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Topical drug delivery devices: A review

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ABSTRACT

For the treatment and prevention of ocular diseases, most patients are treated with conventional drug delivery formulations such as eye drops or ointments. However, eye drops and ointments suffer from low patient compliance and low effective drug concentration at the target site. Therefore, new medical devices are being explored to improve drug delivery to the eye. Over the years, various delivery devices have been developed including resorbable devices, oval- and ring-shaped devices, rod-shaped devices, punctum plugs, contact lenses and corneal shields. Only a few devices (eg. Mydrisart[®], Ozurdex[®], Surodex[®], Iluvien[®], Lacrisert[®] and Retisert[®]) have made it to the market while others are being investigated in clinical trials.

Altogether, there is a need for enhanced topical drug delivery. Only by working together (academia, industry and authorities) and by exploring parallel strategies (new drug delivery devices, enhanced drug formulations, better understanding of the pharmacokinetic properties), the therapeutic effect of drug treatments can be improved.

1. Introduction

Due to the increased prevalence of ocular diseases in the aging population (such as presbyopia, cataract, dry eyes and glaucoma), there is an increased demand for treatment of eye diseases. Aging of the lens may lead to loss of accommodation (presbyopia) or protein aggregation (cataract). Although revolutionary treatments have been discovered, for example lipoic acid (LA) to prevent the loss of accommodation (Garner and Garner, 2016), compound 29 and lanosterol to restore lens transparency in (congenital) cataract (Makley et al., 2015; Zhao et al., 2015) or Kinostat[®] to prevent cataract in diabetic dogs (Kador et al., 2014), they mostly require life-long or long-term administration of eye drops. Also, ocular therapies for dry eyes consist of life-long topical administered artificial tears, gels, ointments or lubricants to relieve symptoms (Pucker et al., 2016). Glaucoma therapy consists of topical applied beta blockers or prostaglandin analogs, laser therapy or surgery to lower the intra ocular pressure (IOP) (Jonas et al., 2017; Lavia et al., 2017; Trese

et al., 2017).

Ocular surgeries range from routine cataract extraction and lens implantation, the most commonly performed surgery worldwide, to rarely performed surgeries such as keratoprosthesis. Due to an increase in the number of surgeries, the odds of infections and inflammations increase if postoperative care is not taken care of properly. A variety of postoperative complications may occur such as cystoid macular edema (CME) (incidence 1.2%–3.5%) after cataract surgery (Jick, 2016; Shah et al., 2016; Wiolders et al., 2017). In order to prevent postoperative complications, patients are treated with ophthalmic anti-inflammatory drugs such as corticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs), and antibiotics (Cantor et al., 2014; Kessel et al., 2014; Kim et al., 2015, 2016; Shah et al., 2016; Wiolders et al., 2015, 2017).

In all ocular therapies and surgeries involving medicines, the route of drug delivery plays an important role. Although systemic drugs do reach the ocular tissues (Vellonen et al., 2016), high doses are required which often lead to side effects. Therefore, the most preferred way of

Abbreviations: Benzalkonium chloride, (BAC); Cystoid macular edema, (CME); Ethylenediaminetetraacetic acid, (EDTA); Ethylene-vinyl acetate, (EVA); Food and drug administration, (FDA); 2-Hydroxyethyl methacrylate, (HEMA); Intraocular lens, (IOL); Intraocular pressure, (IOP); Latanoprost punctal plug delivery system, (L-PPDS); Lipoic acid, (LA); LA and its choline ester, (LACE); Medical device regulation, (MDR); Minimal inhibitory concentration, (MIC); New ophthalmic delivery system, (NODS); Non-steroidal anti-inflammatory drugs, (NSAIDs); Polyethyleneglycol, (PEG); Polylactic-co-glycolic acid, (PLGA); Pre-ocular or post-lens tear film, (POTF); Poly-e-lysine, (peK); Polyvinyl alcohol, (PVA); Retinal pigment epithelium, (RPE); Soluble ophthalmic drug inserts, (SODI); Topical ophthalmic drug delivery device, (TODDD); Union of soviet socialist republics, (U.S.S.R.); United kingdom, (U.K.)

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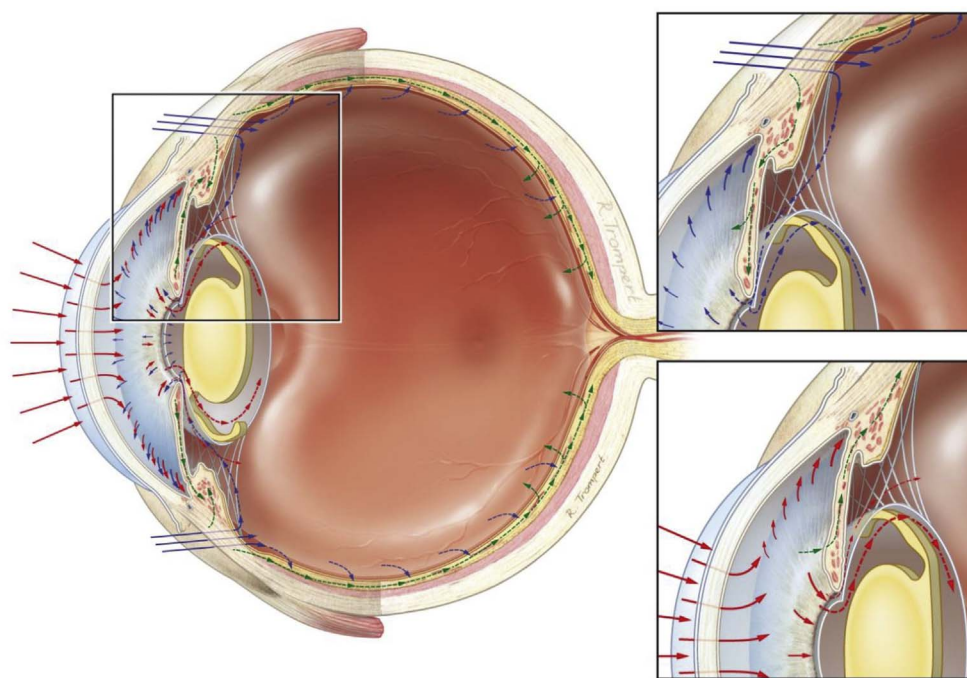


Fig. 1. Drug delivery routes in the eye.

Red arrows show the corneal delivery route with penetration through the cornea into the anterior chamber and clearance via the trabecular meshwork (anterior elimination route). A small part of the drug (dependent on the molecular weight and lipophilicity) will migrate into tissue of the iris or bind to the melanin pigment, from where it can get into the posterior chamber (green arrows). The lower inset shows a magnification of the corneal route.

Blue arrows show the non-corneal delivery route, drugs penetrate via the conjunctiva through the sclera into the choroid and to some extent through the retina into the vitreous cavity (green arrows). In the vitreous cavity, small drug molecules (< 2 nm) will be cleared via the blood-retina barrier (posterior elimination route, blue arrows). Most of the drug will reach the anterior chamber via aqueous humor flow. The upper inset provides a magnification of the non-corneal drug delivery route and drug transport or diffusion into the anterior chamber.

The figure is drawn with an IOL to address that an IOL due to its anatomical position could be used as drug delivery system. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

drug delivery to the eye is topically. Drugs administered topically are absorbed through the corneal or non-corneal absorption route (Fig. 1). Drug molecules with high corneal permeability (eg. small molecules with a hydroxyl group) prefer the corneal route (Fig. 1) (Del Amo et al., 2017; Edward and Prausnitz, 2001). This route starts with passive diffusion of drug molecules via the epithelium, through the stroma and endothelium into the anterior chamber, where the drug will exert its pharmacological function (Edward and Prausnitz, 2001; Ho et al., 2014; Shikamura et al., 2016; Zhang et al., 2004) or bind to the melanin pigment in the iris and ciliary body (Agrahari et al., 2016) or to plasma proteins (Pelkonen et al., 2017) to prolong its pharmacological function. Remaining drugs and drug waste products will be cleared via the trabecular meshwork through Schlemm's channel into the systemic blood circulation (conventional pathway) or via the iris to the uveoscleral tissue (unconventional pathway) and subsequently into the systemic blood circulation (Carreon et al., 2017; Del Amo and Urtti, 2015; Goel et al., 2010; Loewen et al., 2016). A minor part of the drug (dependent on the molecular weight and lipophilicity) will reach the posterior chamber via penetration of the iris and diffusion via the aqueous humor flow resulting in drug concentrations in the vitreous which are 10 and 100 times less than in the aqueous humor and cornea, respectively (Del Amo et al., 2017). It must be noted that these pharmacokinetics can be altered due to eye rotations (Bonfiglio et al., 2015; Stocchino et al., 2007) and ocular diseases (Guo et al., 2017; Ho et al., 2014; Li et al., 2016).

Drugs with low corneal permeability (eg. large molecules and proteins) will penetrate the eye via the conjunctiva and/or the sclera, the so-called non-corneal absorption route (Fig. 2) (Ambati et al., 2000; Bauer et al., 1999b; Del Amo and Urtti, 2015; Hughes et al., 2005; Lee et al., 2008). This route delivers drugs to the vitreous cavity via passive diffusion. Moreover, it is hypothesized that active transport also plays a role. Drugs penetrate or diffuse via the conjunctiva through the sclera into the choroid and through the retina (retinal pigment epithelium (RPE) cells and retinal capillary endothelial cells) into the vitreous cavity (Ahmed and Patton, 1985; Kim et al., 2004; Shikamura et al., 2016; Zhang et al., 2004). Once inside the vitreous chamber the drug will be transported towards the anterior chamber by the flow of aqueous humor or will be cleared via passive diffusion (determined by the LogD7.4 and hydrogen bonding capacity of the drug) by the RPE and

retinal capillary endothelial cells (which form the blood-retinal barrier) through the choroidal circulation into the systemic blood flow (Del Amo et al., 2017; Del Amo and Urtti, 2015; Kidron et al., 2012). The non-corneal absorption route delivers 20 times lower drug concentration into the anterior chamber compared to the corneal absorption route (Ahmed and Patton, 1985).

Conventional ocular dosage forms, such as eye drop solutions (Fig. 2,10) and ointments, account for approximately 90% of currently marketed ophthalmic pharmaceuticals. Their biggest advantages are ease of administration and low costs. Moreover, eye drops are well accepted by most patients and have a rapid and localized drug action (Lang, 1995). Nevertheless, eye drop delivery is associated with several disadvantages. Next to systemic side effects (Farkouh et al., 2016) and toxicity (Palmer and Kaufman, 1995), the main disadvantages of eye drop delivery are low drug bioavailability and poor patient compliance (Table 1). Pre-corneal loss of the drug (by systemic conjunctival elimination, blinking, induced lacrimation, the tear film and rapid tear turnover, see Table 1) results in a very low ocular bioavailability of the drug at its target destination. Typically, less than 5% of the total administered dose reaches the anterior chamber (Hughes et al., 2005; Lee et al., 2004; Urtti and Salminen, 1993). In addition, high aqueous humor turnover washes out the drugs relatively fast (1.0%–1.5% of the anterior chamber volume per minute) (Goel et al., 2010; Lang, 1995), and drug-melanin binding could affect the pharmacological function of the drug (Del Amo et al., 2017; Pelkonen et al., 2017) (Table 1). Another excreting factor influencing pre-corneal loss is lacrimal clearance, which clears aqueous solutions in 60 s and higher viscose solutions such as hydroxypropyl methylcellulose in 4 min (depending on its concentration) (Linn and Jones, 1968).

In order to maintain minimum inhibitory concentrations, ocular drugs need to be administered frequently resulting in poor patient compliance (Hermann et al., 2010; Nordmann et al., 2010; Salyani and Birt, 2005) (Table 1). Low patient compliance is mainly caused by incorrect instillment (timewise and dropwise) of the eye drops, which typically occurs in more cases than assumed by physicians and patients (Eaton et al., 2015; Mohindroo et al., 2015; Newman-Casey et al., 2015; Nordmann et al., 2010) (Table 1). Low patient compliance may result in an increased incidence and severity of postoperative complications (such as inflammation) and under-treatment of ocular diseases (such as

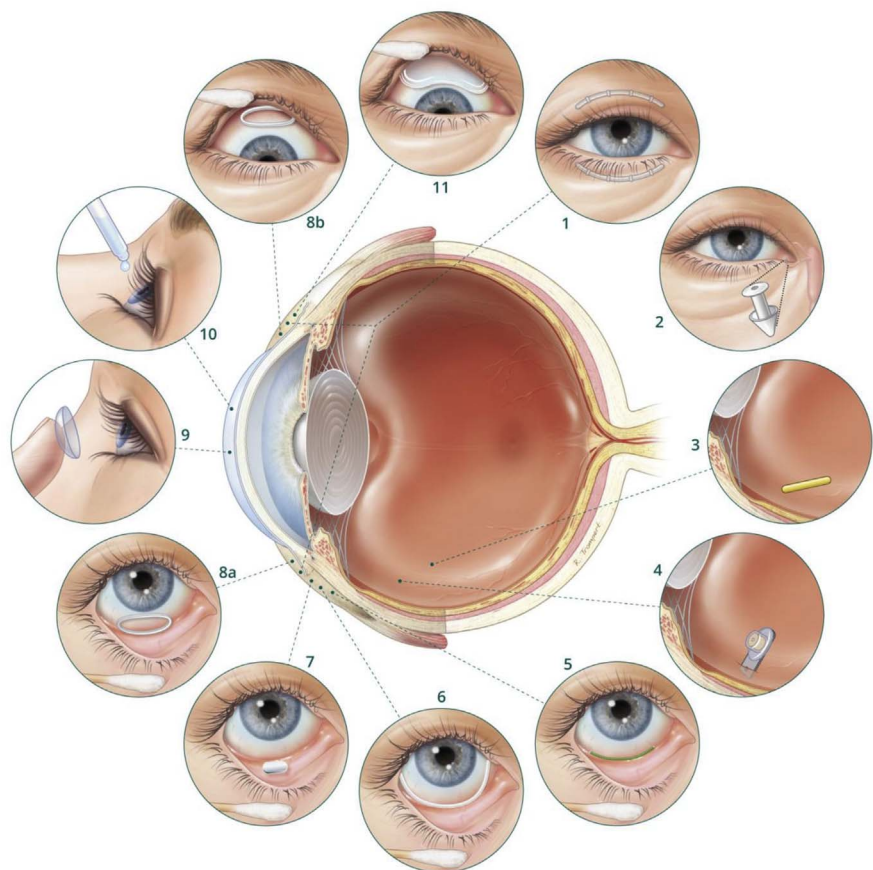


Fig. 2. Overview of drug delivery devices.
1. Conjunctival insert Ocufit SR[®], which can be placed in both, the inferior and superior conjunctival fornix.
2. Punctum plug such as Dextenza[®] or Evolute[®] should be inserted in the inferior punctum.
3. Intravitreal insert such as Iluvien[®] or Surodex[®] which are implanted or injected into the vitreous chamber.
4. Intravitreal insert Retisert[®], which is implanted into the vitreous chamber and is stitched to the sclera.
5. Conjunctival insert OphthaCoil, is a device placed behind the lower eyelid in the fornix of the conjunctiva.
6. Conjunctival insert Helios™. The ring is placed round the globe into the inferior and superior conjunctival fornix.
7. Conjunctival tablet, Lacrisert[®] or Mydrasert[®]. Both tablets are placed in the inferior conjunctival fornix.
8. Conjunctival insert Ocuser[®], can be placed in the inferior (8a) and superior (8b) conjunctival fornix.
9. Contact lens for drug delivery, to be placed on the cornea.
10. Eye drops.
11. Conjunctival insert for the superior conjunctiva, TODDD™.

Table 1
Examples of disadvantages related to eye drops.

Disadvantage	Reference
Systemic side effects	(Farkouh et al., 2016)
Toxicity	(Palmer and Kaufman, 1995)
Low ocular bioavailability:	(Bauer et al., 1999a; Gaudana et al., 2010; Hughes et al., 2005; Lee et al., 2004; Urtti and Salminen, 1985, 1993)
Pre-corneal loss of the drug due to systemic conjunctival elimination, blinking, induced lacrimation, the tear film and rapid tear turnover.	
Low ocular bioavailability:	(Goel et al., 2010; Lang, 1995; Linn and Jones, 1968)
Fast drug wash-out due to high aqueous humor turnover or lacrimal clearance	
Low ocular bioavailability:	(Del Amo et al., 2017; Pelkonen et al., 2017)
Drug binding to proteins	
Poor patient compliance:	(Eaton et al., 2015; Mohindroo et al., 2015; Newman-Casey et al., 2015; Nordmann et al., 2010)
Drop instillation is (too) frequent	
Poor patient compliance:	(Eaton et al., 2015; Mohindroo et al., 2015; Newman-Casey et al., 2015; Nordmann et al., 2010)
Drop instillation is incorrectly performed	

glaucoma), which create a significant burden for the health care system. Therefore, new methods for ocular drug delivery are needed within the ophthalmic field. In this review, an overview of current state of knowledge on topical drug delivery devices is provided.

2. Topical drug delivery devices

In response to the obstacles of conventional drug dosage forms, alternatives have been explored. These are mainly drug-loaded medical devices which use the non-corneal absorption route (Fig. 2). Historically, the first precursors of ocular inserts were small sections of filter

paper impregnated with drug solutions (eg., atropine sulfate, pilocarpine hydrochloride) (Edman, 1993). In the late 1800s, polymeric inserts containing cocaine for local anesthesia were already used in the United Kingdom (U.K.) (Del Amo and Urtti, 2008). In the 1970s, soluble ophthalmic drug inserts (SODIs) were introduced in the Union of Soviet Socialist Republics (U.S.S.R.) (Maichuk, 1975b). SODIs were oval plates made from polyvinyl alcohol (PVA) and impregnated with several drugs. According to a trial in which 500 patients participated, SODIs had good tolerance (Maichuk, 1975a, b). So far, most drug delivery devices have been explored for posterior drug delivery (eg. intraocular pressure lowering drugs for glaucoma) and research has been primarily initiated by the industry. Only vitreous implants have made it to the market, as episcleral implants were not able to deliver enough drugs into the vitreous cavity (Kim et al., 2004; Li et al., 2016). A few vitreous implants are commercially available, including Ozurdex[®] (Allergan inc., Irvine, California, USA) (Fig. 2,3) (0.7 mg dexamethasone for 60–90 days), Surodex[®] (Oculex Pharmaceuticals Inc. taken over by Allergan Inc., Irvine, California, USA in 2003) (60 µg dexamethasone for 7–10 days), Iluvien[®] (Alimera Sciences Inc., Alpharetta, Georgia, USA) (Fig. 2,3) (0.23–0.45 µg/day fluocinolone for 18–36 months) and Retisert[®] (Bausch & Lomb, Bridgewater, New Jersey, USA) (Fig. 2,4) (0.59 mg fluocinolone acetonide for 30 months). These devices are placed in the vitreous chamber by implantation or injection.

Today, there is also interest in exploring these devices for the anterior segment. However, it is difficult to create an implant for the anterior chamber, since it will move due to the low viscosity of the aqueous humor, and thereby causing irreversible damage to the endothelial cells (Bourne, 2003). Although, when Surodex[®] (Allergan, Inc., Irvine, California, USA) was injected in the anterior chamber, it did not result in irreversible endothelial cell damage (Tan et al., 1999, 2001).

Another focus is on improving the bioavailability of ocular drugs

Table 2
Topical drug delivery devices.

Device	Fig. 2 (no.)	Disease	Device size	Material	Distribution route	Drug load per device	Produced by	Current state	Achieved drug delivery or drug effect	Year
Resorbable devices for the conjunctiva										
Lacrisert®	7	Dry eyes	Length 3.5 mm by 1.24 mm in diameter.	Hydroxypropyl cellulose	Noncorneal, via the lower conjunctival fornix	Hydroxypropyl cellulose	ATON Pharma inc.	On the market.	N.A.	2007
New Ophthalmic Delivery System (NODS®)	N.A.	Glaucoma and mydriasis	Length 4 mm, 6.3 mm width, 20 µm thickness.	Water soluble PVA	Noncornea, via the lower conjunctival fornix	• 40 µg, 80 µg or 170 µg pilocarpine, or • 125 µg chloramphenicol, or • 125 µg tropicamide	Nephew Pharmaceuticals Ltd.	Tropicamide made it to the market but was retrieved due to low sales.	• Tropicamide mydriasis 2.8 mm at 30–45 min • Chloramphenicol tear concentration: 1243 mg/L at 8 min • Pilocarpine miosis: 5.5 mm at 2 min with 170 µg	1985
Gelfoam®	N.A.	Multiple diseases	4 mm in diameter by 0.5 mm thickness.	Gelatin	Noncornea, via the lower conjunctival fornix	• 1.7 mg phenylephrine and 0.6 mg tropicamide or, • 0.2–1.0 mg sodium insulin	Negvesky et al.	Never made it to the market	Maximal phenylephrine and tropicamide mydriasis: 5.9 mm at 15.2 min	2000
Oval or ring-shaped devices for the conjunctiva										
SODI	N.A.	Multiple diseases	9 mm length by 4.5 mm width and 0.2–0.3 mm thickness	PVA	Noncornea, via the lower conjunctival fornix	• 2.6 mg pilocarpine, or • 1.5 mg atropine, or • 1.0 mg neomycin, or • 5.2 mg sodium sulfapyridazine, or • 0.75 mg dicaine, or • 10 mg idoxuridine	Maichuk et al.	Off market, reason unknown	No data	1970
Ocusert®	8 a&b	Glaucoma	Length 13.4 mm by 5.7 mm oblong ring-like structure, 0.3 mm thickness.	EVA membranes and retaining ring of EVA, impregnated with titanium dioxide.	Noncornea, via the upper conjunctival fornix	• 5 mg pilocarpine (p-20)	ALZA corp.	Off market in 1998 because of burst release and dislocation problems	No data	1974
PEG-PLGA insert	N.A.	Glaucoma	Length 13.4 mm by 5.7 mm oblong ring-like structure, 0.3 mm thickness.	PEG and PLGA	Noncornea, via the lower conjunctival fornix	• 10 mg brimonidine	Mealy et al.	In preclinical phase	No data	2014
Helios™	6	Glaucoma	Diameter varying from 24 mm to 29 mm thickness of 1 mm.	Polypropylene support structure covered with bimatoprost-loaded silicone	Noncornea, around the eye, in the upper and lower conjunctiva	• 2.5 mg bimatoprost	ForSight Vision5 inc.	Phase III	No data	2016
Scleral/corneal lens	9	Anti-bacterial	13 mm–20 mm in diameter and 0.15 mm–0.40 mm thickness.	HEMA	Noncornea/cornea, placed round the cornea.	• 1.2 mg ofloxacin	Shikamura et al.	In pre-clinical phase	Ofloxacin concentration in aqueous humor: T _{max} : 4 h, C _{max} : 8 µg/mL	2015
Rod-shaped devices for the conjunctiva										
Mydriaser®	7	Mydriasis pre surgery	Length 4.3 mm by 2.3 mm diameter.	Ammonio methacrylate copolymer (type A), polyacrylates glycerol dibehenate and ethylcellulose	Noncornea, via the lower conjunctival fornix	• 0.28 mg tropicamide and 5.4 mg phenylephrine	Thea Laboratories	On the market	No data	2004
Ophthalmic rod	N.A.	Multiple diseases	Length 55 mm, diameter unknown.	Non-toxic acryl plastic	Rub a drug layer on to the lower eyelid	• 20 µg clonidine, or • 30 µg fluorescein, or • tropicamide, or	Alani et al.	Never made it to the market	• Maximal tropicamide mydriasis: 2.8 mm at 30 min • Maximal pilocarpine	1990

(continued on next page)

Table 2 (continued)

Device	Fig. 2 (no.)	Disease	Device size	Material	Distribution route	Drug load per device	Produced by	Current state	Achieved drug delivery or drug effect	Year
Ocufit SR*	1	Glaucoma and anti-bacterial	Length 25 mm–30 mm and 1.9 mm in diameter.	Silicone elastomer	Noncornea, via the upper and lower conjunctival fornix	• pilocarpine, or • oxybuprocaine Multiple drugs	Escalon Medical Corp.	Never made it to the market	miosis: 4.75 mm at 25 min No data	2000
OphthaCoil	5	Multiple diseases	Length 15 mm by 0.6 mm thickness.	Stainless steel covered with SlipSkin® coating	Noncornea, via the lower conjunctival fornix	• 135.6 µg pradoxofloxacin, or • fluorescein, or • ciprofloxacin, or • pradoxofloxacin	Pijls et al.	In pre-clinical phase	(<i>in vitro</i> release) • Fluorescein T_{max} : 100 min, C_{max} : 2.2 µg/mL • Ciprofloxacin T_{max} : 15 min C_{max} : 0.1 µg/mL • Pradoxofloxacin T_{max} : 30 min C_{max} : 7 µg/mL	2004
Punctum plugs										
Evolute*	2	Glaucoma	Sizes not published.	not published	Via the nasolacrimal duct	• latanoprost	Mati Therapeutics inc.	Phase IIb	No data	2015
Dextenza*	2	Inflammation	Length 3 mm by 2 mm in diameter.	PEG	Via the nasolacrimal duct	• 0.4 mg dexamethasone	Ocular therapeutix	Phase III	No data	2017
Other										
Topical Ophthalmic Drug Delivery Device (TODDD ⁽¹⁸⁾)	11	Multiple diseases	Length 20 mm by ~8 mm width and 1 mm thickness.	Elastomer, type not published.	Noncornea, via the upper conjunctival fornix and sclera	Multiple drugs	Amorphex Therapeutics	Phase II	No data	2016
Flexible ocular iontophoretic device	N.A.	Multiple diseases	0.42 cm ² gold gilded electrode to be placed in the lower conjunctival fornix	Polyimide substrate and a gold gilded electrode	Noncornea, via the lower conjunctival fornix	Multiple drugs possible	Zhang et al.	In pre-clinical phase	Enhanced scleral permeability at 1 mA and 600 s	2016

Ethylene-vinyl acetate (EVA), 2-Hydroxyethyl methacrylate (HEMA), Polyethylene glycol (PEG), Poly lactic-co-glycolic acid (PLGA) and Polyvinyl alcohol (PVA).

through the use of different formulations, such as microspheres (Fernandez-Sanchez et al., 2017), nanoparticles (Chiang et al., 2016), liposomes, micelles and prodrugs. These solutions are promising but do not guarantee higher patient compliance than eye drops (Cholkar et al., 2013; Gaudana et al., 2010; Kalita et al., 2014).

Finally, ocular treatments can be improved by better understanding the basic ocular and corneal pharmacokinetics (Chun et al., 2008; Ghate and Edelhauser, 2006; Mannermaa et al., 2006; Shirasaki, 2008; Urtti and Salminen, 1993). Therefore, fundamental research is indispensable and essential for the applied sciences.

In this review, we will cover resorbable devices, oval- and ring-shaped devices, rod-shaped devices, punctum plugs, contact lenses and ocular shields. The characteristics of all these devices are summarized in Table 2.

2.1. Resorbable conjunctival devices

Resorbable drug delivery devices are devices which can be placed in the conjunctival sac and which dissolve and secrete drugs over time. The advantages of resorbable devices are that they are often non-invasive and do not need to be removed. However, most resorbable devices have a limited time of action (typically less than 24 h) and thus may require frequent administration (Calles et al., 2015). Moreover, it is challenging to develop resorbable devices since the complete material and its metabolites should be non-toxic. Other challenges are the prevention of accidental loss of the device, which is not always noticed and the increase in tear production after placement which increases the risk of bulk release of drugs (Calles et al., 2015).

The only resorbable conjunctival device which is on the market is Lacrisert® (Aton Pharma, Lawrenceville, New Jersey, USA) (Fig. 2,7). Lacrisert® is a small hydroxypropyl cellulose tablet which has to be placed in the lower conjunctival fornix (Table 2). It slowly dissolves and creates an artificial tear film to treat dry eyes (Rajasekaran et al., 2010). However, Luchs et al. showed that wearing a Lacrisert® insert can lead to blurred vision which warranted removal of the device in 8.7% of the participants (Luchs et al., 2010). Other known adverse effects related to wearing a Lacrisert® insert are ocular discomfort or ocular irritation because of foreign body sensations, stickiness of eyelashes, photophobia, hypersensitivity, eyelid edema, and hyperemia (Luchs et al., 2010; McDonald et al., 2010).

Another resorbable device called New Ophthalmic Delivery System (NODS®) was developed by Smith and Nephew Pharmaceuticals Ltd. (Gilton Park, Harlow, Essex, UK). The NODS® is made from water-soluble polyvinyl alcohol (PVA) and should be placed in the cul-de-sac of the lower eyelid. The NODS® has been loaded with different drugs eg. pilocarpine, chloramphenicol and tropicamide (Sesha Rao et al., 2003). This device assured an eight-fold increase in drug bioavailability compared to eye drops in healthy volunteers (Diestelhorst and Kriegelstein, 1994; Greaves et al., 1992; Saettone and Salminen, 1995). A small clinical trial with twelve volunteers revealed intense miosis in all test subjects as a side effect (Greaves et al., 1992). In a larger study with twenty-nine volunteers, there were some problems with the detachment of the NODS® from its applicator (Diestelhorst and Kriegelstein, 1994). Eventually, only the tropicamide loaded NODS® was introduced into the market. Although the price was comparable to that of a tropicamide Minims® (eye drops), the product was not commercially successful since it could only be used for diagnostic purposes (Sesha Rao et al., 2003). Therefore, many of the benefits, such as absence of preservative, improved bioavailability and convenience of storage were not relevant (Sesha Rao et al., 2003).

Another group investigated Gelfoam® discs (Pharmacia & Upjohn Company LLC, Peapack, New Jersey, USA) as an alternative drug delivery system. The Gelfoam® discs are made of resorbable gelatin and impregnated with insulin for diabetic patients or mydriatic drugs to widen the pupil. The Gelfoam® discs should be placed in the lower conjunctival fornix and have been tested extensively in rabbits and

human volunteers (Lee et al., 1999, 2002, 1997; Negvesky et al., 2000). Some volunteers (6/20) developed a palpebral conjunctival infection (hyperemia), while other volunteers (3/20) developed superficial punctate erosion (Negvesky et al., 2000). No further use of this device was reported.

2.2. Oval- and ring-shaped conjunctival devices

Several non-resorbable devices shaped as a ring or oval structure have been developed (Table 2). These devices are placed under the upper and/or lower eyelid in the conjunctival fornices and use the non-corneal route to distribute drugs.

One of the first breakthroughs within this field came from ALZA Corporation (Mountain View, California, USA) (acquired by Johnson & Johnson, New Brunswick, New Jersey, USA in 2001). ALZA invented an oblong-shaped device (Fig. 2,8), called Ocusert®, which consisted of two ethylene-vinyl acetate (EVA) membranes filled with pilocarpine and covered by a ring of titanium dioxide impregnated EVA (Table 2) (Saettone and Salminen, 1995). The preferred location to place the Ocusert® was the upper conjunctival sac (Fig. 2,8b) and resulted in one week of drug delivery (Quigley et al., 1975). Ocusert® came on the market in July 1974 and was available in two doses, the Ocusert® Pilo-20 (release of 20 µg/h) and the Ocusert® Pilo-40 (release of 40 µg/h). However, the Ocusert® was discontinued because of foreign body sensation, retention issues, difficulty in handling and only marginal IOP reduction (Kushnick et al., 1996; Langer, 1983; Mealy et al., 2014; Quigley et al., 1975; Saettone and Salminen, 1995). Because of these adverse effects and the low efficacy, the acceptance of Ocusert® by the ophthalmic market was low (Langer, 1983; McGhee, 1992).

More recently, a polyethylene glycol (PEG) and polylactic-co-glycolic acid (PLGA) elliptical insert was created with a similar size and shape to the Ocusert® ring. An *in vitro* study showed that the brimonidine tartrate-loaded insert produced a linear drug-release profile for one month. Further investigation is needed to demonstrate the potential of this drug-eluting device in the treatment of glaucoma (Mealy et al., 2014).

One particular example of a drug-loaded ring structure was developed by a Japanese research group. They developed a 2-hydroxyethyl methacrylate (HEMA) contact lens with a central hole. The device (loaded with 0.3% ofloxacin) could deliver ofloxacin to the anterior and even the posterior parts of the eye in rabbits. Drug delivery to the posterior part of the eye was achieved in 15–60 min after application of the device, via penetration of the conjunctiva and sclera into the choroid. Drug concentrations in the posterior tissue were more than ten times lower than those in the anterior tissue. However, compared to drug delivery from eye drops and corneal hydrogel lenses, drug concentrations in posterior tissue were ten to forty times higher, respectively (Shikamura et al., 2016).

A ring-shaped device (Helios™) (Fig. 2,6) was developed by ForSight Vision5 Inc. (Menlo Park, California, USA). This ring (24–29 mm diameter, 1 mm thickness) consisted of an internal polypropylene support covered with bimatoprost-loaded silicone. The Helios™ ring had to be placed around the eye and can be used for the reduction of the IOP in glaucoma patients (Brandt et al., 2016; Higuchi et al., 1976). A phase II clinical trial (130 patients) demonstrated that the Helios™ ring reduced the IOP (4–6 mmHg) over a six month period. However, this IOP reduction was not significantly different when compared to regular unpreserved timolol 0.5% ophthalmic solution (Valeant Ophthalmics, Bridgewater, New Jersey, USA) (after 6 months a reduction of 3.25 ± 0.32 mmHg with bimatoprost compared to 4.24 ± 0.37 to timolol 0.5% ophthalmic solution). In addition, the drop-out rate was higher in the patient group with the Helios™ device (8 versus 2 in the eye drop group). (Brandt et al., 2016). A 13 month safety study (with a 6-month and 7-month interval) showed a safety profile consistent with bimatoprost exposure except for an increased incidence of eye discharge (mucus). The retention rate after 13 months was 94.7%

suggesting that retention improves as patients gain more experience using the ring (Brandt et al., 2017).

2.3. Rod-shaped conjunctival devices

Another group of non-resorbable devices are the rod-shaped devices. These devices should also be placed in the upper or lower conjunctival fornix to deliver drugs via the non-corneal absorption route.

One small rod-shaped device that is available on the European market since 2004 is Mydriaser[®] (Thea Laboratories, Clermont-Ferrand, France) (Fig. 2,7, Table 2). Mydriaser[®] is an ethyl cellulose tablet which is loaded with tropicamide and phenylephrine hydrochloride to deliver mydriasis 2 h before surgery. However, when compared to topical mydriatic eye drops, there was no significant difference in pupil dilatation. In addition, topical mydriatic eye drops dilate the pupil faster (within 15 min) compared to the Mydriaser[®] insert (Cagini et al., 2014; Torron et al., 2013). The economic benefits of Mydriaser[®] were investigated in a cohort of 1763 patients in the U.K. Although an insert is more expensive compared to eye drops (£4.20 per insert compared to £0.41 per vial for tropicamide 1% and £0.49 per vial of phenylephrine hydrochloride 10%), nurse time could be decreased thereby saving £1.20 per patient. This resulted in a decrease of 18% in the total annual costs (Shah et al., 2015).

In the early nineties, the ophthalmic rod was developed (Alani, 1990; Alani and Hammerstein, 1990). This rod was intended as a single-dose sterile applicator of drugs in order to avoid the problems of preservation, sterility, cross-infection and cross-contamination of eye drops. The non-toxic acrylic plastic rod could be loaded on one end with drugs (eg. tropicamide, oxybuprocaine, fluorescein or pilocarpine) by dipping the rod into an alcohol-drug solution. After evaporation of the alcohol, the drug-film could be used. The drugs were released in the lower conjunctiva by introducing the tip of the rod in the conjunctival sac and rubbing it against the palpebral conjunctiva of the lower lid. In this way, a small drug-film was created on the conjunctiva which was slowly dissolved by the tear film. The development of the rod was discontinued because of the induced mechanical stress on the tissue, drug preservation issues and the problem of its use in combination with other eye drops (Alani, 1990; Alani and Hammerstein, 1990).

Escalon Medical Corp. (Wayne, Pennsylvania, USA) patented OcuFit SR[®], a drug-eluting rod-shaped ocular device which could be placed in the lower and upper conjunctival fornix (Fig. 2,1, Table 2) (Rajasekaran et al., 2010). The cylindrical rod was made of a silicone elastomer and loaded with drugs for the treatment of glaucoma or with antibiotics (Darougar, 1992; Saettone and Salminen, 1995). Although the placebo device could be retained in the upper fornix of the eye for over two weeks in 70% of volunteers (Saettone and Salminen, 1995), the phase I study with the OcuFit SR[®] device was discontinued in 2000 because of reallocation of the company's research and development interests (NewsWire, 2000).

Finally, our group developed the OphthaCoil (Fig. 2,5 Table 2), a coiled stainless steel wire, which is placed in the lower conjunctival sac. The device can be filled with drugs inside its lumen (loaded on microspheres or filaments) or outside on the SlipSkin[®] coating (Dias et al., 2009; Duxfield et al., 2016; Pijls et al., 2004, 2005, 2006, 2007). The OphthaCoil was loaded with pradofloxacin and mydriatic agents (phenylephrine hydrochloride and tropicamide) and tested in Beagle dogs and horses. The pradofloxacin-loaded OphthaCoil resulted in drug delivery concentrations higher than the minimum inhibitory concentration (MIC) and the mydriatic-loaded OphthaCoil resulted in complete dilation 1 h after placement which lasted for one to 4 h after removal of the OphthaCoil (Pijls, 2007). Although tolerability of the OphthaCoil was excellent, the device was lost overnight in dogs and horses (probably because of the third eyelid, also called the nictitating membrane, which covers and protects the eyes during sleep). This is unlikely to occur in humans since humans do not have a third eyelid (Pijls et al., 2005).

In humans (pilot trials), short-term high tolerance and comfort of the device was demonstrated for a period of 2 h (Pijls, 2007; Pijls et al., 2004). Currently, new preclinical and clinical trials are being executed in order to further explore the potential of an ocular coil as an ocular drug delivery device for an extended period of time, up to 28 days.

2.4. Punctum plugs

Other types of ocular devices that show potential to be used as drug delivery devices are punctum plugs (Fig. 2,2, Table 2). These small plugs must be placed in the tear duct and were initially invented for patients with keratoconjunctivitis sicca (dry eye syndrome) (Chee, 2012; Driscoll and Blizzard, 2016; Yellepeddi et al., 2015). The first punctum plug used as an ocular drug delivery device was already developed in 1974 (Freeman, 1976).

In 2012 Mati Therapeutics (Austin, Texas, USA) and QLT Inc. (Vancouver, British Columbia, Canada) started collaborating in the field of punctum plugs (Lazar, 2011; Novelion, 2012; Odrich, 2005). They developed a latanoprost punctal plug delivery system (known as L-PPDS or Evolute[®]) with a small drug reservoir in the head of the plug. After placement, the plug was able to deliver drugs via the lacrimal system into the tear film and to the tear duct (Muller and Utkhede, 2016). In 2015, a phase IIb multicenter trial was started to evaluate the efficacy of the L-PPDS. So far, no results or details have been reported (Business wire, 2015a,b).

Ocular Therapeutix Inc. (Bedford, Massachusetts, USA) developed Dextenza[®], a 0.4 mg dexamethasone containing PEG punctum plug (Fig. 2,2 Table 2) for the treatment of inflammatory eye conditions up to 30 days after a cataract surgery. A phase II trial (n = 60) showed that Dextenza[®] was effective in stopping itching and providing pain relief after cataract surgery (Walters et al., 2015). Another Phase II clinical trial in a group of 28 patients with allergic conjunctivitis (versus 31 patients in the vehicle group) showed improvement of allergic signs and symptoms in a 6 week trial. However, no significant difference in itching and ocular redness was observed between the Dextenza[®] group and the vehicle group (Torkildsen et al., 2017). A phase III trial to demonstrate treatment of ocular itching associated with allergic conjunctivitis was also successful (Business wire, 2015a,b). Another phase III trial investigated the use of Dextenza[®], for the treatment of ocular inflammation and pain after ophthalmic surgery (eg. cataract). Absence of anterior chamber cells and ocular pain on days 4, 14, and 30 after insertion of the insert was shown (Business wire, 2017). With these results, Ocular Therapeutix announced their intention to file a FDA new drug application (NDA) to bring their product to the market (Bethke, 2015; Business wire, 2015a,b; 2017; Cheema et al., 2016; Walters et al., 2015). In July 2017, the FDA rejected Ocular Therapeutix's NDA due to deficiencies in the manufacturing process and analytical testing identified during a pre-NDA approval inspection of an Ocular Therapeutix manufacturing facility (EyeWorld, 2017).

2.5. Contact lenses and corneal shields

Contact lenses and corneal shields have also been investigated for ocular drug delivery (Fig. 2,9). They are able to transport drugs via the corneal route, but must remain transparent in order to prevent vision loss. One potential advantage is that they could simultaneously deliver drugs and enhance vision by correcting the refractive error. After placement of a drug-loaded contact lens on the eye, the drug slowly diffuses into a thin fluid layer between the lens and the cornea, called the pre-ocular or post-lens tear film (POTF), and diffuses slowly through the surrounding tissues (via the cornea, limbus and conjunctiva) into the anterior segment of the eye (Creech et al., 2001; Li and Chauhan, 2006).

Since 1960, contact lenses and shields have been investigated to deliver drugs to the eye (Dixon et al., 2015; Jessen, 1964; Tian et al., 2001a, 2001b; Wichterle and Lim, 1960; Willoughby et al., 2002). Most

of them were made by simply dipping the material (often a hydrogel) into a drug solution (Schultz and Morck, 2010). This ‘soak and release’ approach did not lead to a successful clinical product, mainly because of the short duration of release (Bengani et al., 2013). Currently, more innovative ways of drug-loading are being explored, for example by molecular imprinting or entrapping of nanoparticles into the polymer structure (Ali et al., 2007; Dixon et al., 2015; Li and Chauhan, 2006; Maulvi et al., 2016; Prakash and Dhesingh, 2017).

Although drug-loaded contact lenses result in an increased bioavailability of the drug over eye drops, and *in silico* and animal studies have proven safety and efficacy (Ali et al., 2007; Gause et al., 2016; Li and Chauhan, 2006), drug-eluting contact lenses have not yet reached the market. Contact lenses are associated with an increased risk of contact lens-related corneal damage and infections (Chalmers and Gleason, 2013; Konda et al., 2014; Richdale et al., 2016).

The following examples of drug-loaded contact lenses are promising: a latanoprost secreting PLGA contact lens developed by the department of Ophthalmology Massachusetts Eye and Ear Infirmary from Harvard Medical School (Boston, Massachusetts, USA), which was tested in glaucoma induced monkeys (Ciolino et al., 2016), a poly-L-lysine (pLK) hydrogel bandage lens containing amphotericin B for treatment of fungal keratitis which was tested *in vitro*, and is currently under development by the department of Eye and Vision Science, Institute of Ageing and Chronic Diseases from the University of Liverpool (Liverpool, UK) (Gallagher et al., 2017), and a brimonidine eluting thermosensitive hydrogel (consisting of PLGA-PEG-PLGA) with nanoparticles, which was developed by the department of Ophthalmology & Visual Science and the Department of Pharmacy from the Eye & ENT Hospital (Shanghai, China). This thermosensitive gel is applied between a soft contact lens and the cornea and was tested *in vitro* and in animals for its drug-secreting capacity (Sun et al., 2017). More contact lens and bandage lens related technologies are reviewed in (Maulvi et al., 2016; Papas, 2017; Zidan et al., 2017).

2.6. Other devices

Another example of a drug-delivery device with a particular shape has been developed by Amorphex Therapeutics (Dundee Park, Andover, Massachusetts, USA) (Table 2). The device called TODDD™ (Topical Ophthalmic Drug Delivery Device) is an ‘eight-shaped’ (Fig. 2,11) timolol or prostaglandin-containing elastomer (20 mm length, about 8 mm width and 1 mm thickness) which should be placed on the sclera below the upper eyelid of glaucoma patients (Leahy and LaBombard, 2012). In a human trial, (n = 20) the timolol-loaded device showed that the IOP was reduced by 16%–22% in glaucoma patients after 6 months (Bethke, 2015).

Finally, it is expected that a significant part of the population will have intraocular lenses (IOLs) implanted in the near future based on aging and extended life expectancies. So far, only few attempts have been made to use IOLs as drug delivery agents to prevent postoperative infection (Bouledjoudja et al., 2016; Mehta et al., 2015; Pimenta et al., 2017; Vieira et al., 2017) and inflammation (Bouledjoudja et al., 2016) or posterior capsule opacification, the most frequent complication of cataract surgery (Huang et al., 2013; Wertheimer et al., 2017). As far as we know, this has not resulted in commercial applications.

3. Challenges in pharmacokinetics

Ocular drug delivery devices have demonstrated improved drug uptake over conventional drug formulations. For example, higher uptake was measured through a corneal ring (13 µg/g in the cornea and 4 µg/mL in the aqueous humour) (Shikamura et al., 2016), as compared to a topical solution (6.95 µg/g in the cornea and 1.42 ng/µg in the aqueous humor) (Silva et al., 2017). However, besides on the delivery route, the level of drug uptake can be influenced significantly by a number of factors. Pharmacokinetics of eye drops can be improved by

adapting the pH (affecting the logD7.4) (Del Amo et al., 2017) or adding additives to the formulation like frinstens benzalkonium chloride (BAC), that adds antimicrobial properties and enhances corneal permeability (Freeman and Kahook, 2014). According to some studies, EDTA enhances corneal penetration by chelation of calcium ions involved in opening of tight junctions (Ahuja et al., 2006; Grass et al., 1985; Morrison and Khutoryanskiy, 2014; Rojanasakul et al., 1990). Other studies however show no effect of EDTA in hydrophilic drugs (Pescina et al., 2016; Saettone et al., 1996) or lipophilic drugs (Grass et al., 1985; Kim et al., 2014; Madhu et al., 1996). Another enhancer for corneal permeability of lipophilic drugs is alpha cyclodextrin, which increases the solubility (Måsson et al., 1999; Pescina et al., 2016). Enhanced uptake of drugs can also be achieved by esterified compounds which are often more lipophilic (Bito and Barood, 1987). For example, compared to mice instilled with BAC enriched LA, aqueous humour concentrations of LA were five times higher in eyes of mice following treatment with LA and its choline ester (LACE) (Garner and Garner, 2016). Another example of an esterified drug is latanoprost (a prodrug from prostaglandin F2α) which increases uveoscleral outflow, thereby lowering the IOP by 20%–35% in patients with open-angle glaucoma (Digiuni et al., 2012). Latanoprost was instilled in rabbits (30 µL, 0.005% solution), which resulted in concentrations of 82 ± 35 pg/µL in the aqueous humor ($T_{\max}$ 1 h), 90 ± 34 pg/mg in the conjunctiva ($T_{\max}$ 15 min), 1202 ± 576 pg/mg in the cornea ($T_{\max}$ 15 min), and 264 ± 157 pg/mg in the ciliary body ($T_{\max}$ 15 min) (Daull et al., 2012). These concentrations are in line with results obtained in monkeys (Digiuni et al., 2012; Sjoquist et al., 1999). After topical (50 µg/mL) administration in humans, systemic latanoprost bioavailability was 45% with a maximum concentration ($C_{\max}$) of 53 pg/mL after 5 min ($T_{\max}$). About 88% of the available drug was recovered by the kidneys (Digiuni et al., 2012).

Besides additives and chemical modifications, oral supplementation of antioxidants in combination with topical nutraceutical components leads to decreased reactive oxygen species in the retina and lens, and enhances corneal permeability (Kador et al., 2014). Intravenous injections of the combretastatin A-4 prodrug (vascular disrupting agent) lead to effective drug concentrations for the prevention of neovascular age-related macular degeneration in galactose-fed dogs (Kador et al., 2007) and in patients (Ibrahim et al., 2013).

Furthermore, pharmacokinetics can be altered due to eye rotations (Bonfiglio et al., 2015; Stocchino et al., 2007), ocular diseases (Guo et al., 2017; Ho et al., 2014; Li et al., 2016), ocular surgery (Cantor et al., 2007) and coating and modification of IOL materials (Bouledjoudja et al., 2016; Huang et al., 2013; Mehta et al., 2015; Pimenta et al., 2017; Wertheimer et al., 2017).

4. Discussion and future perspectives

The continuous increase in the number of ocular surgeries, combined with low patient compliance and low drug bioavailability, warrants the development of new drug delivery methods to the eye. Fortunately, progress has been made in recent years. Although conventional drug delivery formulations, such as eye drops and ointments, are easy to use, inexpensive new drug delivery devices should guarantee higher patient compliance and higher drug concentrations at the target site. Furthermore, drug treatments can be improved by combining next generation drug formulations (such as microspheres, nanoparticles and micelles) into the new drug delivery devices and by increasing fundamental knowledge on drug pharmacokinetics.

However, the public domain often lacks crucial information, in particular on achieved drug concentrations and effects in the various intraocular tissues. This may be due to the fact that companies are not keen on sharing proprietary information. Another major reason for the paucity of pharmacokinetic data of intraocular drug concentrations is that there are no non-invasive diagnostic methods to gather these data. Only invasive sampling at the time of surgery can be used or indirect

ways of measuring drug effects, eg. measuring mydriasis when using dilating eye drops or drug delivery systems (see Table 2). This diagnostic measurement barrier makes it complex to compare new drug delivery devices to eye drops.

An important consideration with drug delivery devices is the shape of the device, since this is essential in terms of drug capacity, dislocation/retention and comfort. The question of which shape of device is most functional remains unanswered. In 1977 Katz et al. showed in a comparison study with 68 volunteers (128 rod-shaped devices and 127 oval-shaped devices) that rod-shaped devices were better tolerated compared to oval-shaped devices. Nevertheless, a number of devices of both shapes were lost after waking up by ‘rubbing the sleep out of the eyes’ (Katz and Blackman, 1977).

The idea of ocular ring structures was already patented in 1979 (U.S. 3,995,635 (Higuchi et al., 1976)) The Helios™ ring is visible whilst worn which puts forward the question of whether this is desirable from an aesthetic point of view. Other devices such as the TODDD™ or the OphthaCoil are less visible since they are covered by the eyelids. Both devices are still in the developmental phase and there is no extensive data on retention and comfort outcome parameters in humans available yet. So far, an animal study showed that the OphthaCoil was not retained in dogs, most likely due to the animal's third eyelid (nictitating membrane). Similarly, dislocation of the Ocuser® was described and was one of the reasons for market retrieval (Saetone and Salminen, 1995).

Contact lenses seem promising topical drug delivery devices. However, as they need to remain transparent and oxygen permeable (Papap, 2014) drug delivery via contact lenses is challenging. The newest advanced technologies (eg. nanoparticles (Garcia-Millan et al., 2017), micelles (Hu et al., 2016) and liposomes (Paradiso et al., 2017)) will help contact lenses to become another player in the drug delivery field.

Another way to deliver drugs is by a punctum plug, as currently executed by Ocular Therapeutix. During the first patent of the punctum plug, the possibility of ocular drug delivery was already covered (U.S. 3,949,750 (Freeman, 1976)). Although punctum plugs have shown effective drug delivery up to six weeks (Torkildsen et al., 2017), they have a limited drug loading capacity due to their small size.

Despite these challenges in drug capacity, potential dislocation and discomfort, we believe that the trend towards using ocular devices for drug delivery is inevitable, as this may take away the daily burden of administration of eye drops. For cataract surgery the concept of “dropless cataract surgery”, implying no use of eye drops around the surgical procedure anymore, has recently been introduced (Rhee and Mah, 2016).

Although the applied dose of drugs is often lower in the medical devices, the continuous and more stable release of drugs seems to be more effective and more preferred by the tissues compared to the intervals with higher doses from eye drops (Brandt et al., 2016). Another advantage of ocular devices is the absence of preservatives and absorption enhancers. It is well known that these molecules (eg. benzalkonium chloride and EDTA) can have serious side-effects on the cornea and could eventually lead to the development of intolerable discomfort and allergies. Finally, decreased use of homecare for installation of eye drops in the elderly ophthalmic patient population will result in economic benefits (Shah et al., 2015).

With respect to the ophthalmic market, today there are only two conjunctival inserts available for ‘non-invasive’ drug delivery, i.e. Mydrisart® and Lacrisert®. Although the new European Medical Device Regulation (MDR) will require more evidence on the effectiveness of new devices (for which patient compliance is pivotal, see Fig. 2), more inserts are expected to join the market in the following years. Also the FDA has recognized the need for new drug delivery devices for ocular use. The FDA now accepts first-in-human trials earlier and promised to simplify the approval process of new devices (Eydelman et al., 2016). This provides opportunities for researchers, ophthalmologists

and the ophthalmic industry to realize the goal of improved ocular drug delivery. Only by working together (academia, industry and authorities) and by exploring parallel strategies (new drug delivery devices, enhanced drug formulations, better understanding of the pharmacokinetic properties), the therapeutic effect of drug treatments can be improved.

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Conflicts of interest

The authors declare no conflict of interest.

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