Recent advances in intraocular sustained-release drug delivery devices

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Topical eye-drop administration and intravitreal injections are the current standard for ocular drug delivery. However, patient adherence to the drug regimen and insufficient administration frequency are well-documented challenges to this field. In this review, we describe recent advances in intraocular implants designed to deliver therapeutics for months to years, to obviate the issues of patient adherence. We highlight recent advances in monolithic ocular implants in the literature, the commercialization pipeline, and approved for the market. We also describe design considerations based on material selection, active pharmaceutical ingredient, and implantation site.

Introduction

Older populations have increased incidences of ocular disease [1,2] and, as life expectancy increases, the burden of managing and treating ocular disease will become more prevalent [3]. Many ocular diseases have striking impacts on vision that significantly impact quality of life, eventually making everyday tasks difficult, if not impossible.

Therapeutic treatment of ocular disease falls into two primary modalities: topical drops or intravitreal injections. Topical drops have been a mainstay for decades. Specific to asymptomatic disease, such as glaucoma, compliance is a major challenge to efficacious therapy: a review across five studies showed an average of only 67% of patients with glaucoma sustained their therapeutic schedule after 1 year [4].

Intraocular injections were the first effective back-of-the-eye therapy, most notably with the approval of ranibizumab (Lucentis®, Genentech, Inc.) and the subsequent approval of aflibercept (EYLEA®, Regeneron Pharmaceuticals) for treatment of wet age-related macular degeneration (wAMD). However, recent retrospective studies observed that real-world use and injection frequency did not replicate trial outcomes, largely because of insufficient administration frequency [5].

The first commercial examples of implantable intraocular devices were surgically implanted reservoir-based devices introduced via pars plana incision and sutured to the sclera for long-term residence within the eye. These devices (e.g., Vitrasert® for cytomegalovirus or Retisert® for non-infectious uveitis) release a small-molecule therapeutic over the course of months to years [6,7]. The subsequent generation of devices aimed to reduce the procedural invasiveness by introducing the device with a custom injector. Both degradable (e.g., Ozurdex®) and nondegradable (e.g., Iluvien®) versions became commercially available, in which the rod-shaped implants are deployed by piston or fluid [8,9]. To date, commercial intraocular devices have relied on small-molecule therapeutics, leaving a significant opportunity in highly efficacious protein-based delivery technologies.

Despite some success in device development, novel treatments that could supplant topical drops and intravitreal injection remain poised to advance the treatment of ocular disease. External devices provide a means to maintain the minimally invasive advantage of topical drops, while providing a sustained-release solution [10]. Alternatively, particle technologies are suitable for deployment via the familiar intravitreal injection, while providing an extended duration of therapeutic activity [11,12]. Here, we focus on a final class of sustained-delivery devices that are monolithic and implanted intraocularly, which can be introduced via custom injector or by surgical intervention. We discuss recent advances

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in implantable intraocular devices, covering design considerations based on drug type, and means of delivering devices and final implantation site, as well as commercial and pipeline device development.

Material selection

The material selection for long-acting, sustained-release implants is crucial for tuning the release kinetics, degradation rate, and biocompatibility of the implant. Both biodegradable and nonbiodegradable materials have been used for ocular drug delivery implants reported in literature and currently on the market. Here, we discuss the commonly used materials for ocular drug delivery, including their tunability, biocompatibility, and degradation kinetics.

Nonbiodegradable polymers

Nonbiodegradable implants are commonly used for the first generation of ocular drug delivery implants. This includes Retisert® and Vitrasert®, which comprise drug tablets coated with nonbiodegradable polymers. Commonly used nondegradable materials include polyvinyl alcohol (PVA), ethylene-vinyl acetate (EVA), and silicones. In Retisert®, the drug tablet is coated with a nonpermeable silicone featuring an orifice to allow drug release. Between the silicone orifice and the tablet, there is a permeable PVA membrane to control the rate of diffusion through the orifice. Vitrasert® uses a similar concept of diffusion-limited drug release through the orifice of a nonpermeable coating. Vitrasert® comprises a tablet first coated with PVA, followed by a nonpermeable, discontinuous EVA coating, which is then covered by a second coating of PVA. Other nonbiodegradable implants in the market, such as Iluvien® (Alimera Sciences, Inc), comprise a polyimide tube loaded with a drug-PVA matrix, and capped on one end with a silicone adhesive. Another nondegradable material is crosslinked poly(ethylene glycol) (PEG). For example, PEGDA, a photocrosslinkable PEG hydrogel, has been reported to release triamcinolone acetonide and ovalbumin, a model protein [13].

Nonbiodegradable implants have the advantage of achieving very long-term release and have demonstrated good biocompatibility [14]. However, upon drug depletion, the reservoir material either requires surgical removal or remains at the implantation site. In recent years, focus has shifted toward using biodegradable polymers for ocular implants.

Biodegradable polymers

Biodegradable or erodible polymers have been increasingly used in implants both in academic research and on the market. They have the advantage of eroding after drugs are released to avoid the need for surgical removal. Their degradation kinetics can also be tuned by material composition.

Commonly used biodegradable polymers include poly(lactic-*co*-glycolic acid) (PLGA) and poly(caprolactones) (PCL). The most widely used in both literature and commercially is PLGA. It can be engineered to achieve sustained release for several small molecules [15–17]. Commercially, PLGA is co-extruded with dexamethasone in Ozurdex® (Allergan) to achieve 6 months of drug delivery.

A limitation of PLGA is the formation of inflammatory degradation products. PLGA degrades into lactic acid and glycolic acid, which create a highly acidic environment [18] and cause local inflammatory reactions [19]. In one study, PLGA scaffolds were implanted subcutaneously into rats to observe host-tissue responses after 2 weeks. The authors observed significant host cell and macrophage accumulation near the PLGA scaffold, indicative of a severe inflammatory reaction [19]. These inflammatory effects are alleviated in implants that release anti-inflammatory steroids, such as the case of Ozurdex® (described later). However, when releasing other drugs, the inflammatory responses can cause problematic reactions.

PCL is another biodegradable polymer that has been demonstrated in ocular drug delivery implants in the literature. Similar to PLGA, PCL can be engineered to have highly tunable release kinetics and is easily fabricated into thin films by draw or spin-casting polymer solutions. Studies of PCL in the eye have not elicited significant immunological responses [20–22]. PCL degradation kinetics are slower than that of PLGA but can be tuned by adjusting the polymer molecular weight [23,24].

Although PEG itself is not degradable, it can be conjugated to, and crosslinked by, biodegradable linkers to form an absorbable material. *In situ*-forming PEG-based implants are under development by Ocular Therapeutix to deliver tyrosine kinase inhibitors (TKI) (NCT03630315). Polyorthoesters (POEs) and polyanhydrides are other materials used, although they have not yet been actively used commercially or in the literature in recent years.

Design considerations based on drug type

Sustained delivery of small molecules

Most of the ophthalmic drug delivery technologies are currently targeted towards the sustained delivery of small-molecule therapeutics over the course of several months to years. Small molecules are conventionally delivered via eye drops and can require several administrations per day. A sustained-release implant would obviate the need for daily patient administration in favor of device implantation every few months or years. Drugs can also be co-extruded within polymer matrices to achieve long-term release with desired release kinetics. Release kinetics can be dissolution [20] or solubility limited [21] and depend on drug and polymer properties, including partition coefficient, LogP, molecular weight, and drug solubility [25]. Both zero-order and first-order release profiles have been demonstrated [25–27], and release rate can be tuned by surface area and film thickness. The release duration is dependent on the amount of drug within the reservoir and the polymeric membrane degradation kinetics.

Within the past 2 years, PLGA has been used for the sustained release of small molecules including etoposide [16], lupeol [15], and clindamycin hydrochloride [17] (Table 1), with a release duration on the order of months. Given that PLGA undergoes both bulk degradation and surface degradation [23], the release kinetics of long-acting implants can change during the course of polymer degradation. PLGA can also be formulated as a suspension with the drug of interest and a biocompatible solvent (e.g., *N*-methyl-2-pyrrolidone) that can be injected and formed *in situ*. *In situ*-forming PLGA implants have been used to release triamcinolone acetonide [28] and dexamethasone [29], achieving 42 days and 1 week of sustained release, respectively, *in vitro*. In *in situ*-forming implants, polymer concentration can be tuned to achieve desired release kinetics. PCL thin-film ocular drug delivery devices have demonstrated *in vivo* release of rapamycin for 16 weeks [26] and omidenapag isopropyl (DE-117) for 24 weeks [21]. Given that

TABLE 1

Recent published developments in ocular implants for long-acting drug delivery

Material	Drug	Implantation site	Release profile	Indication	Phase	Refs
Small molecule delivery devices						
PLGA-NMP (*in situ*-forming PLGA)	Triamcinolone acetonide	N/A	42 days release	NA	*In vitro*	[28]
PLGA-NMP (*in situ*-forming PLGA)	Dexamethasone	N/A	Over ~1 week	AMD	*In vitro*	[29]
PLGA	Clindamycin hydrochloride	Intravitreal	6 weeks	Infection	*In vivo*	[17]
PLGA	Etoposide	Intravitreal	50 days	Retinoblastoma	*In vivo*	[16]
PLGA scleral plug	Curcumin	Intravitreal	60 days	Posterior ocular diseases	*In vivo*	[42]
PLGA	Lupeol		7 days	Angiogenesis	*In vivo*	[15]
PCL	DE-117	Intracameral	24 weeks	Glaucoma	*In vivo*	[30]
PEGDA	Triamcinolone acetonide	N/A	21–28 days	AMD	*In vitro*	[13]
Protein delivery devices						
PDMS/PVA	Infliximab	Subconjunctival	3 months	Alkali Burns	*In vivo*	[35]
Hyaluronic acid, embedded with chitosan nanoparticles	Bevacizumab	N/A	60 days	Choroidal neovascularization	*In vitro*	[34]

PCL degradation is much slower, drug release kinetics can be decoupled from polymer degradation kinetics.

Sustained delivery of proteins and biologics

Biopharmaceuticals, including proteins and peptides, have shown great promise as novel therapeutics in the treatment of ocular diseases. Unlike small molecules, biologics have high potency and activity, low nonspecific binding, as well as lower toxicity and drug–drug interactions. With the approval of anti-VEGF therapeutics, such ranibizumab (Lucentis®), the market for ocular biopharmaceuticals is rapidly growing. However, patient compliance to monthly intravitreal injections has been a major hurdle with these treatments. In a recent study, 39.8% of patients with AMD showed inadequate compliance to Lucentis® treatment and follow-up [30]. Anti-VEGF therapies requiring less frequent injections are available (e.g., aflibercept; Regeneron Pharmaceuticals), or under development (abicipar; Allergan). Nevertheless, there is an urgent need for the development of suitable ocular delivery systems for biologics to alleviate patient compliance concerns. Biologics offer many delivery challenges because of their high molecular weight, hydrophilicity, degradation, short half-life, and poor permeability across epithelial barriers [31,32]. Therefore, novel delivery systems are needed to enable the delivery of biologics to ocular tissues.

Much of the focus in protein drug delivery has been on gel-based formulations and reservoir systems. Gel-based formulations comprise liquid or injectable semi-solids with protein suspended in organic solvent that solidify upon injection [32]. The rate and duration of release is influenced by the gelling rate as well as implant porosity, polymer molecular weight, and solvent. Badiee *et al.* used chitosan nanoparticles embedded in a matrix of hyaluronic acid and zinc sulfate to provide long-term sustained release of bevacizumab [33]. They showed that this system enhanced sustained release compared with bevacizumab particles. Another study used a porous polydimethylsiloxane/polyvinyl alcohol composite drug delivery system to deliver infliximab for 3 months in rabbits after an ocular burn [34].

For membrane-based reservoir systems, nonporous membranes used for delivering small molecules do not allow for the diffusion of larger proteins. Macroporous membranes fabricated by mixing porogens with a polymer would allow diffusion of proteins, but cannot achieve zero-order release. To achieve sustained, zero-order release of proteins, nanoporous PCL thin films were engineered with pore sizes on the order of the diffusing molecule size [35]. This nanoporous PCL thin film device was capable of delivering ranibizumab for 12 weeks *in vivo* without exhausting the initial drug payload [26]. Furthering thin film devices, a methodology was developed for the design of such devices that utilized a PEG formulation to control protein solubility [36]. The corresponding devices can be engineered to achieve desired protein stability and release rate. The devices studied released aflibercept over the course of 11 weeks *in vitro*, and devices were well tolerated in African green monkeys.

The Genentech/ForSight Vision 4 Port Delivery System (PDS) is another reservoir device for delivering ranibizumab. The device is a scleral plug comprising a reservoir, a semipermeable, nonbiodegradable membrane, and a port used to reload drug into the reservoir. Initial drug loading typically limits the total drug-release duration and device lifetime and the refillable port was developed to address this challenge. The implant has been loaded with ranibizumab for the treatment of wAMD, and the device is designed to last at least 6 months between refills [37].

With long-acting delivery systems for biologics, understanding the stability of the protein or biologic of interest at physiological temperature is essential. Proteins can undergo structural changes or degradation that lead to loss of biological activity over time. Biologics in long-acting implants can be engineered or formulated to be stable for the required release duration. In some cases, using solubility-limiting excipients can improve protein stability, such as PEG in an aflibercept-eluting thin-film device [36]. However, because of the unique nature of each biologic, particularly antibodies, there is no single formulation that can effectively improve stability for all biologics [38]. Therefore, a thorough understanding of the possible degradation mechanisms for a particular biologic is necessary for their success in sustained-delivery systems.

Despite many advances, no ophthalmic biodegradable implant has been approved to date for biopharmaceutical drugs. With the large and growing numbers of protein and large molecule therapeutics under clinical trials, there remains an urgent need to develop new methods to deliver these highly potent biologics in a controlled and long-term manner.

Cell-based implants

Cell encapsulation is a novel way to deliver large compounds to tissues for an extended period of time. Neurotech Pharmaceuticals used a unique customized NTC-200 cell line derived from normal human retinal pigment epithelial cells that are engineered to have low metabolic activity, increasing likelihood of their survival in the vitreous. The cells can also be genetically transfected to secrete therapeutics and growth factors. The cells are incorporated into a polymeric device that is surgically implanted in the vitreous, and the ocular implant enables continuous production and release of therapeutic proteins to the eye for over 2 years. The device isolates the cells from the vitreous while simultaneously allowing influx of nutrients. Their investigational treatment, NT-501 ECT, provided intravitreal sustained release of soluble ciliary neurotrophic factor (CNTF) receptor. The device was well tolerated but achieved limited efficacy in treating retinitis pigmentosa (RP) [39,40] and geographic atrophy (GA) [41]. Neurotech is now applying NT-501 in clinical studies for the treatment of glaucoma (NCT02862938) and macular telangiectasia (MacTel) (NCT01949324). For glaucoma, Neurotech has completed Phase I trials, and Ohase II studies are underway. Phase I trials of MacTel showed good tolerability and safety for the device [42].

Delivery and implantation site considerations

Implantation site selection depends on the desired pharmacokinetics, biocompatibility, and clinical considerations. An implantation site closer to the target tissue can achieve a high concentration of drug in the target tissue. Drugs can diffuse from the anterior chamber to the posterior chamber by convection and normal movements, although the kinetics depend on the chemistry of the drug [43]. However, drug distribution between the anterior to the posterior segment can be hindered by aqueous flow, clearance to the blood, and the physical barrier of the iris, lens, and ciliary body. Pharmacokinetics of drug transport to various tissues in the eye must be tested for a particular drug and implantation location.

Common methods of implantation are intravitreal injection, subconjunctival delivery [44], and intracameral implantation via incision [27,44]. The most attractive route for delivery to the vitreous is via injection, because it duplicates the standard-of-care for existing anti-VEGF therapeutics. Implantable devices can be injected at the pars plana, which is located posterior to the lens and anterior to the retina. At this location in the vitreous, implant position can be controlled to be out of the visual axis. However, intravitreal implants can risk retinal detachment and endophthalmitis [45] as well as vitreous hemorrhage, cystoid macular edema, and formation of tenacious epiretinal membranes [46]. Placement is also crucial for intracameral implants because of the risk of blocking vision. Development of cataracts because of contact with the lens, or damage to the corneal epithelium [27] are also potential risks. Subconjunctival implantation has also been explored for Ozurdex®, and the implants were well tolerated in a 2-month study in patients with open-angle glaucoma [47].

The injection needle also affects clinical outcomes. Standard intravitreal injections of Lucentis® or EYLEA® use 30-gauge needles, but drug delivery devices require larger gauge needles, such as 22- and 25-gauge for Ozurdex® and Iluvien®, respectively. Larger needles do not necessarily lead to more pain. A study showed that patients receiving 22-gauge injections had similar pain scores to those receiving 29-gauge injections [48]. The shape and size of the needle can also be optimized to improve clinical outcomes. An Ozurdex® study showed that optimizing needle shape can reduce required penetration force, improve the wound architecture, and increase ease of injection [49].

Implantable ocular drug delivery devices on the market or in the commercialization pipeline

The number of companies developing ocular drug delivery implants has skyrocketed over the past decade. Products in various stages of development are being investigated for indications such as glaucoma, macular degeneration, diabetic macular edema (DME), and uveitis.

Recently approved implants

Vitrasert® and Retisert® have been widely reviewed since their approvals in 1996 and 2004. Since then, Ozurdex®, Iluvien®, Yutiq®, and DEXYCU® have been approved for sustained-release intraocular drug delivery (Table 2).

Iluvien® (Alimera) is a nonerodible implant that is injected intravitreally and achieves sustained release of FA for over 3 years. It was approved in 2014 for the treatment of DME in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant increase in intraocular pressure (IOP). Similarly, Yutiq® (EyePoint Pharmaceuticals, Watertown,

TABLE 2

FDA-approved intraocular drug delivery implants on the market

Implant	Approval year	Material	Delivery method	Drug	Indication	Release duration	Clinical Trial/NDA number
Vitrasert®	1996	PVA, EVA	Intravitreal	Ganciclovir	AIDS-related cytomegalovirus retinitis	5–8 months	020569
Retisert®	2004	PVA, silicone	Intravitreal	Fluocinolone acetonide	Noninfectious uveitis	2.5 years	021737
Ozurdex®	2009	PLGA	Intravitreal	Dexamethasone	DME, posterior uveitis	6 months	022315
Iluvien®	2014	Polyimide	Intravitreal	Fluocinolone acetonide	DME	3 years	201923
Yutiq®	2018	Polyimide	Intravitreal	Fluocinolone acetonide	Chronic noninfectious uveitis	3 years	210331
DEXYCU®	2018	Acetyl triethyl citrate	Posterior chamber	Dexamethasone	Postoperative inflammation	2–3 weeks	208912

TABLE 3

Investigational intraocular drug delivery implants in clinical trials

Implant	Phase	Material	Delivery method	Drug	Indication	Release duration	Clinical Trial/NDA number
OTX-TKI/IVT	Phase I	Hydrogel	Intravitreal	TKIs; anti- VEGF	AMD	12 months/4–6 months	NCT03630315
PDS	Phase II	Undisclosed polymer	Intravitreal	Ranibizumab	Wet AMD	~6 months before first refill	NCT02510794, NCT03677934
Brimo PS DDS®	Phase I, II	PLGA	Intravitreal	Brimonidine tartrate	Pars plana vitrectomy, AMD, retinal detachment, geographic atrophy MD	3–6 months[a]	NCT01080209, NCT00972374

[a] As disclosed by company website and press releases.

MA), is a polyimide nonbioerodible intravitreal micro-insert releasing FA over 36 months. It received US Food and Drug Administration (FDA) approval in October 2018 for treatment of chronic noninfectious uveitis affecting the posterior segment of the eye.

Biodegradable implants offer some advantages over reservoir systems. In addition to the ability to be tuned to change release rates based on drug properties, they eliminate the need for extraction, thereby decreasing the risk associated with surgery.

The first sustained-release biodegradable steroid implant, Ozurdex®, was developed by Allergan and approved in 2009 for the treatment of macular edema following vein occlusion and noninfectious posterior uveitis. The intravitreal implant comprises PLGA co-extruded with dexamethasone. It is placed in the vitreous through the pars plana by needle injection and releases peak doses of dexamethasone for 2 months followed by a lower dose for an additional 4 months. Since its approval, many studies have investigated the efficacy of Ozurdex® for the treatment of other indications, such as uveitis and DME [50,51] as well as trying to find ways to mitigate adverse effects of the implant, such as elevated IOP [52].

Another recently approved intraocular drug delivery system uses the EyePoint Pharmaceuticals (previously Icon Biosciences, Inc) Verisome technology, an injectable suspension that allows sustained release of small molecules. DEXYCU® (Icon Biosciences, Inc) is a dexamethasone suspension in acetyl triethyl citrate, and was approved in 2018 for the treatment of postoperative inflammation. The suspension is injected into the posterior chamber of the eye, where gel settles into a small sphere and slowly degrades [53]. The release duration of dexamethasone is 2–3 weeks (NDA 208912). In clinical trial controlled by placebo, DEXYCU® led to a two- to threefold increase in the proportion of patients with clearing of anterior chamber cells, and a lower proportion of patients requiring rescue medications (NCT02006888).

Implants in the pipeline

Intraocular drug delivery implants that are currently in clinical trials are summarized in Table 3. Allergan is currently working on the development of a brimonidine tartrate intravitreal implant (Brimo PS DDS®) in patients with geographic atrophy resulting from AMD. The implant is currently in Phase II clinical trials (NCT01080209). Allergan reported functional recovery after implantation of the Brimo PS DDS® system in a rabbit model of retinal ganglion cell degeneration [54]. Additionally, the implant enhanced spatial acuity in a nonhuman primate model of chronic glaucoma [55]. However, it remains to be seen whether inflammation resulting from PLGA degradation products, which might be masked in Ozurdex® because it delivers an anti-inflammatory agent, would become an issue in the brimonidine implant.

The Genentech/ForSight Vision4 PDS, as mentioned above, is a nonbiodegradable, refillable reservoir device designed to deliver ranibizumab for treatment of wAMD. The refillable port is designed to extend the effective lifetime of the reservoir by delivering additional therapeutic doses when the drug in the reservoir depletes. Phase II results showed that 80% of patients implanted with Vision4 PDS who received a 100 mg/ml dose can go at least 6 months between refills, while achieving similar visual acuity outcomes as monthly ranibizumab injections [37]. Genentech is currently planning Phase III clinical trials.

Ocular Therapeutix uses a hydrogel-based formulation technology for treating various eye diseases. OTX-TIC is a bioresorbable intracameral implant containing micronized travoprost with a target delivery duration of 4–6 months and is intended for patients with glaucoma. A study in beagle dogs showed that the implant was well tolerated and released travoprost with zero-order release kinetics for 4 months [56]. Additionally, a sustained-release TKI implant is under development in Phase I trials [52]. The implant is a bioresorbable hydrogel that contains TKI particles in an injectable fiber, designed for intravitreal injection for a release duration of up to 12 months. Ocular Therapeutix is also collaborating with Regeneron Pharmaceuticals to developing a sustained-release implant for aflibercept (EYLEA®). The device, OTX-IVT, is intended to reduce the frequency of injections to once every 4–6 months (ocutx.com) and is in preclinical development.

Concluding remarks

To date, the only successfully marketed implantable devices release small molecules, either an antiviral or a corticosteroid, and have focused on implantation in the vitreous. With increased acceptance of stent/shunt deployment for glaucoma treatment, the field will likely see new devices enter the anterior segment. Most existing devices are nondegradable, but their use is limited by the device therapeutic duration and requires retrieval or abandonment of depleted devices. For biodegradable devices, PLGA has been successfully used in Ozurdex®; however, the inflammatory nature of PLGA could limit the widespread tolerability of PLGA in intraocular applications beyond the delivery of anti-inflammatory drugs.

A significant need exists to deliver protein therapeutics for treating back-of-the-eye diseases. The PDS is poised to be the first protein delivery system within the eye, and early trial

results indicate significantly extended duration between drug administration. However, there are substantial potential complications, and the required surgical device placement might not be suitable for all patients. An injectable device that only requires administration two to three times per year would be a notable advance in ocular drug delivery devices, particularly if constructed from biodegradable materials. A self-coiling device is compelling because it can be injected and subsequently occupy limited space within the vitreous. An *in situ* gel-based depot or reservoir-based thin film device are other promising approaches for an injectable biodegradable system for protein delivery, which could expand the competitive landscape in the coming years. Although drug delivery to the eye will continue to be a difficult therapeutic area, intraocular device development has remained a source of continued innovation, and ongoing commercial successes are expected to open the field to further acceptance and adoption of novel drug-delivery technologies.

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