A review of the clinical applications of drug delivery systems for the treatment of ocular anterior segment inflammation

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ABSTRACT

Ocular anterior segment inflammation is a medical problem that is seen in cases of cataract surgery and non-infectious anterior uveitis. Inadequately treated anterior segment inflammation can lead to sight-threatening conditions such as corneal oedema, glaucoma and cystoid macular oedema. The mainstay of treatment for anterior segment inflammation is topical steroid eye-drops. However, several drawbacks limit the critical value of this treatment, including low bioavailability, poor patient compliance, relatively difficult administration manner and risk of blurring of vision and ocular irritation. A drug delivery system (DDS) that can provide increased bioavailability and sustained delivery while being specifically targeted towards inflamed ocular tissue can potentially replace daily eye-drops as the gold standard for management of anterior segment inflammation. The various DDS for anti-inflammatory drugs for the treatment of anterior segment inflammation are listed and summarised in this review, with a focus on commercially available products and those in clinical trials. Dextenza, INVELTYS, Dexycu and Bromsite are examples of DDS that have enjoyed success in clinical trials leading to FDA approval. Nanoparticles and ocular iontophoresis form the next wave of DDS that have the potential to replace topical steroids eye-drops as the treatment of choice for anterior segment inflammation. With the current relentless pace of ophthalmic drug delivery research, the pursuit of a new standard of treatment that eliminates the problems of low bioavailability and patient compliance may soon be realised.

INTRODUCTION

The most common forms of ocular inflammation in the front of the eye are post cataract surgery inflammation and non-infectious uveitis. Anterior segment inflammation is an inevitable consequence of cataract surgery which, if left unchecked, can lead to corneal oedema, raised intraocular pressure and cystoid macular oedema. These complications are no longer acceptable in an era where advances in surgical techniques and innovation have raised patients' expectations for perfect surgical outcomes from cataract surgery.[1 2] Similarly, non-infectious uveitis, if inadequately treated, can lead to sight-threatening complications like cataract, glaucoma and macular oedema in up to 25% of patients.[3] Corticosteroid eye-drops are the first-choice treatment for post-cataract surgery anterior segment inflammation,[2] but several limitations exist for topical eye-drop administration including poor bioavailability (less than 5%), compliance with treatment being challenging and patients often have decreased vision immediately after surgery, impairing their ability to instil eye-drops accurately.[4 5]

A recent study of postoperative cataract patients demonstrated that over 90% of patients exhibited at least one of the following behaviours: inability to instil eye-drop accurately into the eye, instilling an incorrect amount of drops, contaminating the bottle tip and failing to realise hand hygiene before instillation.[6] In addition, premature tapering or cessation of steroid eye-drops can lead to a rebound in ocular inflammation, leading to eye pain, redness and blurred vision.[7] The untargeted delivery of steroids to uninflamed ocular tissue may also result in steroid-related side effects such as raised intraocular pressure and glaucoma.[7] The ideal solution would be a drug delivery system (DDS) that can replace daily topical eye-drops by providing increased bioavailability and sustained delivery to ocular tissue while being specifically targeted towards the inflamed tissue.

It is clear from recent reviews on ocular drug delivery in the published literature that many early DDS never progressed beyond early-stage preclinical development, illustrating the daunting challenges these systems face en route to clinical development. In this review, we present the applications of DDSs that are commercially available and those currently in late-stage clinical trials for the treatment of anterior segment ocular inflammation with a focus on steroids and NSAIDs, drugs that are currently used as topical eye-drops for the treatment of ocular inflammation.

NANOPARTICLES

Liposomes

Liposomes are vesicles consisting of lipid bilayers, ranging in size from 0.01 μm to 10 μm, composed primarily of phospholipids and cholesterol surrounding an aqueous internal compartment. Liposomes have several characteristics of an ideal ocular DDS. First, they are completely biocompatible and biodegradable. Second, the lipophilic exterior of liposomes allows greater penetration through ocular barriers. Third, their amphipathic nature provides flexibility for the incorporation of both hydrophobic and hydrophilic drug molecules. Fourth, liposomal encapsulation decreases drug elimination, thereby increasing ocular bioavailability. Fifth, surface modification of liposomes can further enhance solubility

and facilitate their passage through the various ocular compartments.[8–14] Our group studied the effectiveness of liposomal steroids, administered as a single injection in the subconjunctival space, for the treatment of experimental uveitis in a rabbit model of anterior uveitis.[15] After induction of uveitis (Day 0), rabbits were allocated to one of five treatment groups (pred forte 1% eye-drops 4 times a day, subconjunctival free triamcinolone acetonide, subconjunctival liposomal prednisolone phosphate, subconjunctival liposomal triamcinolone acetonide, controls) and received treatment based on allocation on Day 3. Rabbits that received a single injection of subconjunctival liposomal steroids had significantly lower inflammatory scores (threefold to sixfold greater reduction in inflammatory score) than untreated rabbits on Day 4 and Day 8 after induction of uveitis, and twofold greater reduction in inflammatory score than rabbits given steroid eye-drops four times a day for 14 days on Day 8 (p=0.03). The subconjunctival liposomal steroid groups continued to have greater suppression of inflammation than untreated rabbits after a repeat induction of uveitis on Day 8. Subconjunctival injection of free steroid achieved an anti-inflammatory effect that was similar to liposomal steroids on Day 8 (p=0.02 compared with controls). However, this anti-inflammatory effect of free steroid could not be sustained beyond Day 8, with subconjunctival liposomal steroid achieving 1.3–1.5 fold greater reduction in inflammatory score than subconjunctival free steroid on Day 11, 3 days after the repeat induction, although this difference was not statistically significant. Immunohistochemical analyses showed that liposomes accumulated in the iris and ciliary body (the primary inflamed sites in anterior uveitis) were also found within macrophages and persisted in the eye for at least 1 month. In a Phase I/II non-comparative trial for the treatment of post cataract surgery ocular inflammation, a single subconjunctival injection of 0.1 ml of liposomal prednisolone phosphate was performed at the end of cataract surgery in five eyes of five patients. The proportion of patients with AC cell grading of 0 was 0%, 80%, 80% and 100% at day 1, week 1, month 1 and month 2 after cataract surgery, respectively. None of the subjects required additional steroid treatment and no ocular or non-ocular adverse events were observed.[16]

Polymeric nanoparticles

Polymeric nanoparticles are a diverse class of colloidal polymers with diameters ranging from 1 nm to 1000 nm. Polymeric nanoparticles have great flexibility and advantages as DDSs, including (1) the ability to adhere to the precorneal ocular surface by forming gels, thereby increasing drug residence time,[17] (2) sustained and controlled drug release, (3) the ability to carry both hydrophilic and hydrophobic drugs, (4) biodegradability, and (5) modifiable chemical and physical properties for the optimisation of drug delivery to ocular target sites.[18]

KPI-121 1.0% (INVELTYS)

INVELTYS (KPI-121 1.0%, Kala Pharmaceuticals) is a nanosuspension of loteprednol etabonate (LE) delivered by a proprietary nanoparticle-based formulation referred to as mucus-penetrating particles (MPP). MPPs are typically generated by rendering the surfaces of particles non-mucoadhesive for example, by coating with low molecular weight polyethylene glycol.[19] In ex vivo preclinical studies, MPP was found to have the following attributes that favours drug delivery to the eye: even distribution of drug particles on mucosal surfaces (cervicovaginal mucus) enhanced diffusion coefficient of drug particles through mucus compared to uncoated particles and prevents drug particles from becoming entrapped and transported away from its intended target by the mucus layer.[20] In KPI-121, LE is coated with a non-covalently adsorbed surface-altering agent, Pluronic.RTM.F127, which comprises a triblock copolymer, poly(ethylene oxide)-(poly(propylene oxide))-(poly(ethylene oxide)). A preclinical pharmacokinetics study of LE-MPP showed a threefold higher C_{max} in the cornea, iris/ciliary body, aqueous humour and retina compared to LE, demonstrating the increased ocular bioavailability conferred by MPPs.[21] These properties allow KPI-121 to efficiently penetrate the mucin layer of the ocular tear film and enhance drug release to the underlying tissue.

In two multicentred, randomised controlled clinical trials (NCT02163824 and NCT02793817), 386 subjects were treated with KPI-121 1% and 325 were treated with placebo following cataract surgery. Each group was dosed twice a day for 2 weeks. Primary outcome measures were complete resolution of ocular inflammation and complete resolution of subject-rated ocular pain at Days 8 and 15 with no rescue medication before Day 15. KPI-121 1% was shown to be significantly better than placebo for both primary outcome measures. Adverse events were reported more frequently with placebo than KPI-121.[22]

RX-10045

Micelles (10–100 nm) consist of self-assembling, amphiphilic molecules or block copolymers and have a hydrophobic core and a hydrophilic shell. They can solubilise hydrophobic drugs by encapsulation within the hydrophobic core and it has been claimed that their small size and surface hydrophilicity allow efficient penetration of ocular barriers.[23] RX-10045 nanomicellar solution (Auven Therapeutics) is an aqueous micellar dispersion of an isopropyl ester prodrug of resolvin E1. Resolvins are a group of molecules derived from omega-3 fatty acid that can exert anti-inflammatory effects in very low dose ranges in vitro and in vivo. Preclinical testing of topical RX-10045 in new Zealand albino rabbits demonstrated appreciable drug concentration in the anterior segment ocular tissue and its active metabolite, RX-10008 was also observed in the retina/choroid. The formulation was well tolerated with no detectable ocular tissue damage.[24] A Phase II randomised clinical trial was performed (NCT02329743) to assess the safety and efficacy of two concentrations of RX-10045 (0.05% and 0.1%) compared to placebo for the treatment of post cataract surgery pain and ocular inflammation. The trial recruited 256 participants with a 1:1:1 randomisation. Both formulations of RX-10045 were not significantly better than the placebo group in achieving the primary endpoint of clearing anterior inflammation at Day 8 post cataract surgery (22.8% in both treatment groups compared to 16.7% in the placebo group). Similarly, RX-10045 was not better than placebo in controlling post-operative pain: the proportion of patients with no ocular pain on Day 3 post-surgery was 31.6%, 26.6% and 42.3% in the 0.05%, 0.1% and control groups, respectively.[25] It was postulated that the presence of efflux transporters, expressed on the ocular surface, such as p-glycoprotein (p-gp), multidrug resistance-associated protein (MRP) and breast cancer-resistant protein (BCRP), reduced the ocular penetration of RX-10045. In addition, RX-10045 was found to be a strong inhibitor of organic cationic transporter-1 (OCT-1), further limiting its ocular bioavailability.[26]

On the other hand, OTX-101 0.09%, a novel, nanomicellar, clear aqueous solution of ciclosporin developed for the treatment of dry eye disease (Cequa; Sun Pharmaceutical Industries, Cranbury, NJ) has obtained FDA approval after a successful Phase III study that enrolled 744 patients. A significantly larger proportion of eyes in the treatment group achieved the primary endpoint of an increase of 10 mm or more in the Schirmer test score, an objective measurement of the severity of dry eye,

compared to the control group at Day 84 (16.6% vs 9.2%, p<0.001).[27] Of particular interest was that a preclinical pharmacokinetics study showed that a single topical instillation of OTX-101 0.05% resulted in extensive distribution of ciclosporin into ocular tissues. The greatest drug concentration was in the conjunctiva, tears and sclera, but significantly higher concentrations were also found in the iris/ciliary body and aqueous humour with OTX-101 compared to application of free ciclosporin, suggesting enhanced intraocular penetration with the nanomicellar formulation.[28]

Bromfenac durasite

DuraSite technology (Sun Pharma, Alameda, CA, USA) represents a mucoadhesive ocular DDS consisting of a synthetic polymer of cross-linked polyacrylic acid and polycarbophil, and contains small drug molecules in an aqueous matrix. DuraSite increases ocular residence time of the drug formulation, delivered in the form of an eye-drop, by increasing viscosity and bioadhesion to the ocular surface. Both clinical and nonclinical studies have shown DuraSite DDS to be safe and non-toxic. The Durasite technology was used to deliver Bromfenac, a potent topical non-steroidal anti-inflammatory drug (BromSite), for the treatment of postoperative inflammation and ocular pain. A multicentre, randomised, double-masked, vehicle-controlled, parallel-group clinical trial (NCT01576952) was conducted to evaluate the ocular safety, tolerability and efficacy of topical administration of bromfenac 0.075% in Durasite (BromSite) compared to vehicle when dosed twice a day beginning 1 day prior to cataract surgery, the day of surgery and then continuing for 14 days after surgery.

At Day 15, a greater proportion of subjects in the BromSite group as compared to the vehicle group had complete resolution of inflammation in terms of anterior chamber cells (57.1% vs 18.8%, respectively; p<0.00). More BromSite-treated subjects had no pain compared with the vehicle-treated subjects (p<0.001). The trial demonstrated the safety and efficacy of BromSite in reducing inflammation and pain after cataract surgery, leading to FDA approval in April 2016.[29]

DexaSite

DexaSite is a formulation of dexamethasone in DuraSite 2, which uses the same polycarbophil polymer in DuraSite with the addition of a second polymer, Chitosan, to achieve greater viscosity when applied on the eye compared with DuraSite. DuraSite 2 was shown in a preclinical study to achieve the highest mean concentration of ketorolac tromethamine in the aqueous humour when applied topically to rabbit eyes, compared to DuraSite or free ketorolac.[30] In a randomised controlled Phase III clinical trial (NCT03192137) (n=260), a significantly larger proportion of study participants who received treatment with DexaSite applied two times per day for 16 days after cataract surgery had absence of anterior chamber inflammation at Day 15 compared to those who received vehicle (47.9% vs 22.2%, p<0.001).[31]

OCS-01

OCS-01 (Dexamethasone Cylcodextrin Nanoparticle Ophthalmic Suspension 1.5% mg/ml) is an eye-drop formulation of dexamethasone with cyclodextrin designed to treat inflammation and pain following cataract surgery. Cyclodextrins are water-soluble oligosaccharides which form complexes with the lipophilic, water-insoluble dexamethasone, thereby increasing the solubility of dexamethasone without affecting its lipophilicity. The complexation allows dexamethasone to retain its ability to permeate lipophilic ocular barriers, that is, the cornea. The hydrophilic cyclodextrin molecules are unable to penetrate the cornea and are subsequently washed out of the ocular surface by tears. In the recently announced topline results from a randomised, vehicle controlled Phase II trial (NCT04130802) in 153 patients following cataract surgery, OCS-01 applied once a day achieved a higher percentage of eyes with absence of anterior chamber inflammation (51% vs 19.6%, p<0.001) and a higher percentage of eyes with no pain (72.5% vs 54.9%, p=0.005) compared to vehicle at Day 15.[32 33]

INTRAOCULAR IMPLANTS

Surodex

Surodex (Oculex Pharmaceuticals Inc., Sunnyvale, California) is an intraocular implant composed of a biodegradable lactic acid/glycolic acid copolymer and loaded with 60 µg of dexamethasone. This biodegradeable matrix, measuring 1.0×0.5 mm in size, provides sustained release of dexamethasone for up to 10 days after implantation into the anterior chamber of the eye. In the case of eye-drops, however, drug levels decline to non-therapeutic levels within hours of 0.1% dexamethasone eye-drop instillation.[34]

A randomised clinical trial was performed on 60 eyes undergoing extracapsular cataract extraction with intraocular lens implantation.[35] In this trial, Surodex was inserted in the anterior chamber via a surgical incision at the conclusion of surgery in the intervention group while the control group received dexamethasone 0.1% eye-drops four times a day for 4 weeks. The study found significant reduction in anterior chamber flare in the Surodex group from Day 4 post operatively. At 3 months post surgery, flare reduction to preoperative levels were seen in the Surodex group while the control eye-drop group still had raised flare levels. Therapeutic failure, defined as a need for augmentation of steroids, was seen in five (17.9%) eyes in the control group and one (3.1%) in the Surodex group. Lastly, the safety profile of Surodex was acceptable with no eyes developing glaucoma and no significant endothelial cell loss at 1 year post surgery. Oculex Pharmaceuticals was later acquired by Allergan in 2003. Phase III trials were never conducted and Surodex never made it to the commercial market. This was largely attributed to the challenge of obtaining Medicare reimbursement for Surodex at that time. Since then, medicare reimbursement for newly FDA-approved medical devices and drugs has been facilitated by the conferment of transitional pass-through status, which boosts patient access to these innovative therapies.

Dexycu

The Dexycu (Icon Bioscience, Inc. Sunnyvale, CA,) treatment is applied as a single intracameral injection at the end of cataract surgery using Icon's Verisome (Icon Bioscience, Inc.) drug delivery technology to dispense a biodegradable extended-release DDS formulation of dexamethasone. The Verisome proprietary DDS technology allows the formulation of drugs into a slightly viscous gel which, when injected into the eye, coalesces to form a spherule that releases the drug over time. In early 2018, Dexycu was the first long-acting intracameral product to be approved by the FDA in the US for treating inflammation following cataract surgery.

A randomised, double masked multicentre trial (NCT02547623) recruited 394 patients randomised 1:2:2 into 3 arms: (1) 5 µl injections of placebo, (2) 5 µl injections of 342 µg Dexycu and (3) 5 µl injections of 517 µg Dexcyu into the anterior chamber at the end of cataract surgery. Patients were followed for 90 days after surgery. At post-operative Day 8, resolution of anterior chamber cells was achieved in 25.0%, 63.1% and 66.0% of eyes in the placebo, 342 µg and 517 µg treatment groups, respectively (p<0.001). Complete resolution of clinical signs of anterior

segment inflammation (Anterior chamber cell + flare) at post-operative Day 8 was achieved in 33.8%, 63.1% and 67.3% of eyes receiving placebo, 342 µg and 517 µg Dexycu, respectively ($p<0.001$). The safety profile of both Dexycu doses was similar to placebo and no serious ocular adverse events were reported for the whole 90-days observation period.[36 37]

Dextenza

Dextenza (Ocular Therapeutix, Inc., Bedford, Massachusetts) is the first FDA-approved intracanalicular insert to deliver dexamethasone for the treatment of postoperative ocular pain with one treatment for up to 30 days. The insert contains 0.4 mg of dexamethasone.[38] The implant's proximity to the ocular surface allows maintenance of sufficient drug concentration, increasing bioavailability from less than 5% (eye-drops) to more than 70%. The safety and efficacy of Dextenza were assessed in a multicentred randomised double-masked placebo-controlled Phase III trial (NCT02089113) in which 218 adult patients undergoing cataract surgery received Dextenza implant and 222 received placebo. At Day 14, significantly more patients had resolution of anterior chamber cells in the Dextenza arm compared with placebo (52.3% vs 31.1%; $p<0.0001$). Rescue therapy was required in twice as many in the placebo arm than in the treatment arm at Day 14. Dextenza was well tolerated, with a safety profile similar to that of placebo.[39]

Nepafenac punctal plug delivery system[40]

The Nepafenac Punctal Plug Delivery System (N-PPDS) is a L-shaped, non biodegradeable, medical grade silicone punctal plug with a drug eluting core that contains nepafenac, a non-steroidal anti-inflammatory drug. The punctal plug is designed to be inserted into the lower punctum, releasing nepafenac consistently over a month, after which the plug is removed from the punctum. A Phase II, multi-centre, randomised, parallel-arm, double-masked, placebo-controlled study (NCT03496467) was conducted to study the safety and efficacy of N-PPDS. Fifty patients had an N-PPDS inserted in the lower punctum of their scheduled surgical eye, 1–2 days prior to surgery, while 25 study patients had a placebo punctal plug inserted. These plugs were retained for a period of 2 weeks following cataract surgery. The study has completed recruitment but results are yet to be released.[40]

DSP-Visulex

DSP-Visulex is a reloadable dexamethasone sodium phosphate (DSP) DDS that combines a highly concentrated DSP solution with an ocular drug applicator (Visulex). The applicator consists of a medical grade silicone polymer shell shaped like a contact lens and an annular white sponge, fabricated with a proprietary sponge material, along the rim of the applicator. DSP is injected into a drug loader where the applicator is docked, facilitating the permeation of the drug into the sponge. The applicator is then placed carefully over the centre of the eye such that only the sclera is in contact with the sponge.[41] After a single application, the concentration of DSP in most of the ocular tissues, including cornea, sclera, conjunctiva, retina-choroid and anterior chamber, was significantly higher than 1 mg/g which was deemed to be the minimum effective concentration of DSP. The highest concentration of DSP in ocular tissues was within the cornea, followed by the sclera, conjunctiva, retina-choroid, anterior chamber, lens and was lowest in the vitreous. DSP concentration, except in the lens and vitreous, correlated well with both increasing the concentration of DSP loaded in the Visulex system, and the duration of treatment.[42] A randomised Phase I/II clinical trial was performed to assess the safety and efficacy of a 5 min application of DSP Visulex (8% and 15% intervention arms, given twice in the first week and then weekly thereafter) compared to daily prednisolone acetate 1% for non-infectious anterior uveitis (NCT02309385). At Day 29 of treatment, 90%, 88% and 77% of patients had resolution of anterior chamber cells in the 8% DSP-Visulex, the 15% and prednisolone acetate eye-drop groups, respectively. More adverse events were seen in the 15% group, which included headache, eye pain, corneal abrasion, conjunctivitis and keratitis, all of which resolved. IOP elevation was not observed after Day 3 in the DSP-Visulex groups.[43]

OCULAR IONTOPHORESIS

Ocular iontophoresis enhances ocular drug delivery by employing a mild electric charge to induce three processes: (1) electroporation, that is, an alteration of ocular tissue structure and pore formation induced by an electric field, (2) electrophoresis and (3) electro-osmosis, that is, a convective solvent flow through an applied electric potential. This technique can be utilised for anterior segment drug delivery through the transcorneal route.

EGP-437 using the eyeGate II drug delivery system (EGDS)

EGP-437 using the EyeGate II Drug Delivery System (EGDS, Eyegate Pharmaceuticals, Inc.) applies ocular iontophoresis to deliver dexamethasone phosphate for the treatment of post cataract surgery inflammation and non-infectious uveitis. In this system, an applicator is placed at the limbus and a generator connected to an electrode is attached to the patient's forehead. The generator creates an electric field inside the applicator, where the drug is loaded, and an opposite charge on the electrode. The difference in charge facilitates the movement of drug molecules through the conjunctiva and sclera. The need for specialised equipment as well as accurate placement of the applicator on the eye makes it less practical for home use; 80–90% of patients experienced at least one ocular event, with ocular hyperaemia and keratitis being the most common, although the incidence of hyperaemia appeared to decrease with repeated applications of iontophoresis.[44] A Phase II clinical trial was conducted evaluating the safety and efficacy of ocular iontophoretic delivery of dexamethasone phosphate compared to ocular iontophoresis with a placebo in patients planned for cataract surgery (NCT03180255). Treatments were administered on the day prior to cataract surgery. On Day 7, the percentages of patients with anterior chamber cell count of zero in the active and placebo groups were 13% versus 9.1%, respectively, a result that was not clinically significant.[45] With regard to non-infectious anterior uveitis, a Phase III trial showed that EGP-437 (NCT02517619) was indeed clinically efficacious, but it did not achieve non-inferiority compared to prednisolone acetate eye-drops as measured by the proportion of subjects with an anterior chamber cell count of zero at Day 14.[46 47] An imbalance in disease severity, with a greater proportion of subjects in the EGP-437 group having anterior chamber cell scores of 3–4 compared to prednisolone acetate eye-drops (54% vs 41%), and the possible need for an additional iontophoretic treatment was suggested as a possible reason for the failure to achieve the study endpoint.[48]

CONCLUSION AND PERSPECTIVES

A summary of the drug delivery technologies for anterior segment inflammation discussed above is given in table 1. Despite its shortcomings, topical steroid eye-drops are still the most widely

Table 1 A summary of drug delivery technologies for anterior segment inflammation

Study/Drug name	Drug molecule	Delivery mechanism	Indication	Route of administration	Status
Wong *et al*[15]	Prednisolone phosphate and triamcinolone acetonide	PEGylated liposomes	Uveitis, post cataract surgery pain and inflammation	Subconjunctival	Phase 1
INVELTYS[22]	Loteprednol etabonate	Mucus penetrating particles	Postoperative inflammation and pain following ocular surgery	Topical	FDA approved
RX10045[24 25]	Resolvin E1	Nanomicelles	Post cataract surgery ocular inflammation and pain	Topical	Failed phase II
Bromfenac Durasite[49]	Bromfenac	Mucoadhesive DDS (synthetic polymer of cross-linked polyacrylic acid)	Post cataract surgery inflammation and pain	Topical	FDA approved
DexaSite[31]	Dexamethasone	Mucoadhesive DDS (DuraSite 2), a synthetic polymer of cross-linked polyacrylic acid and chitosan	Post cataract surgery inflammation and pain	Topical	Phase III
OCS-01	Dexamethasone	Cyclodextrins	Post cataract surgery inflammation and pain	Topical	Phase II
Surodex[50]	Dexamethasone	Lactic acid/glycolic acid copolymer	Post cataract surgery inflammation and pain	Intracameral	Phase II
Dexycu[37]	Dexamethasone	Verisome drug delivery technology	Post cataract surgery inflammation and pain	Intracameral	FDA approved
Dextenza[39]	Dexamethasone	Intracanicular implant	Post cataract surgery inflammation and pain	Intracanicular	FDA approved
Nepafenac Punctal Plug Delivery System[40]	Nepafenac	Punctal plug	Post cataract surgery inflammation and pain	Punctal implant	Phase II
DSP-Visulex[43]	Dexamethasone	Ocular drug applicator	Post cataract surgery inflammation and pain	Conjunctival	Phase I/II
EGP-437[45–47]	Dexamethasone	Ocular iontophoresis	Uveitis, Post cataract surgery inflammation and pain	Topical	Phase III (uveitis) Phase II (post cataract surgery)

used treatment for anterior chamber inflammation for the past century. This is set to change in the near future, driven by advances in healthcare delivery, nanomedicine and patient expectations. Corticosteroids and other anti-inflammatory drugs, delivered by the ideal DDS, should provide targeted and sustained drug delivery to inflamed tissue while avoiding off-target effects, particularly in the trabecular meshwork which often leads to raised intraocular pressure and glaucoma. The DDS itself should be well tolerated both in terms of the way delivery is performed (non-invasive) and in terms of ocular adverse events. There is great demand, not just for post ocular surgery inflammation, but also for post corneal transplant patients that require long-term steroid use. These patients in particular will benefit from an improvement in the therapeutic index of ocular steroids. DDS have the potential for sustained delivery of the lowest dose of steroid non-invasively and without reliance on patient compliance. Pioneering products paving the future for further improvement of anti-inflammatory ocular DDS therapy are Dextenza, Dexycu, INVELTYS and Bromsite which have achieved FDA approval. However, these products are still not widely accepted by patients and the ophthalmic community. Possible reasons for the low adoption rate include, for example, Bromsite and INVELTYS still require self-administration on a two times per day dosing regimen, Dexycu administration requires an invasive intraocular injection into the anterior chamber, and intracanalicular implants may cause trauma to the tear duct and could be dislodged prematurely. Nanoparticles and ocular iontophoresis form the next wave of DDS that have the potential to replace topical steroids eyedrops as the treatment of choice for anterior segment inflammation. These systems have the advantages of non-invasive (and thus safer) routes of administration by the physician rather than the patient, thereby eliminating patient compliance issues. However, none of the currently available DDS have adequately addressed the issue of off-target effects, specifically the elevation of intraocular pressure by steroids in certain patients. A DDS that can deliver the anti-inflammatory drug directly to inflamed tissue with minimal release of free drug elsewhere is a much needed solution to this problem. With the current relentless pace of ophthalmic drug delivery research, the pursuit of a new standard of treatment may soon be realised.

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