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Local drug delivery systems for inflammatory diseases: Status quo, challenges, and opportunities

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ABSTRACT

Inflammation that is not resolved in due course becomes a chronic disease. The treatment of chronic inflammatory diseases involves a long-term use of anti-inflammatory drugs such as corticosteroids and nonsteroidal anti-inflammatory drugs, often accompanied by dose-dependent side effects. Local drug delivery systems have been widely explored to reduce their off-target side effects and the medication frequency, with several products making to the market or in development over the years. However, numerous challenges remain, and drug delivery technology is underutilized in some applications. This review showcases local drug delivery systems in different inflammatory diseases, including the targets well-known to drug delivery scientists (e.g., joints, eyes, and teeth) and other applications with untapped opportunities (e.g., sinus, bladder, and colon). In each section, we start with a brief description of the disease and commonly used therapy, introduce local drug delivery systems currently on the market or in the development stage, focusing on polymeric systems, and discuss the remaining challenges and opportunities in future product development.

1. Introduction

Inflammation is the immune system's response to infection and injury. If inflammation is not resolved in due course, it becomes a chronic disease, causing damages to host tissue and organ function [1]. Inflammation is initiated by the recognition of pathogens and/or injured tissues by innate immune cells, which activate signaling pathways to produce proinflammatory effectors such as cytokines, chemokines, and prostanoids [1]. Nonresolving inflammation is treated by inhibitors of syntheses or activities of the proinflammatory effectors. Corticosteroids inhibit the production of arachidonic acid, the precursor of prostanoids, by suppressing phospholipase A_2 [2]. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenases (COXs), which catalyze the conversion of arachidonic acid to prostanoids. Alternatively, biologics are used to target proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin (IL)-1 or IL-6 [3,4]. While these anti-inflammatory drugs are effective in relieving symptoms, they are often accompanied by dose-dependent side effects, such as Cushing syndrome, adrenal suppression, and glucose intolerance (corticosteroids) [5], gastrointestinal, renal, and cardiovascular side effects (NSAIDs) [6], and increased risk of serious infections and neurological adverse events (biologics) [7]. Therefore, when inflammation is regionally contained and/or occurs in locations with poor vascular permeability (e.g., eye), it is reasonable to consider local drug delivery rather than systemic administration to reduce off-target side effects.

Local drug delivery aims to deliver the minimum amount of drug locally to the affected tissues over a desired period. Effective local drug delivery systems can suppress off-target side effects, attenuate metabolism or clearance, reduce administration frequency, and improve patient compliance. These features are particularly attractive when the conditions require a long-term medication as in chronic inflammations. Therefore, several local drug delivery systems have been developed and marketed over the years to treat inflammatory diseases. The diversity of the marketed products and experimental approaches reflect the advances in biomaterials and drug delivery technology as well as the complexity of diseases. The primary intention of this article is to review various local drug delivery products adopted in the therapy of chronic inflammatory diseases and understand the status quo. As we collect the

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literature and analyze the findings, it has also become clear that numerous challenges remain despite technical advances in drug delivery, and the technology is underutilized in some applications. Therefore, this review article aims to showcase local drug delivery systems in different inflammatory diseases, including the targets well-known to drug delivery scientists (e.g., joints, eyes, and teeth) as well as the other applications with untapped opportunities (e.g., sinus, bladder, and colon), and discuss the current status, challenges, and future directions.

In each section, we introduce the disease and commonly-used therapy, summarize local drug delivery systems currently on the market or in the development stage with in vivo proof of concept, and discuss the remaining challenges and opportunities. We focus on carriers of corticosteroids or NSAIDs but also use examples of biologics or other disease-modifying agents depending on the applications. Local drug delivery systems are classified to non-injectable (pre-formed) solid implants and injectable formulations. Specifically, pre-formed solid implants refer to non-injectable hydrogels, sponges, films/membranes, fibers and stents, which require a surgical procedure for their implantation and may be removed if the treatment is to be terminated. Injectable formulations include nano/microparticles, in-situ crosslinkable hydrogels, and their combinations, which can be administered via local injections and, in most cases, not intended to be removed. We mainly discuss polymer-based systems due to their widespread use based on biocompatibility and the long history of use in drug delivery, biodegradable [poly(caprolactone) (PCL), poly(lactic acid) (PLA) or poly(lactic-co-glycolic acid) (PLGA)] or non-degradable (silicones, polyurethanes, polyacrylates or poly(ethylene vinyl acetate) [8], and of synthetic or natural origin. Inorganic or metallic systems constitute an emerging area of drug delivery but are not discussed in this review; interested readers are referred to recent review articles [9,10].

2. Arthritis

Arthritis, inflammation of the joint, is a degenerative and chronic inflammatory disease, affecting more than 28 million patients in the United States alone [11]. Osteoarthritis (OA) and rheumatoid arthritis (RA) are two main types of arthritis. OA is the most common form of arthritis, where the inflammation is confined in the joint. RA is a progressive systemic autoimmune disease, initially affecting joints and ultimately progressing to other organs [12]. The pathogenesis of arthritis involves a series of inflammatory pathways: leukocyte infiltration into the synovium of the affected joint, the production of proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukins (IL-1, IL-6), and degenerative enzymes, followed by destruction of articular cartilages or bones [13,14] (Fig. 1a). Both OA and RA involve the progressive loss of cartilage, remodeling of bone, inflammation, and deformation of the joint. Patients usually suffer from pain, stiffness, joint effusion, or even complete disability of the affected joint.

2.1. Common therapy

2.1.1. Systemic therapy

There is no cure for arthritis. Most treatments, which last for life, aim to reduce joint pain and inflammation, maintain joint mobility, and function, and prevent deformity. Oral anti-inflammatory medications such as NSAIDs and corticosteroids are used as the first-line treatments. Other systemic medications include disease-modifying antirheumatic

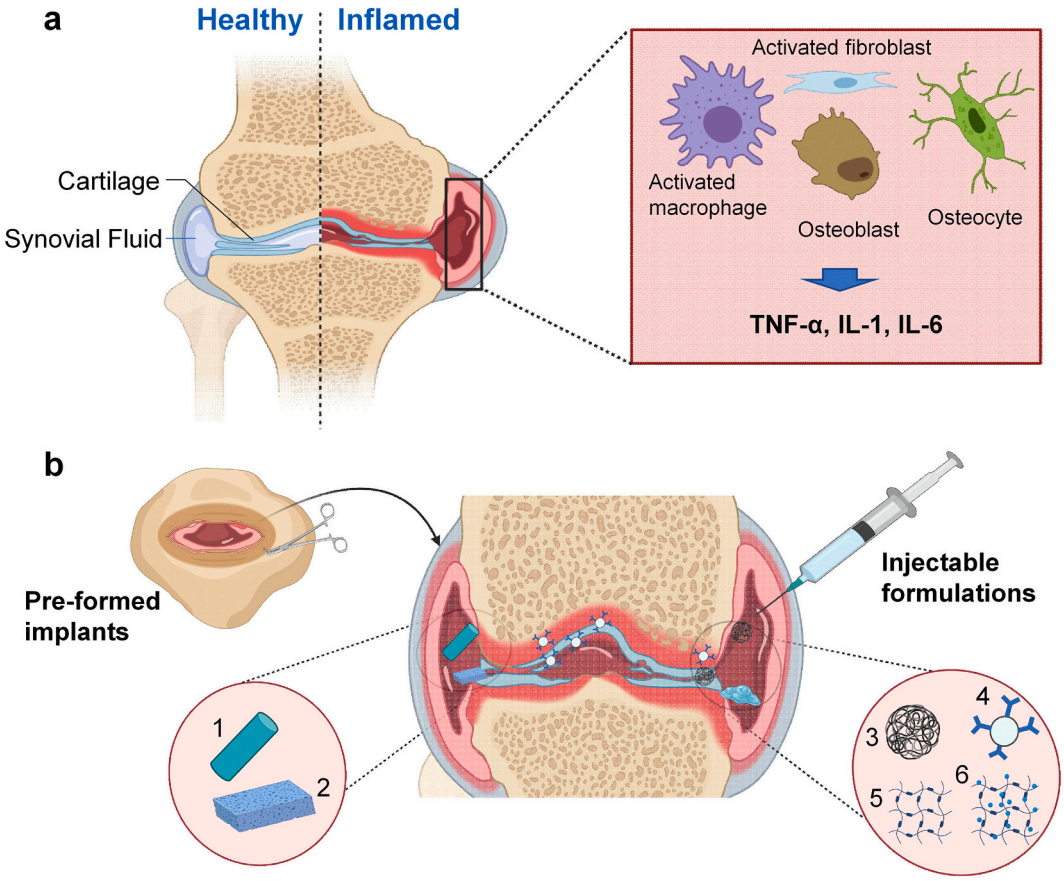

Fig. 1. (a) Schematic representation of normal and inflamed joints (with relevant inflammatory cells and proinflammatory mediators). (b) Strategies for Intra-articular drug delivery. 1: Solid matrix implant; 2: sponge implant; 3: polymeric microparticles; 4: functionalized-nanoparticles; 5: in-situ forming gel; and 6: particle-hydrogel hybrid system. Created with BioRender.com.

drugs (DMARDs) (e.g., methotrexate, leflunomide) and anti-inflammatory biologics (e.g., inhibitors of TNF-α, IL-1, or IL-6). They reduce inflammatory responses and downregulate proteins or cells involved in immune stimulation responses [12]. Systemic drug delivery to the joints and bones is challenging due to the poor blood supply to the inflamed bones [15–17]. Moreover, two or more drugs are commonly used to manage the disease, especially in RA. Coupled with the chronic nature of arthritis, the systemic use of these drugs predisposes to side effects, such as ulceration and bleeding in the gastrointestinal tract, liver problems, and bone marrow deterioration.

2.1.2. Local therapy

Intra-articular (IA) injection can localize a drug to the affected joint and minimize systemic side effects. However, efficient lymphatic system in the joint limits the local drug retention [15,18]. Moreover, frequent IA injections of corticosteroids (> 3 times per year) can cause joint deterioration, bone damage, and worsening symptoms [19–21]. A high dose of IA corticosteroids also cause significant changes in the chondrocyte shape or loss of organelles, altering the cell functions [22]. This, in turn, interferes with the production of proteins, proteoglycans and extracellular collagen fibers responsible for bone and cartilage strength [22,23].

Non-crosslinked hyaluronate (HA) gels, Hyalgan, Supartz, Orthovisc, and Euflexxa and crosslinked HA, hylan G-F 20 (Synvisc) and Durolane are commercially available for IA injection to increase the viscoelasticity of synovial fluid, joint lubrication, and prevent cartilage degradation. However, their clinical application is limited because of the short half-life (1–2 days) in the joint [24] or side effects such as arthralgia and injection-site pain [25].

2.2. Local drug delivery systems (Table 1)

Local drug delivery systems are developed to retain drugs in the joint and reduce the dosing frequency. They are produced with natural or synthetic polymers as drug conjugates [26], microspheres/nanospheres [27], hydrogels [18], sponges [28], films/membranes [29], and fibers [30] (Fig. 1b).

2.2.1. Non-injectable (pre-formed) implants

Biodegradable polyurethane (PU) film was used as a carrier of dexamethasone (DEX/PU films) [31]. The film was prepared by casting an aqueous dispersion of polyurethane and dexamethasone acetate in a Teflon mold. The DEX/PU films released dexamethasone in phosphate buffered saline (PBS) over 120 days in vitro and at least 45 days in subcutaneous tissue of mice based on drug diffusion and polymer degradation [31]. The DEX/PU film was inserted to a non-biocompatible and non-absorbable synthetic sponge, which causes local inflammation and angiogenesis, similar to the inflammatory conditions of arthritis [32,33], and then implanted in subcutaneous tissues of mice. The films suppressed neovascularization and macrophage activation caused by the proinflammatory sponge implant, compared to the untreated group (sponge implants without DEX/PU films) [31]. The PU implants were also applied to local delivery of triamcinolone acetonide (TA) and showed similar results [34]. TA/PU implants released TA over 45 days in subcutaneous tissues in mice and decreased inflammatory cell infiltration into the proinflammatory sponge, thereby decreasing local inflammation and angiogenesis [34].

Poly(ε-caprolactone) (PCL) implants loaded with methotrexate (MTX) [35], tacrolimus [36] or leflunomide [37] were prepared by hot-melt molding for local treatment of inflammation induced by the sponge implant. Placed in or near the sponge (<1 cm distance), PCL implants released 68% MTX, 9.8% tacrolimus, or 27% leflunomide at the inflammation site (dorsal subcutaneous pouch) by diffusion in 10–30 days in vivo. The released drugs reduced the infiltration of inflammatory cells, as measured by the decrease of myeloperoxidase, IL-6 and TNF-α levels compared to blank PCL implants, and attenuated renal or hepatic toxicity and myelosuppression of those drugs. PLGA and PLA are also used to control the drug release from days to months. The drug release rate may be tailored by varying the dimension of the implant, the composition and molecular weight of the polymer, and the drug loading content [38].

2.2.2. Injectable formulations

2.2.2.1. Micro/nanoparticles. Particle formulations with diameters ranging from nano- to micrometers can be administered as a suspension by IA injection for local treatment of OA or RA [39,40]. A recent study showed that a single IA injection of microencapsulated triamcinolone acetonide (TA) had a long-lasting (14 days) anti-inflammatory effect in rats with a chemically induced arthritis compared to a drug suspension

Table 1
Local delivery systems of anti-inflammatory drugs for arthritis therapy.

System	Carrier (materials)	Drug	Development status	Ref
Preformed implants	Biodegradable Polyurethane	DEX or TA	Preclinical (mouse model of local inflammation and angiogenesis induced by non-biocompatible, nonabsorbable synthetic sponge)	[31,34]
Preformed implants	PCL	MTX, tacrolimus, or leflunomide	Preclinical (mouse model of local inflammation and angiogenesis induced by non-biocompatible and nonabsorbable synthetic sponge)	[35–37]
Microparticles (Zilretta®)	PLGA	TA	Marketed (approved by US FDA in 2017)	[48]
Microparticles	PLA/mPEG-PDL	TA	Preclinical (rat model of arthritis induced by CFA)	[41]
Lipid microparticles (Lipotalon®)	Soybean oil, fats, glycerol	Dexamethasone-21-palmitate	Approved in Germany	[49]
Nanoparticles	PLGA-PEG-PLGA	Etoricoxib	Preclinical (rat model of (OA induced by ACLT)	[65]
Nanoparticles	Ferritin/peptide	Metformin	Preclinical (mouse model of OA induced by Papain)	[44]
Nanoparticles	Dextran sulfate	TA	Preclinical (mouse model of OA induced by monosodium iodoacetate)	[47]
Liposomes	DPPC, PEG-DSPE, cholesterol	PLP	Preclinical (mouse model of ICA)	[66]
Preformed hydrogel	Crosslinked Polyurethane derivative	Diclofenac	Preclinical (rat model of PGPS-induced arthritis)	[59]
Microsphere/thermo-sensitive hydrogel hybrid	PLA/mPEG-PDL/poly-PEGMA)	TA	Preclinical (rat model of arthritis induced by CFA)	[62]
Nanocapsule/hydrogel hybrid	hyaluronic acid/fibrin	DEX, Gal-3 inhibitor	Preclinical (rat model of synovial joint inflammation induced by carrageenan	[63]

ACLT: anterior cruciate ligament transection; CFA: Complete Freund's Adjuvant; DEX: Dexamethasone; DMAB: didodecyldimethylammonium bromide; DPPC: dipalmitoyl phosphatidylcholine; Gal-3: galectin-3; ICA; Immune-complex arthritis, MTX: Methotrexate; PCL: Poly(ε-caprolactone); PEG-DEPE: PEG 2000-distearoyl phosphatidylethanolamine; PLA/(mPEG-PDL) diblock copolymer: blend of polylactic acid and methoxy-polyethylene glycol-poly (δ-decalactone) deblock copolymer; Poly-PEGMA: star-shape PEG methacrylate methyl ether; PLGA-PEG-PLGA: poly(lactic-*co*-glycolic acid)- polyethylene glycol- poly(lactic-co-glycolic acid); PLP: prednisolone phosphate; PVA: Polyvinyl alcohol; TA: Triamcinolone acetonide; TGA: Thioglycolic acid; TMP: Trimethoprim.

[41]. The microparticles were prepared with a blend of PLA and methoxy-polyethylene glycol-poly (δ-decalactone) (mPEG-PDL) diblock copolymer. The sustained effect of TA was attributed to the cocrystallization of TA and the *co*-polymer because TA encapsulated in amorphous PLA microparticles showed a relatively short anti-inflammatory effect [41].

Nanoparticles are used to improve the drug retention in the cartilage extracellular matrix and intracellular delivery of the payload [42]. The interaction of nanoparticles with synovial tissues depends on the surface properties of the particles. For example, PLGA nanoparticles coated with quaternary ammoniums were retained in the cartilage explant six times better than anionic particles due to the electrostatic interaction with anionic cartilage ECM [43]. However, the retention of cationic particles is negatively affected by the synovial fluid, which contain macromolecules to adsorb on the particle surface and change the nature of particle-tissue interactions [43]. To ensure a robust interaction with a specific region of the joint such as cartilage or synovium, nanoparticles can be functionalized with cell-interactive ligands. A recent example demonstrated that metformin-loaded ferritin nanocages, decorated with a cartilage-targeting peptide (WRYGRL), could specifically bind to type-II collagen of the cartilage matrix, achieving a 1.5-fold longer retention in the joint and higher levels of metformin in cartilage and synovial fluid than the unmodified nanocages [44]. Another target is class A scavenger receptor (SR-A) [45,46] expressed on the activated, proinflammatory synovial macrophages. A nanoparticulate self-assembly of dextran sulfate-TA conjugate was used to target the activated macrophages, with dextran sulfate serving as a ligand. The dextran sulfate-TA nanoparticles were selectively taken up by LPS-activated RAW 264.7 macrophages than non-activated cells and suppressed synovitis and proinflammatory cytokine expression in mice with monosodium iodoacetate-induced OA, showing a small degree of advantage over free TA [47].

Micro/nanoparticles for IA injection are commercially available. Zilretta®, a PLGA/TA microparticle formulation, prolonged the drug residence in synovial fluid and reduced systemic drug exposure compared to TA crystalline suspension in knee OA patients [48]. However, a clinical study found no advantage of Zilretta® over a standard TA injectable suspension in reducing knee pain after 12 weeks [25]. Lipotalon® is a lipid microparticle formulation of palmitylated dexamethasone (prodrug), preferentially taken up by synovial macrophages after IA injection and transformed to its active form by intracellular esterases, thus preventing the side effects of dexamethasone crystals, such as synovitis and tissue irritation [49]. Many other micro/nanoparticle systems for IA delivery are reviewed extensively in the literature [50–54].

2.2.2.2. In-situ forming gels. Injectable polymer depots can be formulated with a low viscosity polymer solution, comprising a water-insoluble polymer and a water-miscible solvent. The solution forms a polymer depot upon solvent exchange with body fluid in situ. For example, a meloxicam/PLGA solution in the *N*-methyl-2-pyrrolidone (NMP) and PEG 400 mixture was administered to a rat in the hind leg by intramuscular (IM) injection to form a polymer depot [55]. The drug-eluting depot maintained an effective drug concentration in plasma for COX-2 inhibition for 23 days, whereas a drug solution in the same solvent mixture only lasted 2 days [55].

Alternatively, injectable hydrogels are widely explored for IA delivery. Hydrogels made of natural polymers, such as collagen, gelatin, alginate, hyaluronic acid, or chitosan, degrade and release their payloads fast; thus, their utility as a drug depot is rather limited. Synthetic polymers such as PEG, PLGA, or polymethyl methacrylate [30] have been used to form hydrogels with higher mechanical strength and tunable release profiles [56,57]. These hydrogels generally show good biocompatibility and low immunogenicity [18]. For example, an in-situ forming hydrogel made of temperature-sensitive PEG-poly(ε-caprolactone-*co*-lactide) tri-block copolymer (PCLA-PEG-PCLA) was used as a carrier of celecoxib to sustain the drug release in the knee joint [58]. The polymer underwent a sol-to-gel transition at 37 °C, forming an immobile depot that released celecoxib for more than 10 weeks in vitro. Upon a single subcutaneous injection of the drug-loaded hydrogel, celecoxib was detectable in serum at least for 4 weeks in rats [58]. The celecoxib-loaded hydrogel was biocompatible in the healthy joints of rats, showing no histological changes in cartilage or bone upon IA injection [58].

Recently, a fully biodegradable pre-formed hydrogel was directly delivered to the inflamed joint via IA injection (Fig. 2) [59]. A polyurethane derivative was conjugated to diclofenac, crosslinked via PEG diazide by click chemistry, and injected as microgels after trituration. The crosslinked microgels labeled with a fluorescent dye maintained the fluorescence signal for 2 weeks in the joint as opposed to a free dye that lasted only 1 day. The microgels were tested in a rat model of arthritis and found to be effective in reducing knee swelling after a delay unlike IA triamcinolone solution, which was immediately effective [59].

2.2.2.3. Particle-hydrogel hybrid systems. Hydrogels are combined with micro/nanoparticles to increase the mechanical strength [60]. Particles can be designed to interact with chains of hydrogel polymers through hydrophobic, electrostatic interactions, hydrogen or covalent bonding to enhance mechanical properties of the hybrid gels. Moreover, particles incorporated in the gel may provide an additional diffusion barrier for drug release control [61]. A recent study reported TA-loaded polymeric (PLA and mPEG-poly(δ-decalactone)) microspheres, dispersed in a thermoresponsive *star*-shape PEG methacrylate methyl ether (poly-PEGMA) hydrogel, for IA drug delivery [62]. The hybrid gel system released TA following the non-Fickian model. IA injection of TA/microspheres in poly-PEGMA hybrid system significantly reduced the joint inflammation in rats induced by Complete Freund's Adjuvant, better than kenacort® (TA suspension) and TA/microspheres alone [41], likely due to their sustainable and bioadhesive properties (Fig. 3) [62]. Similarly, nanocapsules (NCs) of dexamethasone incorporated in hyaluronic acid/fibrin hydrogel provided a sustained in vitro drug release in simulated synovial fluid for 72 h, twice longer than NCs alone [63]. Consistently, IA injection of NCs/hyaluronic acid/fibrin hydrogel containing an inhibitor of Gal-3 (protein triggering the proinflammatory process in arthritis) suppressed the carrageenan-induced knee joint inflammation, twice better than Gal-3 inhibitor/NCs alone at 3× dose [63]. The comparison of particles and hybrid systems provides an insight into the beneficial role of hydrogels in retaining particles in the joint. However, these studies did not compare the hybrid gels with drug/hydrogel controls; thus, we are unable to tell if and how much particles may have helped to extend the therapeutic activities. The superiority of the hybrid system over either hydrogel or particle system alone was demonstrated previously in the literature [61,64].

2.3. Remaining challenges and opportunities

The above examples have extended drug residence time in the joint to varying degrees, but it is not long enough to warrant clinical application. Moreover, solid implants need to be designed with a consistent and reproducible shape and surface area, so they fit the joint physically. Remaining challenges in IA-injectable particles are the low drug encapsulation efficiency, burst drug release in the initial period, and the limited retention time. Specifically, microparticles of size less than 10 μm were reported to be engulfed by phagocytes and leaked out of the inflamed joint in mice [67,68]. Nanoparticles smaller than 250 nm rapidly escaped from the joint through the fenestrae of synovial membrane and were difficult to retain in the synovial fluid [68,69]. Because of the limited retention, the locally administered particles do not necessarily avoid systemic absorption [49]. Hydrogels may help retain drugs in the injection site, but fast dissolution (e.g. chitosan-based hydrogel), low mechanical strength, rapid and uncontrolled drug release remain challenges [70]. Hybrids of particles and hydrogels are worth further exploring, as each component can complement the other:

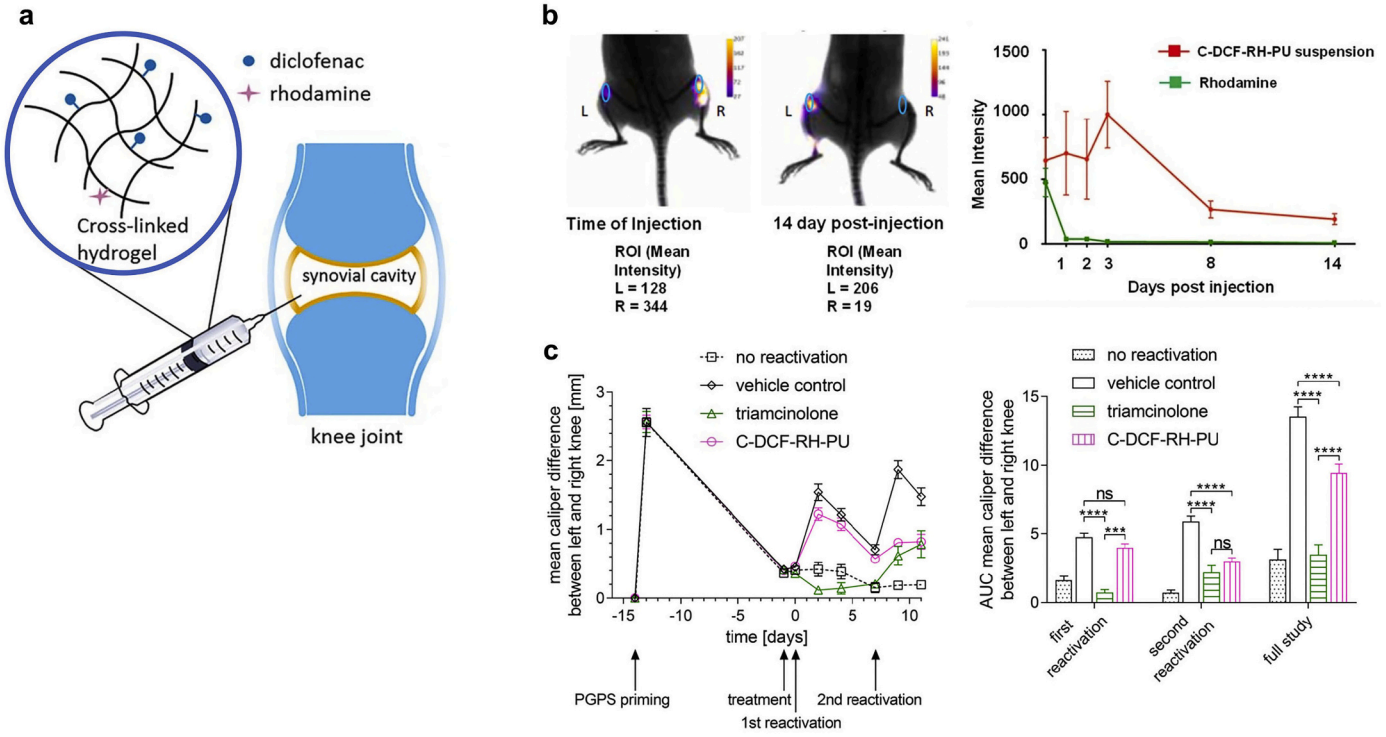

Fig. 2. Crosslinked polyurethane-diclofenac hydrogel for intraarticular injection. (a) Schematic representation of crosslinked polyurethane-diclofenac conjugate hydrogel. (b) In vivo fluorescence images and corresponding quantitative mean fluorescence intensity showing the retention of rhodamine-labeled crosslinked hydrogel injected in the left knee joint (L) of a rat compared to free rhodamine in the right knee joint (R) after 14 days. (c) Efficacy of crosslinked hydrogel based on knee caliper measurement differences between arthritic right knee joint and normal left joint to assess inflammation. Arthritis was induced by peptidoglycan polysaccharide (PGPS) priming of the right knee, followed by two intravenous injections of PGPS (1st and 2nd reactivation). No reactivation: PEG400 (vehicle) without reactivation; vehicle control: PEG400 (vehicle) with reactivation; triamcinolone: clinical benchmark; C-DCF-RH-PU: crosslinked polyurethane-diclofenac hydrogel. Reprinted with permission from [59].

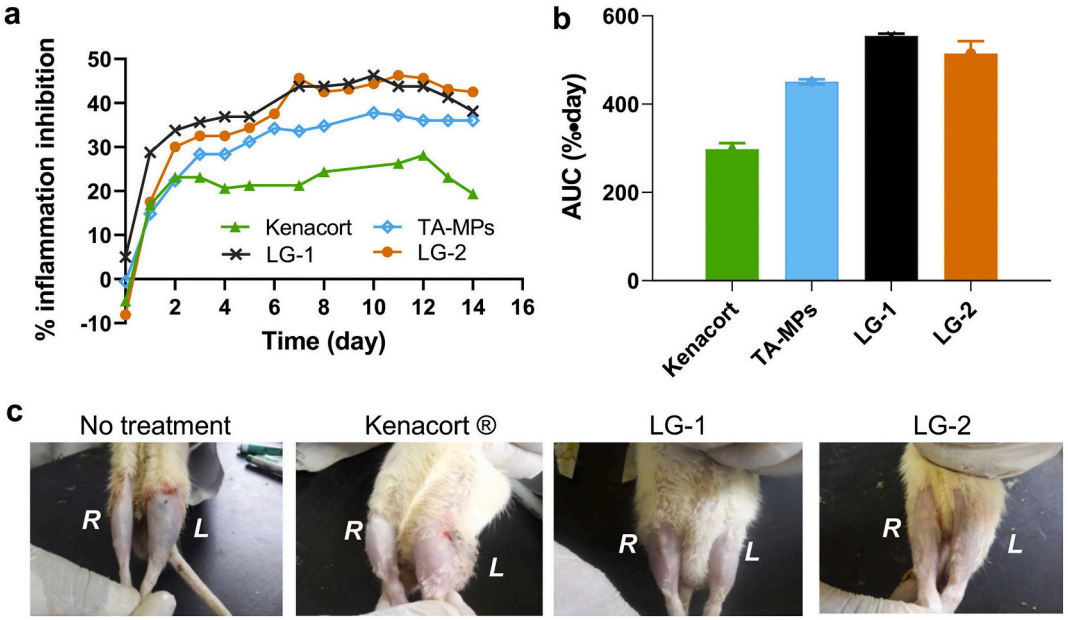

Fig. 3. Microparticles-in-thermoresponsive polyethylene glycol hydrogels. (a) Percent inflammation inhibition vs. time profile of PLA/PEG-PDL microparticles dispersed in 20% (LG-1) and 30% (LG-2) poly(PEGMA) hydrogels compared to marketed product (Kenacort®) and TA/microspheres (TA-MPs). (b) AUC (0–14 days) calculated from (a). (c) Photographs of rat knee joints at the 14th day from the first treatment in rats with CFA-induced arthritis. L: arthritis + treated; R: no arthritis (negative control). Reprinted with permission from [41,62].

hydrogels help to retain the particles in the joint, and particles to control the drug release.

3. Uveitis

Uveitis, derived from Latin words *uva* or *uvae* (grape) and *itis* (inflammation), describes an inflammation of the uveal tract of the eye that includes iris, ciliary body, and choroid. Clinically, uveitis refers to inflammations of all parts of the eye, including anterior, middle, and posterior segments. Uveitis is broadly classified to three types based on the site of inflammation (Fig. 4a). Anterior uveitis refers to the inflammation of iris (*iritis*) and anterior ciliary body (*anterior cyclitis* or *iridocyclitis*); intermediate uveitis to the inflammation of the vitreous cavity (*hyalitis*), pars plana (*pars planitis*), and posterior ciliary body (*posterior cyclitis*); posterior uveitis to the inflammation of choroid (*choroiditis*), retina (*retinitis*) or both (*chorioretinitis*, *retinochoroiditis*); and panuveitis is a diffusive uveitis affecting many areas of the eye [71,72]. Uveitis is the third leading cause of preventable vision loss affecting more than 2.3 million patients worldwide, mostly in people aged 20–60 years (90–95%) but also in children (5–10%) [71,73]. Uveitis may be noninfectious, idiopathic, or associated with systemic conditions such as autoimmune diseases or medications [71,74–76]. Symptoms include pain, redness of the eye, photophobia (light sensitivity), lacrimation, flare, impaired vision, and abnormal eye movement [76].

3.1. Common therapy

Corticosteroids have been the mainstay of uveitis therapy. Corticosteroids may be administered topically (eye drops), locally (periocular injection), or systemically (oral or intravenous/intramuscular injections) (Fig. 4a). Immunosuppressive drugs, such as antimetabolites (e.g., methotrexate, azathioprine, leflunomide), T-cell inhibitors (e.g., cyclosporine, tacrolimus), or alkylating agents (chlorambucil, cyclophosphamide), are also used to reduce severe side effects (e.g., ocular hypertension) associated with long-term corticosteroid therapy. Topically applied drugs are only suitable for managing anterior uveitis because of poor drug penetration through the ocular barriers. Periocular injection can achieve a higher local concentration of drug at the site of application. However, long-term maintenance of the therapeutic level is challenging due to the rapid diffusion and clearance of the drug. Frequent injection is thus required for the management of chronic uveitis, but it involves significant discomfort to the patients. Most uveitis patients ultimately rely on systemic corticosteroids; however, the blood-retinal barrier at the posterior segment limits drug transport from the

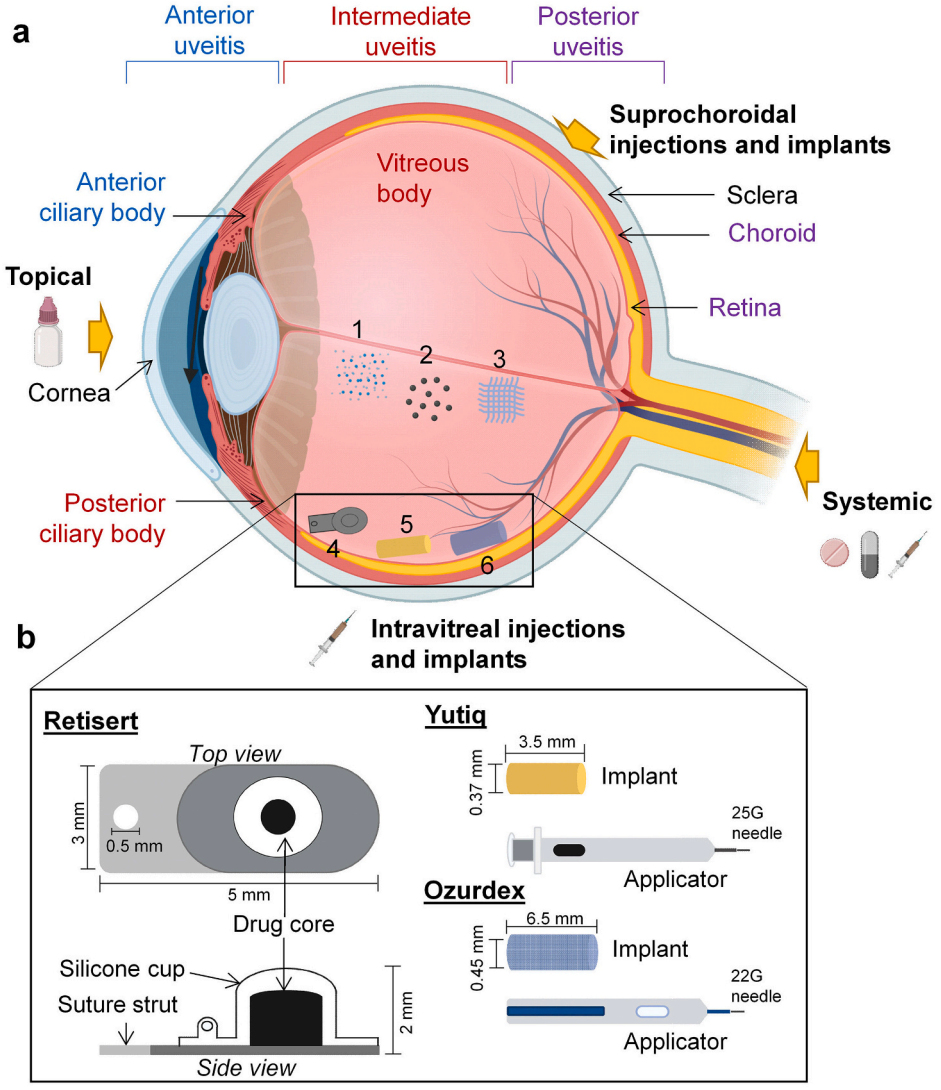

Fig. 4. (a) Eye structure with key anatomical features, types of uveitis, and routes and strategies for ocular drug delivery: (1) Nanoparticles; (2) microparticles; (3) hydrogels; (4–6) implants. (b) Ocular implants approved for uveitis treatment: Retisert® (fluocinolone acetonide) implant; Yutiq® (fluocinolone acetonide) implant; and Ozurdex ® (dexamethasone) implant. Created with BioRender.com.

circulation to the eyes [77–79]. High systemic doses are required to achieve therapeutic concentration in the eyes at the expense of systemic side effects [80,81].

3.2. Local drug delivery systems (Table 2)

3.2.1. Ocular implants (Fig. 4b)

Ocular implants have been developed to achieve sustained therapeutic levels of drugs in the eye. Implants are placed around or in the eye. Despite the invasive administration, implants are preferred because of several advantages, such as long-term drug delivery (from a few months to years), controlled drug release, direct access to the site of action, less frequent procedures than injections, and reduced systemic side effects. Ocular implants are made of nondegradable or biodegradable polymers according to the desired drug release properties [81,82].

Retisert® (Bausch & Lomb, Inc.) was the first polymeric implant approved by the US FDA for the treatment of chronic noninfectious uveitis. Retisert® is a nondegradable implant for sustained release of fluocinolone acetonide (FA), a corticosteroid with poor water solubility (0.0547 mg/mL) [83]. With a dimension of 3 mm (width) × 2 mm (height) × 5 mm (length), it is placed surgically in the vitreous through pars plana and sutured to the sclera [83,84]. The implant has three components: a drug tablet (1.5 mm diameter), an impermeable silicone elastomer cup with an orifice for drug release, and a polyvinyl alcohol (PVA) membrane between the tablet and the orifice that controls the rate of drug diffusion [85–87]. Retisert® contains a total of 0.59 mg of FA and releases the drug over 2.5 years at a rate of 0.6 μg/day for the first month, followed by a steady-state release rate of 0.3–0.4 μg/day.

Yutiq® (Eyepoint Phannaceuticals, Inc.), approved by the US FDA in 2018, is another nondegradable intravitreal implant delivering FA for the treatment for chronic noninfectious uveitis in the posterior segment. FA (0.18 mg) is contained in an impermeable polyimide tube measuring 3.5 mm (length) × 0.37 mm (diameter), with a permeable PVA membrane in one end and an impermeable silicone plug on the other end [88]. It is placed intravitreally by an applicator (6-in. length) containing a 25-gauge needle [89–91]. Yutiq releases FA at an initial rate of 0.25 μg/day in the vitreous chamber over 36 months.

Ozurdex®, formerly Posurdex (Allergan, Inc.), is a biodegradable intravitreal implant containing 0.7 mg dexamethasone in a PLGA sustained drug delivery system called Novadur®. Ozurdex® is a rod-shaped implant (6.5 mm length, 0.45 mm diameter), applied to the posterior segment of the eye through a 22-gauge single-use needle applicator. It was approved by the US FDA in 2009 for the treatment of macular edema (following branch retinal vein occlusion or central retinal vein occlusion) and noninfectious uveitis affecting the posterior segment. It releases dexamethasone over 6 months, including a faster drug release for the initial 2 months, followed by a slower drug release for the remaining 4 months. The initial drug release is governed by both drug diffusion and polymer degradation, and the later phase by polymer degradation [92–96].

3.2.2. Injectable formulations

3.2.2.1. Polymeric particles. Biodegradable polymeric particles have been extensively explored for ocular drug delivery. Triamcinolone acetonide (TA)-loaded PLGA microspheres with a mean diameter of ~50 μm was prepared for intravitreal application [97]. Microspheres showed a longer drug release (up to 87 days) as compared to drug suspension (46 days) in vitro. In a rabbit model of endotoxin-induced uveitis (EIU), microspheres maintained the drug effect for 8 weeks, evident from the response to endotoxin challenge (lower uveitic score, leukocytes count, and protein content in aqueous humor than drug suspension) [97].

PLGA-based nanoparticles have also been explored for enhancing cell interactions. TA was loaded in PLGA nanoparticles with a mean diameter of ~80 nm, where mPEG was incorporated in the polymer matrix to improve drug release. Nanoparticles showed a sustained drug release for >45 days in vitro and a marked decrease in IL-17 and an increase in IL-10 levels as compared to TA in experimental autoimmune uveitis rats [98]. Nanoparticles have been used for subconjunctival (SCT) injection. Dexamethasone sodium phosphate (DSP), a water-soluble form of dexamethasone, was loaded in PLGA nanoparticles (mean diameter 210 nm) including zinc ions (Zn^{2+}), which formed an ionic bridge between DSP and PLGA to increase drug loading (6% w/w) [99]. With single SCT injection of DSP-Zn PLGA nanoparticles to healthy rats, DSP was detectable for at least 3 weeks in the eye but not in the blood. In a rat model of autoimmune uveitis, the DSP-Zn PLGA nanoparticles reduced the expression of inflammatory mediators (TNF-α, IL-17, and IL-1β), improved the clinical score with fewer signs of inflammation (no pus accumulation in the anterior chamber and relatively low inflammatory cell infiltration and retinal vessel enlargement) (Fig. 5a), and reduced the inflammatory microglial cell density in the retina significantly (Fig. 5b), as compared to phosphate buffer saline and free DSP [99]. Similarly, fluorometholone has been encapsulated in PLGA nanoparticles for ocular delivery. Fluorometholone-loaded PLGA nanoparticles (mean diameter 150 nm) showed greater anti-inflammatory effect than commercial formulation (Isoptoflucon®) in pig eyes upon topical administration [100]. The improved anti-inflammatory effect of nanoparticles was attributed to greater and faster corneal permeation and sustained drug release [100].

3.2.2.2. Lipid-based particles. TA or prednisolone phosphate have been

Table 2
Local delivery systems of anti-inflammatory drugs for uveitis therapy.

System	Carrier (materials)	Drug	Development status	Ref.
Retisert® (Polymeric implant)	PVA, silicone elastomer	FA	Marketed (approved by US FDA in 2005)	[83–87]
Yutiq® (Polymeric implant)	Polyimide, PVA, silicone	FA	Marketed (approved by US FDA in 2018)	[88–91]
Ozurdex® (Polymeric implant)	PLGA	DEX	Marketed (approved by US FDA in 2009)	[92–96]
Microspheres	PLGA	TA	Preclinical (rabbit model of EIU)	[97]
Nanoparticles	PLGA	TA	Preclinical (rat model of AU)	[98]
Nanoparticles	PLGA	DSP	Preclinical (rat model of AU)	[99]
Nanoparticles	PLGA	Fluorometholone	Preclinical (pig model of SA induced inflammation)	[100]
Liposomes	DPPC, cholesterol, PEG-DSPE	TA, prednisolone phosphate	Preclinical (rabbit model of AIU)	[101]
Liposomes	PC, cholesterol	VIP	Preclinical (rat model of EIU)	[104]
In situ gel	PNMHTI	Indomethacin	Preclinical (rabbit model of BSA-IU)	[105]

AIU: antigen-induced uveitis; AU: autoimmune uveitis; BSA-IU: bovine-serum albumin induced uveitis; DEX: dexamethasone; DPPC: dipalmitoyl phosphatidyl choline; DSP: dexamethasone sodium phosphate; EIU: endotoxin-induced uveitis; FA: fluocinolone acetonide; PC: phosphatidylcholine; PEG-DSPE: PEG2000 distearoyl phosphatidylethanolamine; PLGA: poly(lactic-*co*-glycolic acid); PNMHTI: poly(N-isopropylacrylamide -*co*-methacrylic acid-co-2-hydroxylethyl methacrylate-g-poly(trimethylene carbonate)-indomethacine); PVA: polyvinyl alcohol; SA: sodium arachidonate; TA: triamcinolone acetonide; VIP: vasoactive intestinal peptide.

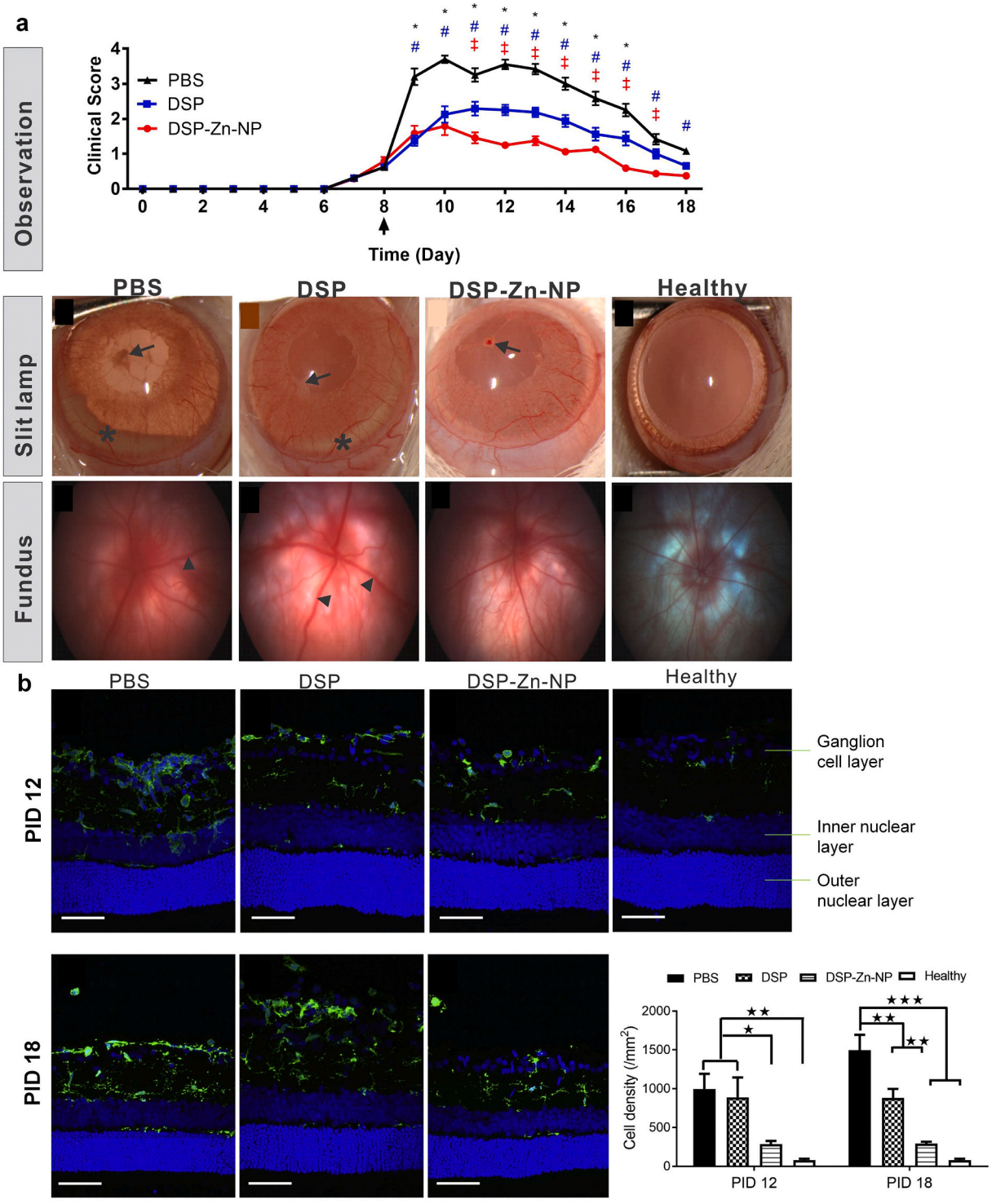

Fig. 5. (a) Disease severity in EAU rats with different treatments. Clinical observation of EAU rats treated with SCT injection of PBS, DSP and DSP-Zn-NP (arrow: day of treatment). Middle: Slit lamp images; Bottom: fundus images at post-immunization day (PID) 12. PBS treated groups and DSP treated groups showing ocular inflammation. DSP-Zn-NP treated group showing decreased ocular inflammation. Healthy animals as control. Pus accumulation in the anterior chamber between cornea and lens (hypopyon, indicated as asterisks), inflammatory cell infiltration (arrows), and retinal blood vessel enlargement (triangles) were more evident and frequent in the groups that received PBS or soluble DSP. Mean ± SEM (n = 12–24 eyes). Two-way ANOVA followed by Tukey's multiple comparison test. * $p < .05$ PBS vs DSP; # $p < .05$ PBS vs DSP-Zn-NP; ‡ $p < .05$ DSP vs DSP-Zn-NP. (b) Microglial density in the retina of EAU rats at PID 12 and PID 18. Green: Iba1; blue: DAPI. The number of Iba1-positive cells in EAU retina was significantly decreased by DSP-Zn-NP treatment at PID 12 and PID 18. Heathy retina was used as the control. Bar graph: Microglial cell density expressed as mean ± SEM (n = 3). Scale bar, 50 μm. *$p < .05$; **$p < .01$; ***$p < .001$, Student's t-test. Mean ± SEM, n = 3 eyes/treatment. Reprinted with permission from [99]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

encapsulated in liposomes for SCT injection and tested in a rabbit model of antigen-induced uveitis [101]. A single SCT injection of liposomal steroids, administered in between two uveitis inductions (3 days after the first induction and 5 days before the second induction), showed sustained anti-inflammatory effects, comparable to frequent eyedrops (4 times a day from the third day after the first induction), and less inflammatory cells in the ciliary body than eyedrops [101]. Liposomal formulations have also been used for delivering immunosuppressants such as tacrolimus [102] and sirolimus [103], and peptide delivery [104] to the eyes. Vasoactive intestinal peptide (VIP) was encapsulated in liposomes (mean diameter 300–600 nm) for intravitreal application and evaluated in a rat model of EIU. Twenty-four hours after intravitreal injection, the animals treated with liposomal formulation showed a 15 times higher concentration of VIP in ocular fluids of the aqueous humor and vitreous body and 2 times reduction in EIU clinical score, as compared to VIP solution in saline [104].

3.2.2.3. In-situ forming gels. In-situ gels containing drug(s) or drug-loaded particles have been explored to increase the residence time in the eye, control and prolong the drug release, and reduce the dosing frequency. The sol-gel transition is controlled by temperature, pH, or ions. Thermoresponsive in situ hydrogel composed of poly(N-isopropylacrylamide-*co*-methacrylic acid-co-2-hydroxylethyl methacrylate-g-poly(trimethylene carbonate)-indomethacine) (PNMHTI) was developed to deliver indomethacin to the vitreous body by intravitreal injection [105]. The PNMHTI solution (15 wt%) gelled at a temperature $> 33\ ^{\circ}C$. The gel contained in a dialysis bag showed a sustained drug release (~85% indomethacin in 2 weeks) based on diffusion and poly (trimethylene carbonate) degradation, whereas free drug was released to ~90% in 24 h. In a rabbit model of bovine-serum albumin induced uveitis, the PNMHTI gel-treated group showed reduced inflammation for 14 days with no infiltration of inflammatory cells in all examined layers of the eye. In contrast, free drug did not maintain the anti-inflammatory effect for 7 days, and the free drug-treated animals exhibited inflammatory cells, including neutrophils, lymphocytes, and leukocytes in the eye when examined at 14 days from the treatment [105].

3.3. Remaining challenges and opportunities

Eyes present unique drug delivery challenges due to its complex anatomical structure. The treatment of anterior uveitis by eye drops requires frequent administration due to rapid clearance. Particles and gel formulations have been used for topical application to improve drug retention [106–111]; however, a caveat is the potential to interfere with the vision or cause irritation. Achieving a therapeutic drug concentration by systemic administration is also difficult due to the blood-retinal barrier in the back of the eye [77–79]. The challenges in topical and systemic administration create opportunities for local drug delivery based on implants or injectable formulations. The marketed implants deliver small molecules, especially corticosteroids, and have been used for posterior segment uveitis. Injectable formulations, such as polymeric nano/microparticles, liposomes, and in-situ gels, have been explored in research for the treatment of intermediate and posterior uveitis but need to be validated clinically. Two critical aspects of injectable implant systems are the dosing frequency and inflammatory responses to the system. Administration of biodegradable systems, two to three times per year, would markedly improve patient compliance and reduce side effects associated with ocular injections or surgical procedures. For reducing the dosing frequency, a slow-degrading polymer or a refillable nondegradable implant may be a reasonable solution. On the other hand, a long-resident implant can cause inflammatory responses or foreign body reaction [112], necessitating surface passivation for the lifetime of the implant.

4. Periodontal diseases

Periodontal diseases (PD) are a group of destructive inflammatory diseases of periodontal tissues, including gingivitis and periodontitis, with undesirable impacts on oral functions and overall quality of life [113]. PD begins with the inflammation of gingival tissues and progresses into pocket formation, which favors the growth of anaerobic microorganisms, leading to bone loss, tooth mobility, and exfoliation [113]. While mechanical approaches are the mainstay of PD therapy, local or systemic antibiotics also make an important adjunctive therapy [113]. Timely management of PD is often challenging because most patients report to the dentist at the very late stage of the inflammation; nevertheless, effective local drug delivery systems can be useful for the therapy of mild to moderate PD [114].

4.1. Local drug delivery systems

Given the complications of systemic antibiotics and the accessibility of target tissues, PD has been one of the most reasonable targets of local drug delivery systems. Traditional local drug delivery systems include medicated irrigation solutions [115,116], drug-eluting fibers [117,118], films/strips [119–121], gels [122–124], and polymeric depots [125] (Fig. 6). Recent approaches also include microparticles [126–128] and nanoparticles [129–131]. Several products have been introduced to the market. Actisite® periodontal fiber (discontinued) was the first drug-eluting filament approved by the FDA in 1994 [132]. Actisite® was made of nondegradable ethylene/vinyl acetate copolymer, releasing 12.7 mg of tetracycline HCl for 10 days [133]. A biodegradable version of tetracycline-releasing fiber, introduced later, is Periodontal Plus AB™ (Advanced Biotech Products, Chennai, India), fibrillar collagen containing 2 mg of tetracycline HCl, with therapeutic effects lasting 3 months [134]. PerioChip® (Perio Products Ltd., Jerusalem, Israel) is an FDA-approved biodegradable gelatin based strip, with a dimension of 5 × 4 × 0.3 mm, releasing chlorhexidine gluconate 2.5 mg for 7 days [135]. Atridox® (Atrix Laboratories, NJ) is an in-situ forming gel, consisting of PLA and NMP, delivering 50 mg doxycycline hyclate for 7–10 days [136] and proving to be as effective as mechanical therapy in reducing clinical signs [136,137]. Arestin™ is a PLGA microsphere system delivering minocycline HCl 1 mg in the periodontal pocket for 2 weeks [138]. Additional local drug delivery systems for PD treatment are thoroughly reviewed in recent articles [114,139].

These local drug delivery systems are also considered for the delivery of anti-inflammatory drugs and their analogs in PD therapy. These

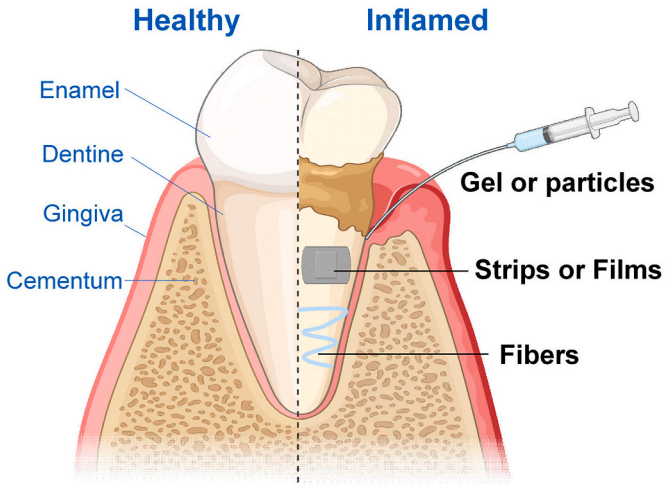

Fig. 6. Healthy and inflamed tooth structure with key anatomical features and local drug delivery system in periodontics: Gels or nano−/microparticles; strips or films; fibers. Created with BioRender.com.

efforts subscribe to the notion that the host's inflammatory response to commensal bacteria is responsible for the pathogenesis of PD [140,141]. The benefits of NSAIDs in PD therapy has been shown in preclinical [142] and clinical [143] studies. Systemic administration of these drugs involves adverse effects; thus, the use of local drug carriers is well justified. An injectable and thermosensitive hydrogel consisting of chitosan, β-sodium glycerophosphate, and gelatin was used as a local carrier of aspirin and erythropoietin for anti-inflammation and periodontium regeneration, respectively [144]. The gel released the two drugs over 8 days in vitro and showed significant therapeutic effects in a rat model of periodontitis [144]. Another recent example demonstrates the local delivery of chlorhexidine and ibuprofen combination for antimicrobial and anti-inflammatory effects [145]. For extending local duration of drugs, a mixture of PLGA and hydroxypropyl methylcellulose (HPMC) dissolved in NMP was used as a carrier, which formed a water-insoluble implant upon intra-pocket administration [145]. The drug release was sustained for two weeks in vitro, and the reduction of inflammation and periodontal wound healing were demonstrated in a mouse model of periodontitis [145].

4.2. Remaining challenges and opportunities

Due to the accessibility, PD was one of the earliest disease targets for local drug delivery. Various carriers have been explored over the years, with a number of products on the market and in the pipeline [114,139]. A critical challenge in local periodontal therapy is maintaining an effective concentration of an active agent for a prolonged period in an environment that is constantly exposed to salivary flow, chewing, and brushing. An effective carrier should conform to the application site making a full contact with the lesions and avoid premature dislodging or degradation in such unaccommodating conditions. A slow-degrading polymer system can help extend the duration but may cause inflammation if empty polymer persists at the periodontal pocket long after exhausting the drug [146]. Another challenge is the limited volume of periodontal pockets, which does not leave a large room for drug delivery systems, thus requiring a high drug loading capacity. These challenges also create unique opportunities for formulation development. By minimizing the carrier content and controlling the solid state of the drug, it may be possible to synchronize drug release and removal of drug carriers, where the carriers help retain the slowly-dissolving drug but do not leave traces once the drug is completely released. Alternatively, with the recent advances in biomaterials, it is conceivable to make the carrier materials serve dual functions – not only control the drug release but also facilitate periodontal healing and bone regeneration.

5. Chronic rhinosinusitis (CRS)

Rhinosinusitis is an inflammatory disorder of sinus mucosa [147,148], affecting 5–15% of the population worldwide [149,150]. Symptoms include nasal obstruction, thick nasal discharge, loss of smell, and facial pain polyposis, mucopurulent discharge, and edema or obstruction of sinuses and nasal cavity [151]. Rhinosinusitis is considered to be chronic when symptoms have persisted longer than 12 weeks [149]. Chronic rhinosinusitis (CRS) may be classified to two types according to the presence of nasal polyps: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) [150,152,153]. The first-line treatment of CRS is corticosteroids, such as dexamethasone, fluticasone and mometasone, and antibiotics for bacterial infection, administered by nasal sprays and/or oral formulations [154–158]. Complex cases of CRS may progress to airway diseases, such as asthma and chronic obstructive pulmonary disease (COPD) [159–162].

5.1. Common therapy

5.1.1. Drug therapies

Systemic (oral) corticosteroids are commonly used in CRS therapy but not always effective [163–165]. For example, systemic corticosteroids are not as effective in CRSwNP with increased neutrophilia as in neutrophil-negative CRSwNPs or CRSsNPs [166], much akin to steroid-resistant asthma [167–169]. Antibiotics (roxithromycin or clarithromycin) are also given orally but have shown a limited efficacy in CRSsNP patients with elevated immunoglobulin E levels [170]. To minimize the side effects of systemic drugs, various topical therapies have been used, such as nasal drops, sprays, nebulized droplets, and nasal irrigation [171]. For example, corticosteroids are delivered locally via nasal spray [172]. However, the effectiveness is variable due to the blockade of the nasal passage [173,174] and poor compliance of patients [175].

5.1.2. Surgery

When CRS is not effectively managed by drug therapies, functional endoscopic sinus surgery (FESS) can be performed to ventilate sinus, clear polyps and improve nasal patency [147,176–178]. More than 250,000 FESS are performed in the United States each year [179]. However, polyposis recurs or persists after surgery [180], with an average of 20% requiring revision surgery within 5 years [179]. Polymeric devices are often used as a post-operative treatment to prevent common complications such as recurrent inflammation, synechiae/adhesion, and stenosis [181,182].

5.2. Local drug delivery systems (Table 3)

Nasal implants have gained increasing interest as not only post-operative treatments but also drug delivery systems for local management of CRS [182,183]. Most representative nasal implants are nasal packing and sinus stents [183] (Fig. 7).

5.2.1. Packing (dressing)

Nasal packing is made of absorbable or nonabsorbable polymers and traditionally used after FESS to control bleeding or secure a space in the middle meatus to reduce scarring complications and prevent post-operative edema and infection [187–189]. Examples include Merocel (Medtronic Inc., Minneapolis, MN, USA), a nonabsorbable polyvinyl alcohol (PVA) sponge [190]; Merogel, an absorbable hyaluronic acid nasal packing [190–192]; and carboxymethyl cellulose, a biodegradable foam [193,194]. Nasal packing has also been used with drugs, off-label. For example, Nasopore (Stryker, Kalamazoo, MI, USA), a polyethylene glycol (PEG)-containing polyurethane foam [195], soaked with triamcinolone (synthetic corticosteroid), has improved postoperative healing in patients up to 6 months, compared to a control packing without the steroid [196]. Another example is Sinu-Foam, a carboxymethyl cellulose foam (Arthrocare, Sunnyvale, CA, USA) [193], loaded with dexamethasone [197]. However, the dexamethasone-eluting Sinu-Foam did not improve postoperative outcomes as compared to a standard post-operative care protocol (saline irrigation and short-term systemic steroids) in a clinical study [197]. A major limitation of drug-eluting packing is the uncontrolled and inconsistent drug release [198].Therefore, drug-eluting devices are developed for sustained release of corticosteroids.

5.2.2. Implants

5.2.2.1. Removable, non-biodegradable implants. An example of non-biodegradable drug-eluting devices is the Relieva Stratus™ MicroFlow Spacer (Acclarent, Menlo Park, CA, USA), originally approved by the FDA for saline delivery [199]. This system consists of a *spacer*, a microporous membrane reservoir surrounding a catheter shaft, and a *deployment guide*, which helps implant the spacer in the ethmoid sinus [200]. In its off-label use, TA was loaded in the microporous reservoir and installed around the frontal sinus to gradually release the drug into the target area for 2–4 weeks [200]. It was initially reported to have

Table 3
Local delivery systems of anti-inflammatory drugs for chronic rhinosinusitis therapy.

System	Carrier (materials)	Drug	Development status	Ref
Nasopore	PEG-containing polyurethane foam	Triamcinolone	Clinical trial (Canada)	[196]
Implant	Ethylene-vinyl acetate	Dexamethasone	Clinic trial (Phase I)	[202]
Implant	Styrene–butadiene–styrene block copolymer	Doxycycline	Repurposed placebo-controlled trial	[204]
Propel Sinus Implant	PLGA, PEG	Mometasone furoate	Marked (Approved by US FDA in 2011)	[212]
Propel Sinus mini	PLGA, PEG	Mometasone furoate	Marked (Approved by US FDA in 2012)	[214]
Sinuva	PLGA, poly(L-lactide-co-ε-caprolactone), PEG	Mometasone furoate	Marked (Approved by US FDA in 2017)	[215]

PLGA: poly(lactic-*co*-glycolic acid); PEG: polyethylene glycol.

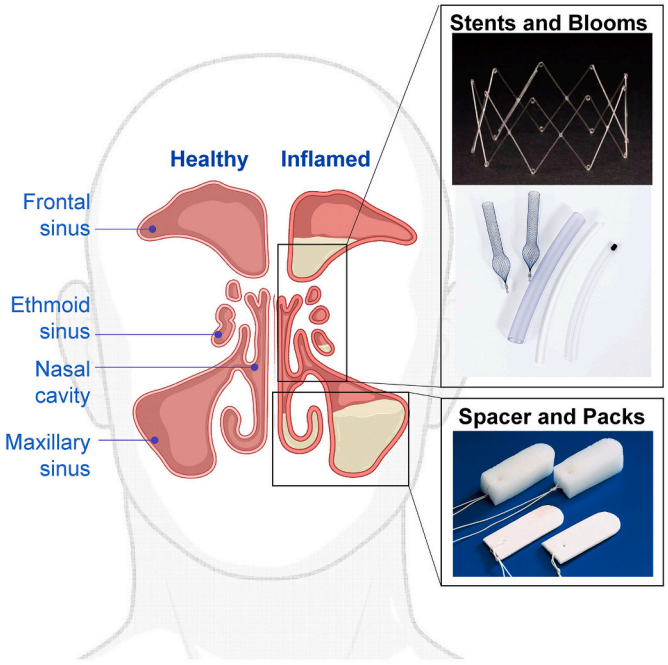

Fig. 7. Healthy and inflamed sinus structure with key anatomical features and local drug delivery system in CRS: Stents and blooms (Reprinted with permission from [184,185]); Spacer and packs (Reprinted with permission from [186]). Diagram created with BioRender.com.

improved outcome scores with good safety [200], but an extended clinical study did not find significant benefits compared to nasal spray [201]. After a legal dispute with the FDA, the device was withdrawn from the US market in 2013 [199]. Another experimental approach used a rolled thin sheet of ethylene-vinyl acetate (EVAC) for sustained delivery of dexamethasone [202,203]. The EVAC sheet was loaded with dexamethasone by solvent casting and inserted into the frontal sinus after surgery [202]. The drug was released over 25 days in vitro, and the preliminary clinical data showed regeneration of nasal mucosa in the area covered by the drug-eluting sheet [202]. The dexamethasone-eluting stent was later compared with a silicone foil control in a rabbit model of sinus injury, showing relatively thin stroma thickness and small granulation tissue during the epithelial regeneration, a favorable outcome for reducing restenosis [203]. For local delivery of doxycycline, serving as an inhibitor of restenosis, a drug-eluting frontal sinus stent was produced by hot melt extrusion of doxycycline (20 wt%) and styrene-based polymer mixture [204]. Doxycycline was released over 14 days in vitro. In a pilot clinical study, the drug-eluting stent placed after FESS helped lower matrix metalloproteinase-9, an enzyme responsible for restenosis, suppress bacterial growth, and improve postoperative healing quality, compared to the drug-free placebo stent [204,205].

5.2.2.2. Biodegradable implants. Nonbiodegradable devices are associated with a high risk of chronic inflammation at the application site [154,206,207]. Therefore, biodegradable drug-eluting devices are considered desirable. Propel Sinus Implant (Intersect ENT, Menlo Park, CA, USA) is a spring-like, self-expanding implant delivering mometasone furoate, the first drug-eluting sinus implant approved by the FDA in 2011 for postoperative CRS treatment [208–211]. Propel consists of PLGA backbone, covered with a layer of PLGA, PEG, and mometasone furoate mixture, which releases the drug over 30 days as the polymer dissolves in a similar time frame [212,213]. The stent is placed in the ethmoid sinus cavity following the FESS for maintaining sinus patency and controlling inflammation [212,213]. Approved in 2012, Propel Sinus mini is a smaller version of Propel Sinus Implant, applicable to patients with smaller nasal cavities or less extensive surgery [214]. The second-generation sinus implant eluting mometasone furoate, called Sinuva (Intersect ENT, Menlo Park, CA, USA), was approved by the FDA in 2017 for the treatment of recurrent nasal polyposis in patients with a history of FESS [215]. Sinuva is a stiff, badminton shuttlecock-like implant, made of PLGA and poly(L-lactide-*co*-ε-caprolactone) coated with a layer of mometasone furoate-releasing PLGA/PEG [215]. It can be placed with local anesthesia by in-office procedures and delivers 4-times more drug for a longer period than Propel (1350 μg vs. 375 μg; 90 days vs. 30 days) [215]. A recent review of clinical studies with the Propel family and Sinuva finds that these steroid-releasing stents have improved postoperative outcomes after FESS and the treatment of recurrent nasal polyps, serving as satisfactory substitutes for systemic steroids [182].

5.3. Remaining challenges and opportunities

Local anti-inflammatory treatment of CRS by polymeric implants has proven effective clinically. The type of polymers, drug loading content, and release modifiers help to control the drug release and duration of the implants. A long-term effectiveness of the second-generation implant remains to be seen. With a limited number of products and the relatively short history of use, it is difficult to generalize the promise and challenges. However, remaining challenges in drug-eluting implants for CRS therapy likely include the cost and convenience of the procedure, customizable fit to accommodate anatomical complexity and interpersonal variability, and diversifying the choice of drugs (steroids, antibiotics, and their combinations). With the recent technical advances, three-dimensional printing may find a unique opportunity in this field [216].

6. Interstitial cystitis (IC)

Interstitial cystitis (IC), also known as painful bladder syndrome, is a chronic disease of unknown etiology, characterized by urinary frequency, urgency, suprapubic pain, and pressure on pelvic area without any infections [217]. There are two types of IC, one with distinctive lesions of inflammation on the bladder wall, called Hunner's ulcers, and the other with bleeding areas on the bladder lining, called glomerulations [218]. It is proposed that IC is caused by damages in the mucin layer of the inner bladder lining, which increase bladder wall permeability (Fig. 8a) and allow solid and toxic substances in the urine to reach the underlying bladder wall and infiltrate into the urothelium [219]. This breach leads to stromal inflammation, lymphocytes and plasma cell

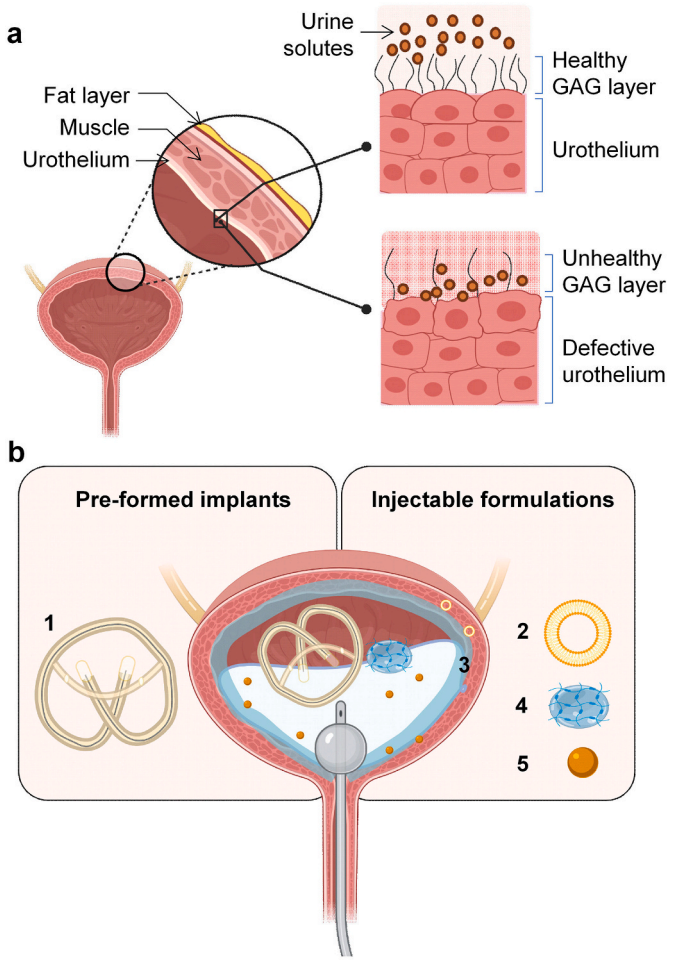

Fig. 8. (a) Schematic representation of bladder anatomy. Normal urothelium: Heathy glycosaminoglycan (GAG) layers prevent urine solutes from reaching urothelium. Defective urothelium: Unhealthy GAG layers allow urine solutes to reach urothelium. (b) Schematic illustration of local intravesical drug delivery systems. 1: LiRIS device; 2: liposomes; 3: in-situ forming hydrogel; 4: floating hydrogel; 5: polymeric microparticles. Created with BioRender.com.

invasion, mastocytosis, and sensitization of nociceptor [220].

6.1. Common therapy

6.1.1. Systemic treatment

There is no specific treatment of IC. Multiple therapeutic modalities, with or without drug, are combined to control bladder pain, improve bladder lining or decrease bladder instability [221]. Oral drugs, such as NSAIDs, antihistamines, muscle relaxants, tricyclic antidepressants are used mostly to improve signs and symptoms associated with IC [222]. Pentosan polysulfate sodium, Elmiron®, approved by the FDA specifically for treating IC, is a highly sulfated polysaccharide similar to heparin sulfate and expected to form a protective layer over the bladder inner lining to reduce inflammation [223]. However, none of these peroral treatments have shown sufficient effects in a broad population of patients. Even with very high doses, systemic drug delivery to the bladder is quite limited due to their poor absorption, first pass metabolism and/or irregular distribution [224,225].

6.1.2. Local treatment

Given the difficulty in systemic therapy, IC is managed locally, by intravesical instillation of a drug through a urethral catheter. Since the drug can be localized in the bladder, the required dose and systemic side effects may be reduced [225]. Traditionally, 50% DMSO (Rimso-50) was regularly used as a maintenance therapy due to its anti-inflammatory and mast cell stabilizing properties [226]. Rimso-50 has also been combined with other drugs such as steroids, local anesthetics, or heparin [227]. Hyaluronic acid solution was also used as an effective treatment [228]. Local instillation of hyaluronic acid solution decreased the production of proinflammatory cytokines by the inflamed urothelium, inhibited the immune cell migration, and enhanced the production of sulfated glycosaminoglycans to decrease the bladder wall permeability [229]. Other treatments, such as capsaicin [230], resiniferatoxin [231,232] or botulinum toxin [233] acting as neuromodulators, have also been used locally in clinical settings.

Direct instillation of a drug solution through an intravesical catheter improves drug exposure to the affected bladder lining. However, bladder treatment is very challenging. The therapeutic effect is diminished by progressive dilution of the instilled drug following the periodical urine voiding [225]. In addition, the low permeability of the urothelium [234] impedes drug penetration even in the disease state, leading to a short drug residence time in the bladder (maximum 2 h) [235] and low local drug bioavailability. Traditional strategies to overcome these problems include emptying the bladder completely before drug instillation, limiting the fluid intake during the treatment [236], and enhancing drug penetration physically (applying a small electric current to the bladder wall) [237] or chemically (with some risks of side effects and worsening the symptoms) [238,239]. Despite all the options, drugs still have to be administered frequently via repeated catheter insertion, with accompanying discomfort and a risk of infection [240,241].

6.2. Local drug delivery systems (Table 4)

Current efforts are focused on drug-eluting devices or formulations that can resist frequent voiding and release a drug in a sustained manner (Fig. 8b).

Table 4
Local delivery systems of anti-inflammatory drugs for interstitial cystitis therapy.

System	Carrier (materials)	Drug	Development status	Ref
Preformed implants (LiRIS®)	Dual-lumen silicon tube	Lidocaine salt	Phase II clinical trial (2018)	[243-246,275]
Liposomes	Sphingomyelin	Tacrolimus	Preclinical (Rat model of chemically induced IC)	[251]
Liposomes	Sphingomyelin	Botulinum toxin	Phase II clinical trial (2017)	[252]
In situ forming hydrogel	PEG-PLGA-PEG	Misoprostol	Preclinical (rat model of cyclophosphamide-induced cystitis)	[269]
TC-3® gel	Poloxamer 407, PEG, and HPMC	Botulinum toxin-A	Clinical trial (Phase I, II, 2016)	[270,271]
Floating gel	Poloxamer 407, $NaHCO_3$, NH_4HCO_3, perfluoropentane	Heparin	Preclinical (Rabbit model of acute bladder injury)	[273]

FITC: Fluorescein isothiocyanate; HPMC: Hydroxy propyl methyl cellulose; $NaHCO_3$: Sodium bicarbonate; NH_4HCO_3: Ammonium bicarbonate; PEG: Polyethylene glycol; PEG-PLGA-PEG: Polyethylene glycol- poly(lactic-*co*-glycolic acid)- Polyethylene glycol.

6.2.1. Non-injectable (pre-formed) implants

Implantable devices can retain drugs up to 14 days in the bladder [242,243]. LiRIS®, TARIS Biomedical, a non-resorbable lidocaine-eluting device, was developed for intravesical delivery of lidocaine for pain management [243,244]. LiRIS® is a dual-lumen silicon tube: one lumen with a micromachined orifice contains lidocaine salt crystals, and the other includes a shape memory wire to help retain the device in the bladder. The device is inserted into the bladder via cystoscopy, and lidocaine salt is dissolved by the infused fluid creating an osmotic pressure and released through the orifice [243]. This device completed Phase I clinical trials, showing favorable safety and long-lasting pain reduction following the removal of device [243]. Phase II trials were completed in 2018 [245,246].

6.2.2. Injectable formulations

Biodegradable polymeric drug delivery systems including micro/nanoparticles or in-situ gelling systems have been widely explored for local treatment of bladder diseases [238]. These systems have focused on extending the residence time beyond the first voiding after instillation by enhancing cellular uptake of a drug, mucoadhesion and/or the exposure time.

6.2.2.1. Liposomes. Intravesical administration of liposomes has been widely investigated in preclinical and clinical studies for local delivery of neurotoxins (pain control) or immunosuppressive agents (anti-inflammatory effects) [247–252]. Liposomes helped to decrease the adverse effects of botulinum toxin [249] and tacrolimus [253], solubilize tacrolimus [251], prevent degradation of botulinum toxin [254], and enhance the drug uptake by urothelium cells compared to drug solution [255,256]. Liposomes are explored as not only a drug carrier but also an active pharmaceutical agent, which can fuse with bladder cells of defective urothelium and form a protective lipid film to enhance urothelial barrier [250,257–260]. Liposomes enhanced the barrier function of the urothelium and attenuated the bladder irritation in a rat model of chemically-induced IC [258,259]. In a clinical study, liposomes (once/week instillation for 4 weeks) were effective in decreasing inflammation and controlling symptoms (pain and urgency) for 24 patients up to 8 weeks, comparable to oral pentosan polysulfate sodium (three times/day for 4 weeks) without showing any adverse effects [260].

6.2.2.2. Polymeric nanoparticles. Chitosan [261] or thiomers [262] are used to make mucoadhesive nanoparticles, which can adhere to the bladder mucosa, survive periodic voiding, thereby prolonging drug exposure to the urothelium [225]. Due to the amine groups, chitosan can adhere to negatively charged mucous glycoproteins of bladder surface through electrostatic or hydrogen bonding [261,263]. Thiolated nanoparticles acquire mucoadhesiveness by interacting with cysteine-rich domain of mucous glycoprotein to form a disulfide linkage [264]. In an in-vitro test of mucoadhesiveness, thiolated silica nanoparticles were detectable on mucosal surface after 7 washing cycles with 10 mL of artificial urine, though not as tenacious as chitosan nanoparticles, whereas PEGylated (with 750 Da PEG) silica nanoparticles were almost gone after 6 washes [265]. To improve mucoadhesion, the two mucoadhesive chemical moieties have been combined: thiolated chitosan nanoparticles were shown to be retained in rat bladder 14 times more than unmodified chitosan NPs [266].

6.2.2.3. In-situ forming hydrogels. Thermoresponsive hydrogels based on natural (chitosan, gellan gum) [225,267] or synthetic polymers (poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide), PEO-PPO-PEO or poloxamers; PEG-PLGA-PEG) [268,269] are used to retain a drug in the bladder wall. A drug is mixed in an aqueous polymer solution at a temperature below the lower critical solution temperature (LCST) and administered by intravesical instillation. At the physiological temperature (>LCST), the polymer solution forms a hydrogel inside the bladder, which releases the loaded drug slowly into the urothelium. Intravesically administered, PEG-PLGA-PEG hydrogel was able to retain small molecules, such as FITC and misoprostol (PGE1 analogue, cytoprotective drug), in the bladder. The misoprostol-loaded hydrogel significantly reduced micturition frequency and ulceration in the epithelium layers, as compared to free misoprostol in a rat model of cyclophosphamide-induced cystitis [269]. TC-3® is a commercially available system for intravesical application, composed of Poloxamer 407, PEG, and HPMC [270], and widely used as a drug carrier in therapy of bladder diseases [271]. TC-3® gel carrying botulinum toxin-A was clinically used for 15 IC patients and reduced the symptoms for 6 weeks without significant adverse effects [271].

Since hydrogels can cause irritation and urinary obstruction during adherence and its detachment, a floating hydrogel was developed as an alternative. Floating gels are produced by incorporating porogens such as $NaHCO_3$ [272], NH_4HCO_3 [273], or perfluoropentane [274], which generate microbubbles. The floating Poloxamer 407 hydrogel maintained a model dye in the bladder through the third voiding, whereas the non-floating counterpart did not survive the first voiding [273]. However, the entrapped microbubbles increased the contact area of the gel and medium, shortened the erosion time [274], and did not allow the gel to retain drug longer than 10 h [273,274].

6.3. Remaining challenges and opportunities

The most important challenge in intravesical drug delivery is maintaining the device or formulations in the bladder through periodic voiding. Nanoparticle-based intravesical therapy is an emerging area, mostly in the bladder cancer arena. Nanoparticles are expected to enhance the penetration of a drug to bladder tissues; however, most nanoparticles so far have shown drug retention no more than a week. Moreover, the safety and efficacy of nanoparticles in intravesical applications remain to be investigated [276]. Liposomes have demonstrated some promise as a drug carrier and an active ingredient in preclinical IC treatment, but the clinical benefit is unclear. Hydrogel is a promising drug carrier for intravesical delivery; however, the challenge is resisting shear forces and bladder contractions without disturbing urine flow and causing bladder obstruction or irritation. TC-3 hydrogel has been clinically tested as a carrier of botulinum toxin in IC therapy with reasonable safety profiles, but the improvement in clinical scores lasted no longer than 6 weeks [271]. In general, physical hydrogels such as poloxamer gels are mechanically weak and have a limited control over the drug release and bladder retention [270,277]. Chemical crosslinking may improve the gel stability, but the toxicity of crosslinker and the difficulty in controlling the crosslinking kinetics may pose a challenge in clinical translation [277]. Alternatively, nano/microparticles may be added to hydrogels to enhance hydrogel strength and extend drug release [278].

7. Intestinal inflammation

Inflammatory Bowel Disease (IBD), comprising two forms - Crohn's Disease (CD) and Ulcerative Colitis (UC), describes a group of intestinal disorders resulting from inappropriate inflammatory response to intestinal microorganisms in genetically sensitive patients [279]. IBD features the infiltration of immune cells into the lamina propria and the overproduction of proinflammatory cytokines due to the intestinal microbiota exposed via the defective intestinal barrier [279,280]. CD-related inflammation is often transmural with a discontinuous pattern in any region of the intestine. UC is typically confined to the mucosa with uninterrupted pattern in the partial or entire region of the colon [279]. IBD causes debilitating symptoms such as diarrhea, abscesses, fistulas, abdominal pain and stenosis, affecting 1.5 million Americans [281] and 3 million Europeans [282]. The occurrence is increasing in industrialized countries, posing a substantial economic burden to the

healthcare system and society [283,284]. Therefore, significant efforts have been made to develop effective medical interventions of IBD.

7.1. Common therapy

The current therapy of IBD aims to maintain remission and avoid disease progression by aminosalicylates, corticosteroids and biological drugs [285]. Local therapy based on enemas, foams, or suppositories has limitations in reaching far enough to cover the affected parts [286]. Moreover, patients suffering from diarrhea and fecal urgency often find it difficult to retain enema solutions or suppositories for an extended period of time, resulting in poor adherence to the regimen [287]. Oral administration is the most common and preferred route due to the convenience and flexibility in formulation design. However, conventional oral formulations, which are systemically absorbed in the upper intestinal region, do not deliver a sufficient amount of drug to the inflamed tissues [286,288]. Therefore, specialized oral formulations have been pursued to avoid systemic absorption and release the drug mostly at the inflamed intestinal tissues [286,288–290]. To deliver the drug to the inflamed target, drug release is controlled by the transit time [291], pH change [292–294], intraluminal pressure [295], and enzymatic activation by gut microbiota [296]. However, the effectiveness of conventional colon-targeted oral drug delivery is challenged due to the variability of gut environments, transit time, colon enzymes and gut microbiota [297]. Some of the drugs, including biologics, are administered via parenteral routes, such as subcutaneous, intramuscular, or intravenous injections at the expense of systemic toxicity and high medical cost [297–299].

7.2. Local drug delivery systems

Given the limitations of traditional local therapy or oral formulations, new drug delivery approaches have focused on targeting the site of inflammation based on electrostatic or mucoadhesive interactions to increase the residence time and contact with the inflamed intestinal tissues.

7.2.1. Pre-formed hydrogels

For local delivery of an anti-inflammatory drug, ascorbyl palmitate, an amphiphilic Generally Recognized As Safe (GRAS) material, was used as a carrier [300]. Ascorbyl palmitate forms a microfiber self-assembly hydrogel with a hydrophobic core, loaded with a hydrophobic drug (dex-21 palmitate, a dexamethasone prodrug), and an anionic surface, which can bind to the inflamed colonic mucosa with cationic buildups [301,302] via electrostatic interactions. The drug-loaded hydrogel was formed by cooling a heated mixture of ascorbyl palmitate and dex-21 palmitate and administered as a rectal enema. Dexamethasone was released by enzymes secreted from bacteria and inflammatory cells, which hydrolyzed the prodrug linker and the hydrogel, over 4–5 days in vitro [300]. The drug-loaded hydrogel adhered to the inflamed mucosa in mice with colitis and showed local anti-inflammatory effects reducing systemic drug exposure [300]. Ascorbyl palmitate hydrogel has also been considered for local delivery of biologics [303]. Fluorescently-labeled dextran (4 kDa) was used as a model drug, and 60% was released in 5 h in vitro [303]. Alternatively, a genipin-crosslinked chitosan hydrogel was explored for local delivery of sulfasalazine, a prodrug of 5-aminosalicylic acid [304]. Chitosan was modified with catechol to enhance the mucoadhesiveness, and the drug was simply mixed into the genipin-crosslinked chitosan gel. The drug-loaded hydrogel was injected to mice with experimental UC by rectal injection, achieving therapeutic effects comparable to oral sulfasalazine with reduced systemic exposure [304]. These studies show the potential to minimize systemic drug absorption using hydrogels as a local drug carrier; however, the improvement in anti-inflammatory effects was marginal as compared to free drug counterparts, leaving a room for improvement in duration of the gel and drug release control.

7.2.2. In-situ forming hydrogels

In-situ forming hydrogels have several advantages over pre-formed ones, including less invasive application and the adaptability to variable surfaces. Body temperature and intestinal pH have been used to trigger the gel formation. Collagen type 1, which undergoes sol-to-gel transition at physiological pH and temperature by forming fibril structure, was used as a carrier of mesalamine (5-aminosalicylic acid) [305]. The collagen hydrogel released mesalamine in 8 h in vitro. A cold suspension of mesalamine in collagen was applied to mice by intrarectal injection to form a gel in distal colon. The drug-loaded collagen gel showed superior clinical and histological scores to those of free mesalamine suspension in a mouse model of experimental UC [305]. Another thermosensitive hydrogel considered for IBD therapy is a chitosan-glycerophosphate complex, which forms a gel at 37 °C in 15 min and sustains the release of drugs with a broad range of molecular weight [306].

7.3. Remaining challenges and opportunities

Drug-loaded hydrogels, pre-formed or in-situ forming, which can be locally administered as enemas, have the potential to overcome traditional challenges of oral formulations or enema solutions (Fig. 9a). They can conform to the contours of intestinal tissues, ensuring adhesion to the surface and long-term residence and drug release. Biologics may be loaded in the hydrogels in mild conditions, beneficial to maintaining the stability. Hydrogels based on extracellular matrix components such as collagen or hyaluronic acid may further contribute to the repair of inflamed tissues [305]. Nevertheless, the application of hydrogels to IBD local therapy is surprisingly rare in the literature. One of the potential reasons is the difficulty in long-term control of drug release kinetics, which currently lasts no more than a day. A short-lasting hydrogel system will find it difficult to motivate patients to adhere to the regimen. Therefore, a hydrogel system with robust retention and long-term release kinetics is highly desirable. In this regard, it will be worth considering hybrid systems based on bioadhesive hydrogels and drug-eluting particles, which can prolong the retention and drug release, respectively.

Alternatively, polymeric intestinal stents may be repurposed for long-term local drug delivery to the inflamed intestines (Fig. 9a). Endoscopic procedures such as balloon/bougie dilation and stent implantation are performed for the treatment of bowel obstruction (Fig. 9b). Metal stents have been used since early 1990s [307], and biodegradable intestinal stents have also become available recently [308]. A biodegradable stent made of polydioxanone (SX-ELLA BD biodegradable stent, ELLA-CS, Hradec Králové, Czech Republic) for the treatment of small and large intestinal stenoses was first reported in 2009 [309]. Stent integrity and radial force were maintained for 6–8 weeks after the implantation, and pH-dependent stent degradation occurred in 11–12 weeks. Subsequent cases validated the technical success of biodegradable stents in intestinal insertion [310–312] (Fig. 9c). Drug-eluting biodegradable stents have mostly been used for treating biliary stenosis or cancer-induced bowel obstruction [313–315]. Given that 25–35% of UC patients and 70–90% of CD patients will eventually need surgery [316,317], the drug-eluting polymeric stents may be applicable to IBD patients for a long-term local delivery of anti-inflammatory drugs.

8. Post-surgical inflammation

Open surgery causes significant injuries to patients, accompanied by alterations in neuroendocrine, metabolic and immune functions. Pain, inflammation and infection are common complications of surgery; thus, pharmacotherapy is a critical part of postoperative care [319,320]. NSAIDs and corticosteroids are used to manage post-surgical inflammation. However, systemic medication may delay wound healing, cause metabolic disturbance, and inhibit bone healing [320,321], rather

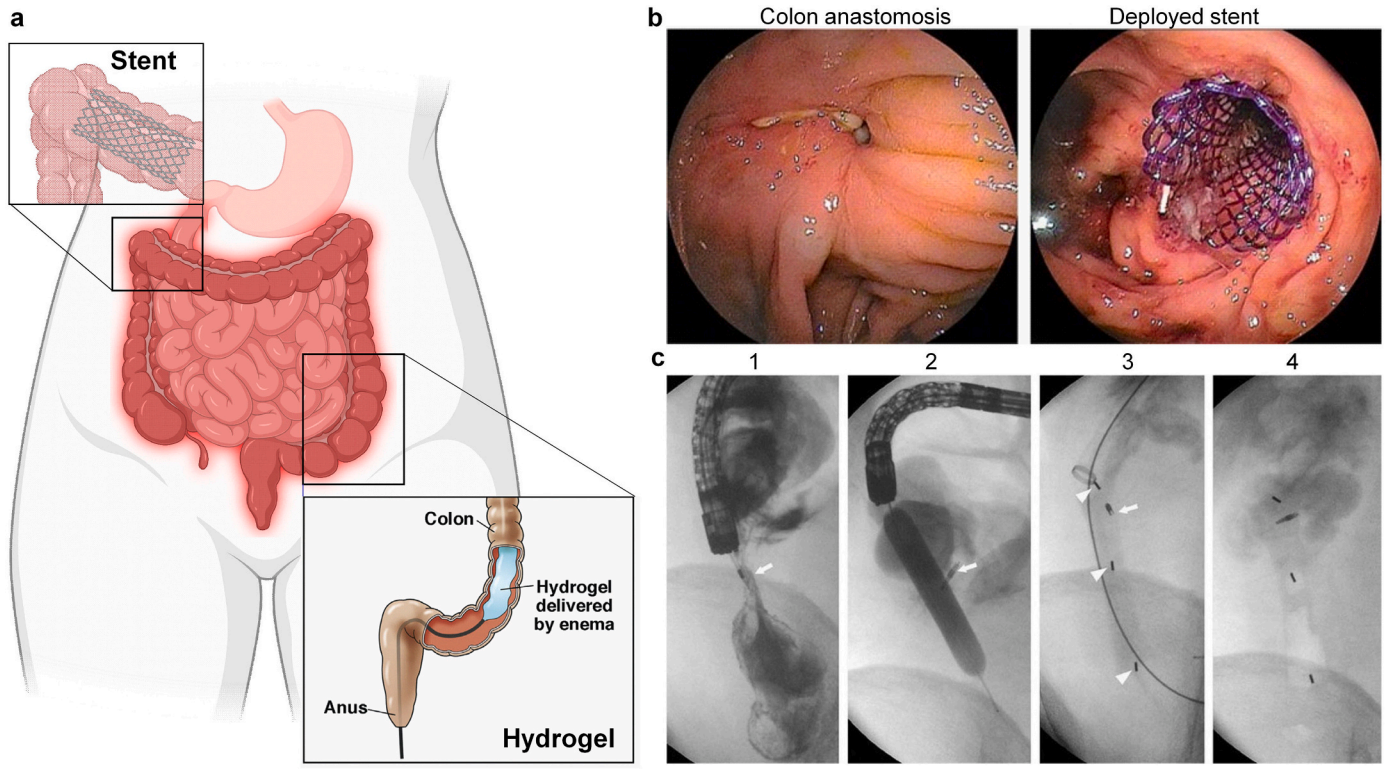

Fig. 9. (a) Local drug delivery systems in IBD: stent; hydrogel (reprinted with permission from [318]. Created with BioRender.com. (b) Endoscopic views of a typical stenosis before and after biodegradable stent insertion. Left: Anileo-ascending colon anastomosis with a tight stenosis and ulcer. Right: A deployed biodegradable stent in the stenotic anastomosis immediately after its insertion. (c) Fluoroscopic images before and after biodegradable stent insertion from the same patient as shown in (b): (1) Stenosis (arrow) of the ileo-ascending colon anastomosis. (2) Balloon dilation of the stenotic area. The distal margin of the anastomosis is marked with a metallic clip (arrow). (3) Biodegradable stent, with three radio-opaque markers (arrowheads), in situ immediately after its deployment from the introducer. The distal margin of the stenosis is marked with a metallic clip (arrow). (4) Appearance of the biodegradable stent at the end of the procedure. Reprinted with permission from [308].

counteracting post-surgical prognosis. Therefore, when the surgical injury is contained and/or occurs in the site with poor blood supply, local drug delivery systems are desirable. For example, Surodex®, a rod-shaped PLGA/HPMC implant delivering dexamethasone at 60 μg for 7–10 days, is indicated for the treatment of inflammation after cataract surgery [322,323]. Other products introduced in the uveitis application may be repurposed for post-operative care of the eyes.

Pharmacotherapy following orthopedic surgeries needs to address not only the pain, infection, and inflammation but also bone regeneration, which takes weeks to months [324]. Therefore, the efforts to develop skeletal drug delivery systems are often combined with bone implants [30,325,326]. For example, poly(D,L-lactide-*co*-lactide) implant dip-coated with eugenol (anti-inflammatory, analgesic, antibacterial agent) and dexamethasone was developed to release the drugs for 8 weeks in vitro [327]. Polyetheretherketone (PEEK) implant coated with liposomal dexamethasone and minocycline via polydopamine was introduced to prevent infection and inflammation [328]. The liposome-modified PEEK implant showed bacteriostatic, anti-inflammatory, and osteogenic properties (additional function of dexamethasone) in a dog model after 8 weeks of femur implantation [328]. One of the challenges in skeletal drug delivery is that the bone implants satisfying the mechanical requirements are not necessarily conducive to drug loading (and vice versa). This conflict may be addressed by chemical or mechanical pretreatment of the surface, which however can compromise bioinertness of the implant.

9. Inflammatory lung diseases

Asthma, COPD, cystic fibrosis (CF), and non-CF bronchiectasis are representative inflammatory lung diseases, accompanied by airway obstructions, emphysema, and tissue remodeling. According to the World Health Organization report, ~235 million people are currently suffering from asthma, and > 3 million deaths occur each year due to COPD worldwide [329].

9.1. Commonly used therapy

Although the etiology and phenotypic features vary, these lung diseases use common treatment strategies, which aim to alleviate airway inflammation and restore the normal airways [330]. Asthma and COPD are primarily managed by inhaled corticosteroids and bronchodilators [331]. While oral and IV corticosteroids may be used in acute and severe conditions [332], drugs targeting lung inflammation are commonly administered by inhalation (Table 5) because they go directly to the lower airways, require low doses, and reduce systemic side effects compared to oral drugs [330]. Despite the prevailing usage, it remains challenging to control the local effect of inhaled drugs. Small molecule drugs can be quickly absorbed to the circulation, which limits their residence time in the lung. Hydrophobic drugs may be retained in the lung relatively long; however, they are subject to the mucocilliary clearance [333].

9.2. Local drug delivery systems

Nanoparticles and microparticles based on polymers and lipids have been investigated to improve drug localization and prolong the drug release in the lung [345]. Particle formulations for inhalation, mostly in preclinical stage, have been reviewed in the recent literature [346]. The main challenge in development of inhalable particles is to control the particle size to obtain the optimal aerodynamic properties, thereby

Table 5
Local delivery systems of anti-inflammatory drugs for therapy of inflammatory lung diseases.

Disease	Product	System	Drug	Development status	Ref.
Asthma	Arnuity Ellipta	DPI	FF	Marketed (approved by US FDA in 2014)	[334]
	Qvar®	MDI	BD	Marketed (approved by US FDA in 2000)	[335]
	Pulmicort Respules®	Jet nebulizer	Budesonide	Marketed (approved by US FDA in 2000)	[336]
	Pulmicort Flexhaler™	DPI	Budesonide	Marketed (approved by US FDA in 2006)	[337]
	Asmanex® HFA	MDI	MF	Marketed (approved by US FDA in 2014)	[338]
	Alvesco®	MDI	Ciclesonide	Marketed (approved by US FDA in 2006)	[339]
	Symbicort	MDI	Budesonide and FFD	Marketed (approved by US FDA in 2006)	[340]
	Dulera®	MDI	MF and FFD	Marketed (approved by US FDA in 2010)	[341]
COPD	Breo Ellipta	DPI	FF and vilanterol	Marketed (approved by US FDA in 2013)	[342]
	Trelegy Ellipta	DPI	FF, umeclidinium, and vilanterol	Marketed (approved by US FDA in 2017)	[343]
	Advair Diskus	DPI	FP and SX	Marketed (approved by US FDA in 2000)	[344]

BD: beclomethasone dipropionate; DPI: Dry powder inhaler; FF: fluticasone furoate; FFD: formoterol fumarate dihydrate; FP: fluticasone propionate; MDI: metered-dose inhaler; MF: mometasone furoate; SX: salmeterol xinafoate.

ensuring their deposition in the desired region of the lung. Aerosol devices and the patient's skills to use the devices also play a critical role in optimal drug delivery to the lung.

9.3. New opportunities

Severe lung inflammation may progress to central airway obstruction [347,348]. Airway stents are used to restore airway patency [349]. Airway stents are made of silicone or metallic materials and require removal when the condition is under control or the stent is no longer effective [350]. Critical complications of stenting are the risk of tissue ingrowth into the stent, which hampers its removal, and the difficulty of maintaining the position in place [350]. Biodegradable stents with customizable shapes and dimensions are attractive alternatives [351,352]. Furthermore, drug-eluting airway stents have been pursued to improve local delivery of active agents that prevent airway stenosis and treat malignant airway obstructions [353–355]. For example, a biodegradable drug-eluting PCL stent, coated with PLGA and cisplatin, was implanted in rabbit trachea to achieve local drug release for >5 weeks [353]. Anti-inflammatory drugs may be delivered via airway stents likewise to control pathological inflammation and tissue responses to the implanted stents.

10. Local delivery of anti-inflammatory biologics

Proinflammatory cytokines are key mediators of inflammatory processes and thus make important therapeutic targets [1]. The activities of proinflammatory cytokines are regulated by biological agents that neutralize the cytokines, block their receptors, or counteract the functions. Examples include anti-TNF antibodies, anti-IL-1 antibodies, anti-IL-6 receptor antibodies, recombinant TNF decoy receptor, recombinant IL-1 receptor antagonist (IL-1Ra), and antibodies targeting TH17 [356], indicated for RA, IBD, CRS, and other autoimmune diseases [357,358]. Like small molecule drugs, anti-inflammatory biologic therapies also bear the risks of diverse systemic side effects [359–361]. Polymeric delivery systems have been explored for local delivery of anti-inflammatory biologics, such as porous polydimethylsiloxane block [362], fibrin-genipin sealant [363], or chitosan-based thermogel [306] for anti-TNF-α antibody and hyaluronan/heparin-based hydrogel for IL10 delivery [364]. A challenge specific to biologics delivery is the potential effect of carriers on the structure of the drug, which can negatively affect its activity and release control. Hydrophobic polymers can be detrimental to the protein conformation due to the disruption of the hydrophobic effect; thus, hydrogel carriers are widely pursued for the delivery of biologics [70].

11. Conclusion

Polymeric drug delivery systems have been used for local drug delivery, achieving commercial and clinical success in several cases, but challenges remain. An issue common to most applications discussed in this review is the control of drug release kinetics and the duration of delivery devices. Polymeric solid implants are excellent platforms for long-term drug delivery; however, they may not be compatible with the organs and tissues mechanically and/or biologically. Injectable formulations based on particles or hydrogels are therefore preferred options for locations with complex contours, such as joints, sinus, or colon; however, the drug release control from these carriers is typically not long enough. Moreover, empty carriers remaining after exhausting anti-inflammatory drugs may become a new cause of inflammation; thus, they need to be physically removed or degraded synchronously with the drug release. These challenges may be overcome by personalized design of drug carriers by three-dimensional printing, combination of different carriers with complementary features, and adaptation of existing medical devices with drug-eluting compartments. It is also worthwhile to investigate drug release modifiers, which can be included along with a drug and help control the drug release kinetics without depending on the polymer degradation kinetics. Another important opportunity is the development of new biofunctional, immunomodulatory biomaterials, which can facilitate the healing process while serving as a drug carrier.

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