, gelatin, and alginate have great potential for use in these systems. Compared to synthetic polymer-based systems, biopolymer-based approaches provide many advantages. Drug loading of naturally-derived biopolymer implants can be achieved through either aqueous-based loading or solid mixing, which supports expansion of the types of APIs that can be loaded with high efficiency. Additionally, biopolymers can be fabricated into various materials formats to match local tissue requirements. The release of drugs from these implants may be modulated in order to achieve passive release or stimuli-responsive release profiles. The ability of naturally-derived biopolymers to degrade in vivo also eliminates the need for secondary surgeries to remove the materials. Further, the degradation mechanisms can be tuned by controlling the amount of enzyme incorporated into the delivery system. Lastly, naturally-derived biopolymer implants elicit low inflammatory responses in vivo.

6. Expert opinion

6.1 Drug loading and material formats

Natural biopolymers provide unique features in drug delivery implants compared to synthetic delivery systems. Many synthetic delivery systems use organic solvents during material processing and drug loading, resulting in decreased bioavailability of APIs. Material processing of natural biopolymers often utilizes aqueous and ambient processing conditions, thus maintaining the bioavailability of APIs, which is especially beneficial for the delivery of biologics. Additionally, surface functional groups on biopolymer-based systems support chemical modifications that allow for chemical grafting of small hydrophobic molecules, solving solubility issues. Natural biopolymer-based systems also offer versatile delivery formats, and non-inflammatory degradation products, making them advantageous as drug implant materials.

6.2 Degradation

Natural biopolymer systems offer particularly tunable features for degradation compared to synthetic polymer systems. Biopolymer degradation typically utilizes enzymatic mechanisms, as opposed to the chemical hydrolysis in most polyester synthetic polymers. With enzymatic degradation, the mechanism is mainly based on surface erosion, whereas chemical hydrolysis leads to bulk degradation. In terms of drug release and structural integrity, surface degradation is a more controlled process that can be engineered: since the implant is degraded layer by layer, the integrity of the implant is maintained without abrupt failure. Conversely, synthetic polymer-based implants degrade through chemical hydrolysis, driven by bulk degradation, where the implants are likely to collapse, leading to burst release and a more inflammatory response *in vivo*.

Enzyme-controlled biopolymer degradation can be tuned. One potential strategy is to encapsulate enzymes in the biopolymer implant, which can revert the degradation mechanism to bulk degradation, allowing for faster degradation when needed. The amount of enzyme encapsulated can be used to tune the degradation kinetics, and stimuli response elements can be added to trigger the release and therefore rapid degradation on-demand after drug release. The effect of the embedded enzymes on the surrounding tissue must also be considered.

6.3 Stimuli responsive and staged release

Creating stimuli-responsive and staged release profiles for multi-drug delivery systems is an important future direction for biopolymer systems. Staged release systems offer control of multi-drug release timing, duration, and dosage, while creating the drug delivery cycles that are customized to fit clinical needs. This approach is particularly useful with multi-drug loaded implants, allowing for a more complex range of treatment cycles. Although staged release can be designed through diffusion or degradation control, stimuli response-based approaches are most often utilized. Besides stimuli responsive drug release, stimuli triggered degradation designs should be considered for future work.

6.4 Silk as a promising biopolymer for local drug delivery

Silk protein is a particularly interesting delivery system because of its robust mechanical properties, biocompatibility, biodegradability, water-based processing, and its ability to stabilize complex proteins. Silk fibroin's amphiphilic structure has 12 hydrophobic "crystallizable" and 11 hydrophilic "amorphous" domains, as a result, its dominant hydrophobicity supports the sustained release of hydrophobic small molecules like chemotherapy drugs. We have demonstrated that release profiles can be tuned by changing the crystallinity of silk protein, the molecular weight, and the degree of crosslinking. Additionally, due to its hydrophobicity and control of crystallization, silk can protect therapeutics from environmental changes (e.g., temperature, moisture, pH), therefore, silk serves act as a stabilizing matrix for APIs, supporting the storage of implants loaded with therapeutics.

Silk has been used in a variety of drug delivery systems, such as microneedles, films, hydrogels, reservoir systems, thermoplastic implants, foams/sponges, and micro/

nanoparticles. Silk has been successful in the delivery of genes, growth factors, chemotherapy drugs, hormones, antibiotics, and other chemicals. Furthermore, as a potential medical implant, unlike synthetic polymer-based materials with low thermal stability, silk can be sterilized by autoclave, ethylene oxide, filtration, and gamma radiation.

6.5 Limitations of Biopolymers

Despite the success naturally derived biopolymers have had in the drug delivery field, there remain challenges that limit more widespread clinical use. As naturally derived materials, they can exhibit batch-to-batch variability due to differences in purification or sources, which can influence parameters that are important for controlling drug release, mechanics/integrity of the material and degradation. This is a concern for the scalability of biopolymers in the pharmaceutical industry. To address this issue, future studies should focus on a fundamental understanding of biopolymer structure and function, to fine-tune and offer more precise control for manufacturing. Bioengineered versions of these biopolymers also offer options to ameliorate this issue. As more research is done to utilize naturally derived biopolymers in local drug delivery, a shift toward scalability and quality control must be made to achieve widespread clinical use.

6.6 Future directions

For the successful design and application of local drug delivery system using naturally derived biopolymer, matching local tissue features, mechanical properties and local responses with the mechanical properties of the biopolymer based materials is essential; for instance, softer biopolymer drug delivery systems such as hydrogels and sponges may be more appropriate for the brain, while mechanically robust systems such as films and thermoplastic molded implants may be better suited for orthopedic and dental tissues. Therefore, one of the important future directions should be focused on building a comprehensive database on the mechanical properties for biopolymers with different formats to match local tissue environment. To propel the future development of biopolymer-based drug delivery systems, continued research to achieve sustained release, activated stimuli responsive release, and mitigating the toxicity of drug for local healthy tissue are also important. In addition, continued investigation into the properties of natural biopolymers that prevent or minimize inflammatory responses are important moving forward. Finally, the commercial aspects for substituting synthetic polymers with biopolymers in pharmaceutical and medical devices related industries needs to be explored for future directions.

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** of considerable interest

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Article highlights

- Advantages of natural biopolymer-based drug systems for local delivery and processing strategies utilized to load and deliver drugs.
- Drug release mechanisms include passive and active options; diffusion, wireless activation, and other modes to control release and staged release
- Implant design with degradation
- Healthy tissue responses to drug-loaded natural biopolymer-based implants

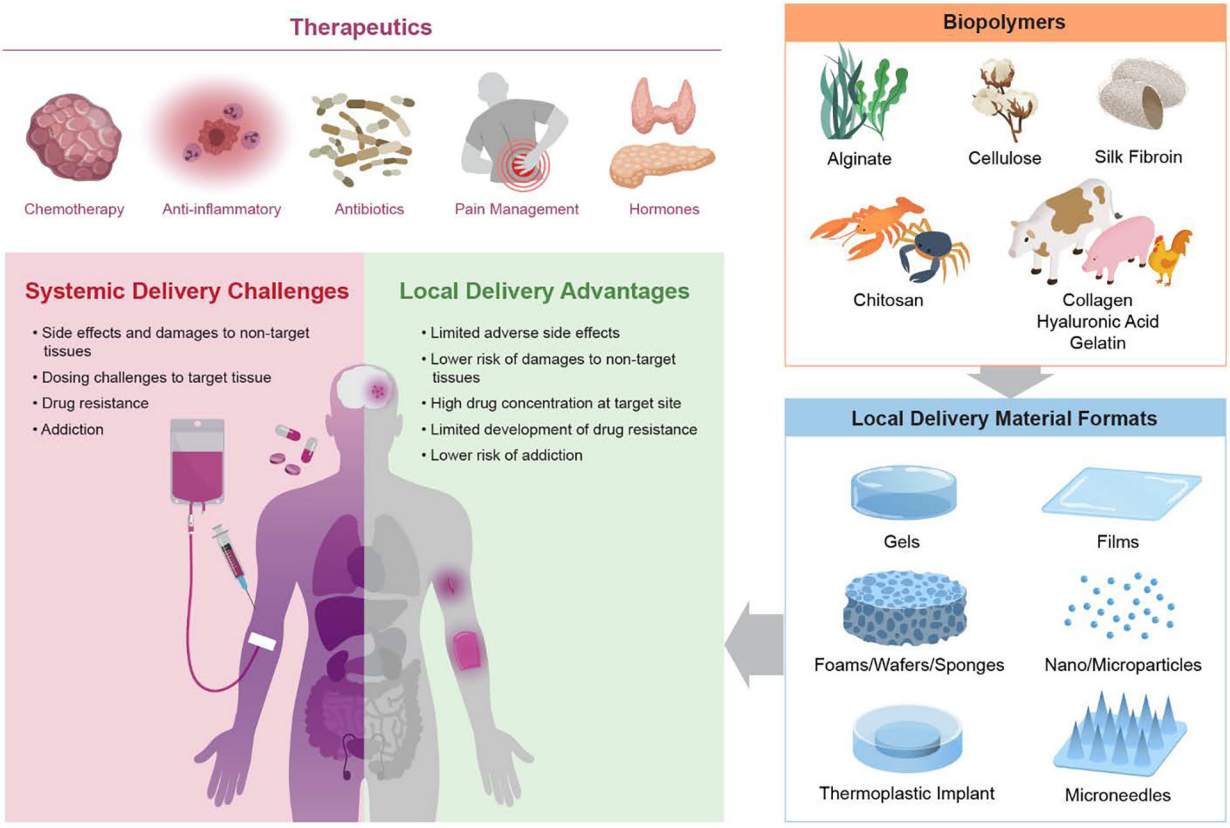

Figure 1.
Illustration of biopolymer based local delivery approach for multiple diseases.

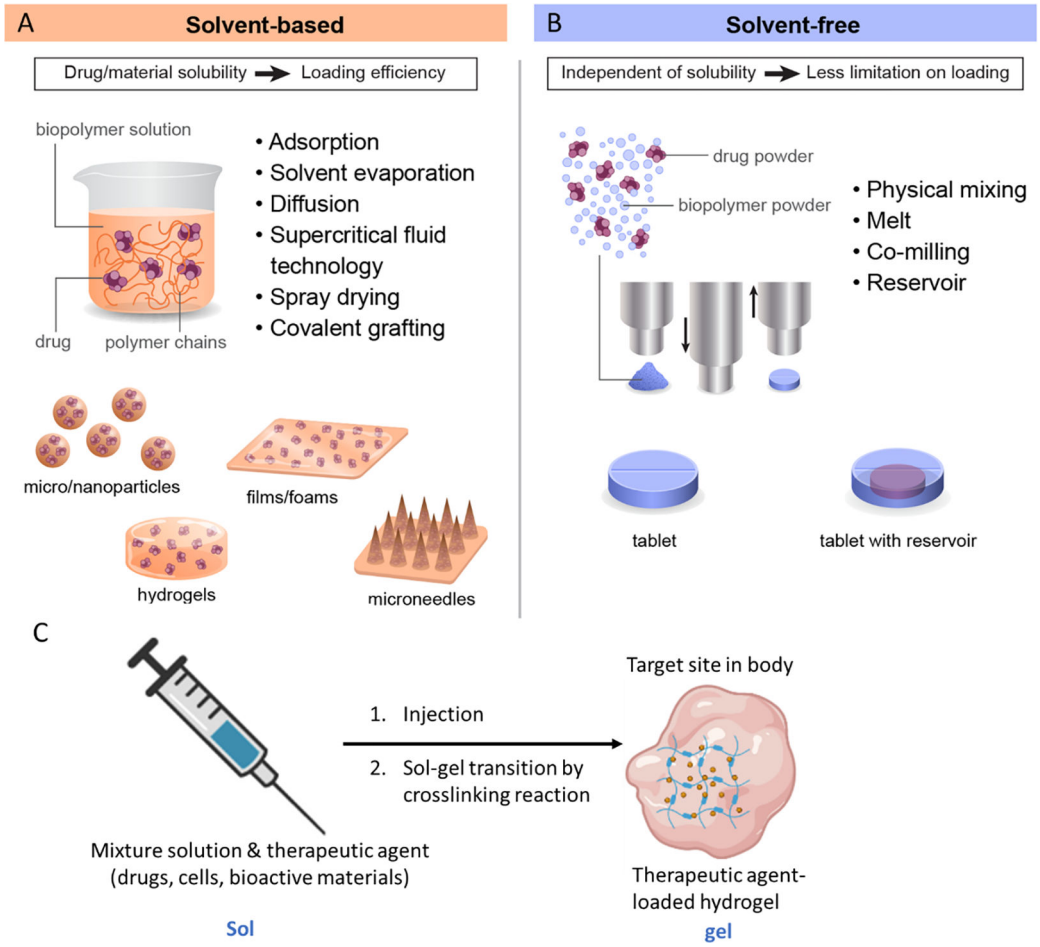

Figure 2.

Material fabrication and drug encapsulation using biopolymers. (A) Methods for drug encapsulation. (B) Material formats from solvent-based methods. (C) Material formats from solvent-free powder-based methods. (D) Schematic for the formation of injectable hydrogels through sol-gel transition induced by physical or chemical crosslinking reactions. Created with BioRender.com. Open access from reference (67).

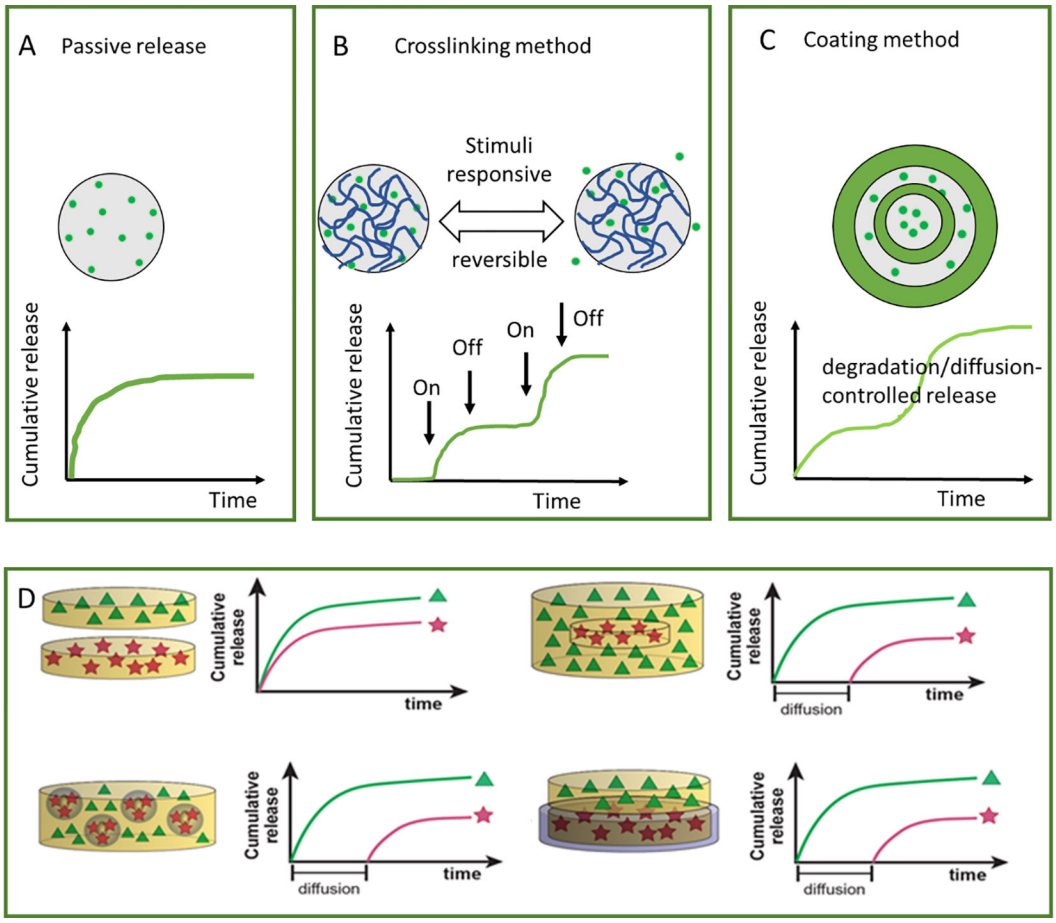

Figure 3.

Strategies to achieve staged release. (A) Sustained release of therapeutics from biopolymer-based materials. (B) Reversible stimuli responsive strategy for controlling release “on” and “off”. (C) Diffusion based coating method design for staged release. (D) Strategies to achieve dual drug staged release systems.

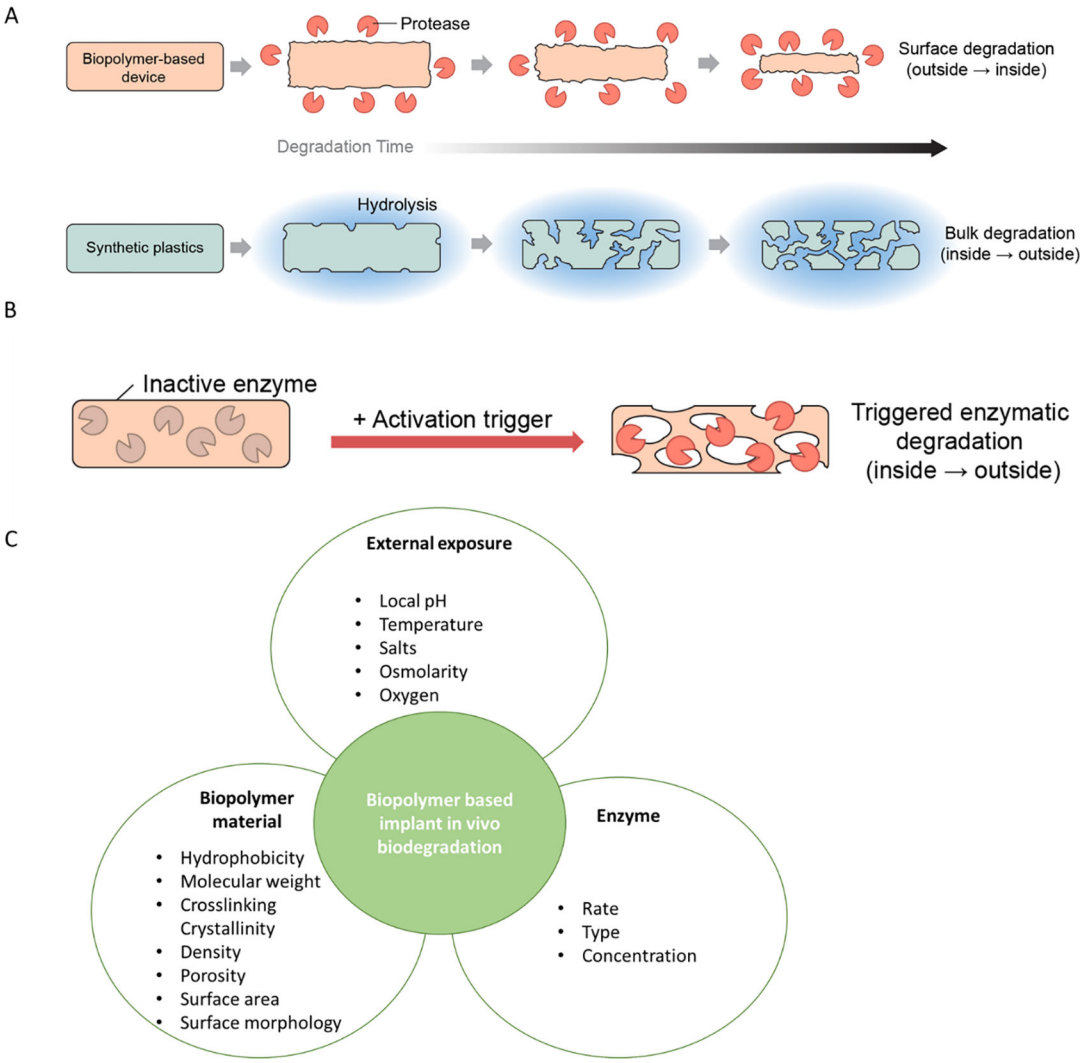

Figure 4.

Device biodegradation mechanisms. (A) Degradation – differences between biopolymer-based implants and synthetic plastic-based implants. (B) Design of activation triggered enzymatic degradation from inside to outside. (C) Factors that impact the in vivo biodegradation of implants for drug delivery.

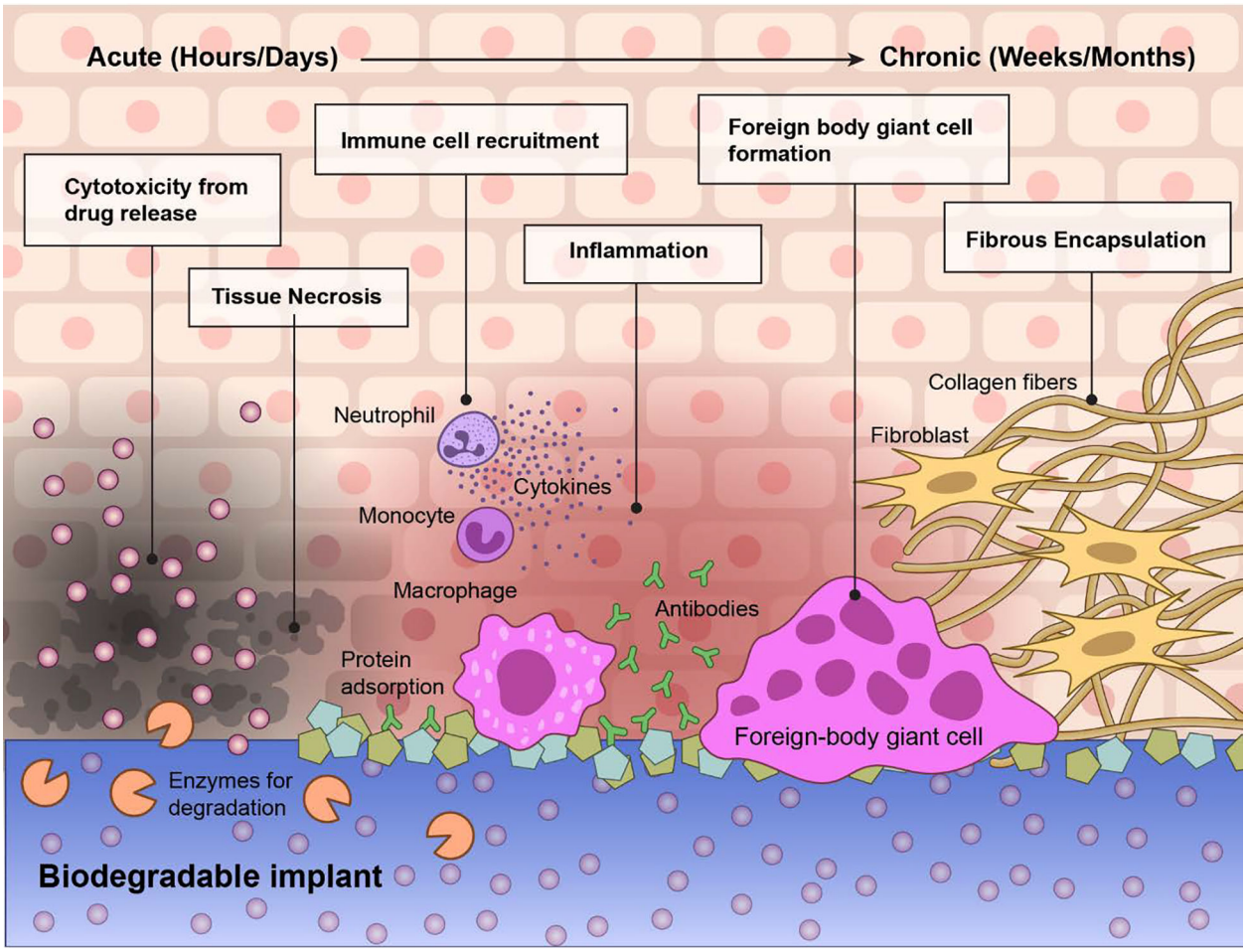

Figure 5.
Tissue responses to local drug delivery systems.

Table 1.

A list of current biopolymer-based implants for local treatment

API Category	Disease/Injury/ Target Location	Drug Delivery System	Outcome/Impact	References
Chemotherapy	Glioblastoma cavity	Chitosan-coated solid lipid nanoparticles embedded in o-carboxylmethyl chitosan nanofibers.	Chitosan-coated solid lipid nanoparticles demonstrated higher accumulation in human GBM cells than non-coated nanoparticles. In aqueous media, the nanofibers would dissolve and release the solid lipid nanoparticles	(45)
	Glioblastoma cavity	Gelatin-based hydrogel loaded with paclitaxel-releasing polyethylene glycol-methyl ether-poly(D, L-lactide) MPEG-PDLLA copolymer nanoparticles	Paclitaxel has poor solubility and cannot normally cross the BBB. *In vitro* and *in vivo* tests show the nanoparticles were cytotoxic to rat glioma cells, and the gelatin gel degraded after 5 weeks.	(46)
	Neuroblastoma, on the tumor	Doxorubicin-releasing silk fibroin films	Tumor growth was slower than non-drug loaded controls in an *in vivo* neuroblastoma mouse model, and cellular necrosis was observed at the interface of the silk films and the tumor	(47)
	Neuroblastoma, in or near the tumor	Cisplatin entrapped in powder form inside silk-based reservoirs	Cisplatin was able to release up to 30 days in the reservoirs. Intertumoral implantation of the reservoirs into a neuroblastoma mouse model demonstrated decreased tumor growth.	(48)
Antibiotics	Periodontitis, in periodontal pocket	Periochip®: Gelatin crosslinked by glutaraldehyde PerioCol-CG®: Type 1 collagen Periochip® and PerioCol-CG® are loaded with 2.5 mg chlorhexidine gluconate	Exhibit burst release of 40% in the first 24 hours of implantation, followed by sustained release of the drug for 7–10 days. Extensively reduces periodontal pocket depth when compared to surgical debridement alone. FDA approved.	(49)
	Periodontitis, in periodontal pocket	Xanthan gel loaded with 1.5 % chlorhexidine (Chlosite®)	Mucoadhesive and dissolvable within 10–30 days upon placement into the periodontal pocket and does not get washed away by saliva. Greatly improved periodontitis when compared to surgical debridement alone.	(49)
	Acute osteomyelitis	Heparinized nanohydroxyapatite/collagen biocomposite granules loaded with vancomycin	Vancomycin released for 19 days after an initial burst release, which eradicated bacteria in vitro. Can potentially be used to encourage bone regeneration while also decreasing risk of infection.	(50)
	Lacerations, inside the wound	Vancomycin and tobramycin -loaded chitosan sponge	Extremity wounds were created in 11 adult goats, and infected with bacteria. The wounds were debrided and irrigated, and then either treated with dressings alone or dressings and loaded chitosan sponges in the wound. In the sponge-treated group, there was nearly complete eradication of all bacteria. Animals treated with dressings alone had a 2-log increase in total bacteria after 48 hours.	(25)
	General infection	Silk fibroin films, hydrogels, and microspheres embedded in hydrogels loaded with ampicillin or penicillin (water soluble)	Silk films released half of their load within 24 hours of exposure to bacteria. Silk hydrogels released penicillin for 48 hours and ampicillin for 72 hours. Microspheres that were loaded with antibiotics and embedded in hydrogels released antibiotics up to 4 days. In an infected murine model, antibiotic-loaded silk hydrogels showed significantly reduced bacterial infection.	(51)
	General infection	Silk fibroin sponge reservoirs and films loaded with rifampicin or erythromycin (water insoluble)	Rifampicin was released from silk sponges and films for 8–9 days and 24 h respectively, while erythromycin was released from silk sponges for 31 days.	(52)
Anti-inflammatories/Pain Management	Dental pain/ inflammation	Collagen sponges for delivery of piroxicam	When taken systemically, piroxicam can cause gastrotoxicity. Piroxicam was released from collagen sponges for 10 hours, with a burst release after 30 minutes.	(53)

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API Category	Disease/Injury/ Target Location	Drug Delivery System	Outcome/Impact	References
	Chronic leg ulcers	Lidocaine and silver nanoparticles loaded in hyaluronic acid-based wafers	Lidocaine and silver nanoparticles were loaded into carrageenan and hyaluronic acid dressings. In vitro release showed a controlled release of lidocaine for 6 hours. *In vitro* cytotoxicity in keratinocytes showed that the system was not cytotoxic to cells but had significant antimicrobial effects when exposed to bacteria.	(54)
	Laceration/wound	Gelatin-alginate tissue adhesives loaded with bupivacaine and ibuprofen for wound repair	The adhesives released for 3 days, with slight cytotoxicity in bupivacaine loaded gels against fibroblasts in vitro. This system could provide alternatives to staples and sutures in wound healing, which can be painful to the patient.	(55)
Contraceptives/ Hormonal APIs	Birth control, intravaginal	Spermicidal chitosan/cellulose films for local delivery of metronidazole	In vitro pharmacokinetic results show a burst release at approximately 20 minutes, with sustained release for another 70 minutes.	(38)
	Birth control, transdermal patch	Silk fibroin microneedle patch for delivery of levonorgestrel	Although not a local delivery platform, microneedle patches avoid first pass metabolism and the use of daily pills. Silk patches released levonorgestrel *in vitro* for up to 100 days when loaded directly into the silk patches, and over a year when loaded into silk microparticles prior to casting the patches.	(42)

Table 2.

Characteristics of biopolymers used for implants for local delivery.

	Structure	Advantages	Material format
Cellulose (56)	β-D-Glucopyranose structure	Easy to functionalize Inexpensive production Water-based gelling system	Nano/microparticles, hydrogels, films, implants, sol-gel system
Chitosan (57–61)	A linear polysaccharide of randomly distributed β-(1→4)-linked D-glucosamine (deacetylated unit) and N-acetyl-D-glucosamine (acetylated unit)	Mucoadhesive – mucosal delivery In situ gelling system Permeation enhancing Colon targeting Easy to functionalize Inexpensive production	Nano/microparticles, hydrogels, films, implants, sol-gel system
Silk (62)	Protein structure consists of heavy and light chains linked by a disulfide bond at the c-terminus. The hydrophobic and hydrophilic domains of amino acid sequence form into crystalline and amorphous regions	Biocompatibility β-sheet formation to control drug delivery Water-based – hydrophilic drug, protein peptide, gene-based drug encapsulation Protection, stabilize protein and peptide-based drugs Mucoadhesive properties	Nano/microparticles, hydrogels, films, implants, sol-gel system, microneedle, minifoam, sponge
Alginate (63)	Polysaccharide – two (1Ñ4)-linked α-L-guluronate (G) and β-D-mannuronate (M) monomers	Solubility and pH sensitivity Crosslinkable by Ca^{2+}	Nanoparticles, hydrogels, films, microspheres,
Hyaluronic acid (64)	Linear mucopolysaccharide of alternatingly glucuronic acid and N-acetylglucosamine	Recognize specific receptors overexpressed on tumor cells: cell surface adhesive receptor 44 (CD44) Short lifetime and rapid degradation Gel formation with water	Nanoparticles, gels, cationic polymer carrier system, nanoemulsion system, polyelectrolyte microcapsule, microsphere, film
Gelatin (65)	Water soluble polypeptide	physical crosslink, chemical crosslink Gel formation with water to entrap cargo	Nano/micro particles Fibers, hydrogels, bioadhesives

Table 3.

Challenges with local delivery of small molecules, protein and peptides, antibodies and nucleic acids (68)

	Characteristics	**Challenges**	**Biopolymer Benefits**
Small molecule	Less than 900 Da	Improve solubility Control release kinetics Improve permeability Reduce off-target toxicity	Enhance solubility by chemical grafting (69, 70) Controlled release by tuning polymer crystallinity (71–73) Controlled release by crosslinking (74)
Proteins and peptides	Protein – 50 or more amino acids with secondary, tertiary folded structures Peptide – 2–50 amino acid polymeric chains	Improve stability Control release kinetics	Silk stabilization (75)
Nucleic acids/gene	Ribonucleic acid (RNA) and deoxyribonucleic acid (DNA)	Improve stability Control release kinetics Prevent off-target gene editing	Stabilization (43)
Live cells / microorganisms	Live organisms Can be depleted from stress, infection, antibiotic use and environmental factors	Control unpredictable release kinetics *In vivo* persistence and viability Maintain therapeutic cell phenotype Manufacturing and scale up	Living materials from encapsulating microorganisms (67, 76, 77)