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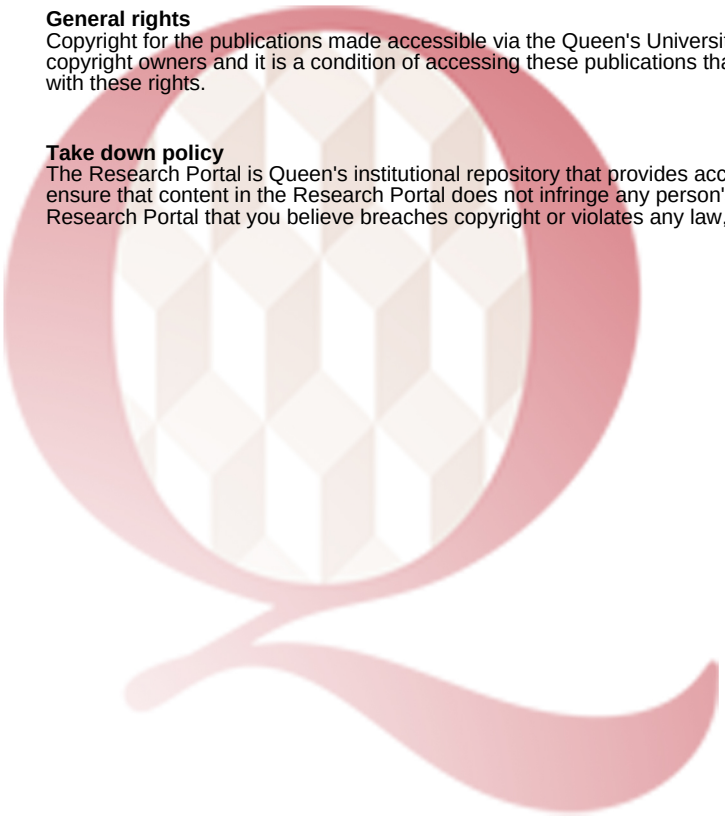

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Punctal plug: a medical device to treat dry eye syndrome and for sustained drug delivery to the eye

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Keywords: Punctal plug; dry eye syndrome; SmartPLUG™; silicone; bacterial conjunctivitis; drug-loaded punctal plugs.

Teaser: Punctal plugs are miniature medical devices used for the treatment of a variety of ocular diseases either by punctual occlusion or by providing sustained delivery of drugs to the eye.

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Punctal plugs (PPs) are miniature medical implants that were initially developed for the treatment of dry eyes. Since their introduction in 1975, many PPs made from different materials and designs have been developed. PPs, albeit generally successful, suffer from drawbacks such as epiphora and suppurative canaliculitis. To overcome these issues intelligent designs of PPs were proposed (e.g. SmartPLUG™ and Form Fit™). PPs are also gaining interest among pharmaceutical scientists for sustaining drug delivery to the eye. This review aims to provide an overview of PPs for dry eye treatment and drug delivery to treat a range of ocular diseases. It also discusses current challenges in using PPs for ocular diseases.

Introduction

Ocular diseases range from a simple inflammation (e.g. conjunctivitis) to serious loss of vision (e.g. age-related macular degeneration). Depending upon the origin of ocular disease, drug delivery can be achieved through different routes such as topical, transscleral and intravitreal. Drug delivery to the eye can also be classified anatomically into two segments, namely anterior and posterior segment drug delivery. Ocular diseases if left untreated can lead to partial or complete loss of vision. For example, anterior segment diseases that can cause serious vision impairment include eyelid anomalies (e.g. Sjögren's disease, injuries, radiation or mucin deficiency), glaucoma, bacterial keratitis, uveitis, herpes simplex keratitis, refractive surgery, blepharitis and dry eye syndrome (DES) or keratoconjunctivitis. Similarly, chronic posterior segment diseases such as diabetic retinopathy, diabetic macular edema, age-related macular degeneration and other chorioretinal diseases can lead to vision impairment or blindness if left untreated.

Development of therapeutics for treatment of ocular diseases is a challenging task for pharmaceutical formulators and scientists. This is because of the sensitivity of the ocular tissues and the presence of various physicochemical and biological barriers for drug delivery. Of the different routes of drug delivery, topical administration (e.g. eye drops) remains the most widely accepted and preferred route of administration because of its ease of access and patient compliance. However, the bioavailability of topically administered drugs is compromised by factors such as blinking, tear production and barrier function of the cornea, which allows only 1% or less of the total dose to be administered. Thus, drug delivery modalities that can increase drug bioavailability (extending the duration of release, decreasing the amount of drug delivered,

minimizing systemic exposure and improving patient compliance and adherence) will certainly offer many advantages over conventional eye drops [1,2]. Some of these approaches include use of mucoadhesives, prodrugs, nanospheres, liposomes, inclusion of permeability enhancers, implants and punctal or punctum plugs (PPs). This review will focus on the ocular applications of PPs. First, it reviews the use of PPs as a medical device initially developed to physically block the puncta of the eye to treat DES. Second, it reviews the application of PPs for drug delivery to the anterior segment of the eye.

Dry eye syndrome

DES or keratoconjunctivitis sicca is one of the most common ocular disorders frequently discussed in the office of eye-care specialists. In the USA, the average annual cost of managing a patient with DES was US$783 (or US$3.3 billion in total) in 2011. Furthermore, from a societal perspective it was estimated that DES costs US$11 302 per patient (or US$55.4 billion overall) in the USA [3]. The symptoms of DES often include dryness, photophobia, burning and stinging, itching, eye fatigue, pain and redness (hyperemia) [4,5]. DES is estimated to affect between 14% and 33% of the population worldwide, henceforth it is a significant public health concern [6]. The pathophysiology of DES usually includes poor production of the ocular tear film and evaporation of tears. In addition, causes of DES include formation of unstable tear film associated with abnormality of the lipid, protein and mucin profiles and inflammation of the ocular surface and tear producing glands [4]. Better understanding of complex pathophysiology and underlying mechanisms of DES has led to development of numerous pharmacological and nonpharmacological treatment options for DES. However, a detailed discussion on treatment of DES is out of the scope of this review, readers can refer to reviews in the literature [7–11].

Treatment of DES

There is no cure for DES but there are treatment strategies to mitigate symptoms. For example, the National Health Service in the UK provides a range of choices for treating DES. The primary nonpharmacological treatment of DES involves the use of tear substitutes, also called artificial tears or lubricant treatment, that consist of a range of drops, gels and ointments. Tear substitutes improve lubrication and enhance humidity at the ocular surface. Tear substitutes usually contain additives such as polymers including carboxy methyl cellulose, polyvinyl alcohol, hydroxypropyl methylcellulose or carbopol 940, which act as lubricants, buffers to maintain the pH of natural human tears (pH 7.4) and electrolytes to maintain osmolarity [12–15]. However, use of artificial tears will provide short-term symptomatic relief but will not solve the underlying problem with long-term DES: inflammation. In such cases, anti-inflammatory treatments are prescribed such as steroid eye drops and ointments, oral tetracyclines and cyclosporine eye drops. Another alternative in treating DES is the use of PPs, which is discussed in greater detail in the sections below.

PPs for DES and other ocular applications

Punctal or tear duct occlusion involves temporary blocking of the puncta using PPs or permanent blocking by cauterizing [16]. Blocking the punctum results in increased tear fluid accumulation and thus keeps the eye moist. PPs cause occlusion of tear drainage by blocking the tears through the canaliculi, which connects the eye to the nose (Figure 1). Because of their ability in tear preservation, PPs are indicated in certain cases of laser *in situ* keratomileusis and contact lens

intolerance [17]. It was also reported that insertion of PPs improves tear film stability, tear osmolarity and functional visual acuity in dry eye patients [18,19].

Unlike temporary or short-term relief provided by the artificial tears, PPs can provide long-term relief owing to enhanced tear retention and, therefore, enhanced patience compliance. Although developed initially to physically block the puncta, PPs have also been engineered for controlled drug delivery enabling treatment of DES and other anterior ocular conditions [20]. Foulds introduced the first PPs in 1961, which involved dissolvable gelatin implants to block the puncta temporarily [21]. Recently, Qiu *et al.* reported a clinical study that compared efficacy of PPs versus artificial tears for treating primary Sjögren's syndrome with keratoconjunctivitis sicca. The results indicated that punctal plugs were significantly better at improving dry eye symptoms in comparison with artificial tears [22]. However, in 1975, Freemen developed the modern PP design that was a dumbbell-shaped plug made of silicone. To date, this concept of plug designs remains the prototype and, recently, a number of designs were developed either to enhance plug retention or to provide drug delivery or both [23].

PPs are either semi-permanent or temporary depending on the material used for their preparation. Semi-permanent PPs are made using silicone, Teflon®, hydroxyethyl methacrylate (HEMA), polycaprolactone (PCL) or polydioxanone; and temporary PPs are made from animal collagen. Semi-permanent PPs either dislodge spontaneously or should be removed by a physician. Plugs fabricated using collagen dissolve within four to seven days; or certain polymer-based plugs last for variable periods of time ranging from three days to six months [13,24,25]. Table 1 lists a few examples of currently marketed PPs that have been fabricated from different materials. For an extensive list readers are requested to refer to [26]. The plugs are either preloaded onto an

applicator or applicator/inserters are provided to aid application into the eye. To facilitate insertion of PPs across the punctum local anesthesia and/or a lubricant is applied.

Although insertion of PPs is an effective therapy for treatment of DES many complications are associated with their use. Some of the recognized complications of PPs include epiphora (overflow of tears), suppurative canaliculitis (infection of the lacrimal gland causing surface abnormalities), punctal ring rupture or spontaneous dislodging and abrasion of the corneal and conjunctival surface [29-32]. Therefore, the criteria for designing the PP is dependent upon many factors such as the purpose of application (tear retention or drug delivery), required length of retention (short-term or long-term), patient compliance and/or commercial value. Interesting examples of various PP designs were proposed by Eagle Vision, as shown in Figure 2. Here, assorted PP designs have been engineered from silicone. Similarly, to enhance retention of PPs in the puncta, SmartPLUG™ (Medenium, CA, USA) was developed. SmartPLUG™ is made from biocompatible hydrophobic thermosensitive copolymer compositions of poly (stearylmethacrylate) (SMA) with methylmethacrylate (MMA). These polymeric materials are blended to form a composition, which has a glass transition temperature (T_g) or melting temperature (T_m) at or below human body temperature (37°C). SmartPLUG™ is a slender rod that is solid at room temperature with a diameter of 0.4 mm and length of 9 mm prior to insertion. After insertion into the ocular channel the diameter increases up to 1 mm and its length decreases to 2 mm. This expansion results in the adaptation and subsequent fixation of SmartPLUG™ to the size and shape of a patient's punctum or canaliculum [18,33]. In another attempt to improve patient tolerability of PPs, Form Fit™ intracanalicular plugs were developed. Form Fit™ plugs are made of a hydrogel containing hydrophilic and hydrophobic domains. The hydrogel is prepared by copolymerizing a hydrophilic monomer such as water-soluble *N*-vinyl

carbazole with a hydrophobic monomer *N*-vinylpyrolidone derivative. The hydrogel expands into a soft, pliable, gelatinous material after coming into contact with tear film. Form Fit™ plugs absorb tear fluid and expand 20-times in volume after approximately 10 min of insertion, filling and conforming to the size and shape of the vertical canaliculus [34,35].

PPs as controlled drug delivery implants

Since the introduction of PPs for the treatment of dry eyes by Freeman in 1975 [23], many different types of PPs have been developed and are in widespread use. PPs have recently been investigated for the controlled delivery of drugs to the tear fluid of the eye and the nasolacrimal duct. PPs can offer numerous advantages over topical drug delivery such as reduction in loss of drug and/or formulation owing to tear formation, reduction in lacrimal drainage of drug, ability to achieve controlled drug delivery, patient compliance and possibly reduced costs.

Drug loading and drug release from PPs can be achieved in different ways (Figure 3). For example, the drug can be loaded within the core of the PPs within the surrounding impermeable layer: the drug essentially diffuses out from the cross-section which is in contact with tears (Figure 3). Alternatively, pre-formed plugs can be coated with drug solution; however, considering the dimensions of the PP, the quantity of drug coating might be limited owing to the small surface area. Nevertheless, drug-releasing PPs not only improve the ability of drug to avoid rapid clearance from the ocular surface but also release the drug into the ocular cavity for an extended period of time.

The latanoprost PP delivery system (L-PPDS) was recently developed for controlled elution of latanoprost for the treatment of open-angle glaucoma (OAG) and ocular hypertension (OH). The L-PPDS comprises a reservoir containing a polymeric blend of latanoprost which is housed in a

PP and this reservoir has an opening through which drug will be released after coming into contact with tear film. A 44 µg L-PPDS has one-third the amount of drug in latanoprost eye drops given continuously over three months [36]. L-PPDS recently completed a Phase II clinical trial evaluating the safety, efficacy and dosing for the treatment of OAG and OH patients. Results have indicated that L-PPDS showed positive efficacy trends with statistically and clinically significant findings [37]. The PP device used in L-PPDS is also being investigated as a platform to deliver the anti-allergy drug olopatadine for treatment of patients with allergic conjunctivitis. Interim results from a Phase II proof-of-concept trial have shown that olopatadine PP drug delivery system (O-PPDS) did not show significant difference in efficacy when compared with placebo-PPDS with respect to reduction in the signs and symptoms of allergic conjunctivitis [38]. The reason for the lack of efficacy of O-PPDS was reported to be due to the environmental exposure chamber (EEC) model utilized in the trial not being sensitive enough to demonstrate the potential benefit of the O-PPDS [39]. Latanoprost was initially loaded into PLGA microspheres and incorporated into hydrogel-based PPs. The *in vitro* release profile of latanoprost from PPs has shown that drug is released up to 90 days and the release profile is dependent upon PLGA crosslinking and its chemical nature. Moreover, the PPs did not show any initial burst release of latanoprost in any of the formulations [40].

Gupta and Chauhan reported a cyclosporine-A-releasing PP delivery system for treating dry eyes. These PPs consisted of a cylindrical hydroxyl ethyl methacrylate (HEMA) cross-linked with an ethyeneglycol dimethacrylate (EGDMA) core containing cyclosporine microparticles covered by an impermeable silicone shell. Cyclosporine A was released for three months at a zero-order rate of about 3 µg/day [41]. The *in vitro* release studies have shown that PPs with drug loading of 20% released drug at a rate of 3.5 µg/day for a period of one month without any

initial burst release. The release was reasonably zero-order for the first ten days for these PPs. However, the release was decreased when crosslinking of HEMA with EGDMA was increased and the release profile was non-zero-order for the entire duration. An ocular pharmacokinetic model was developed by performing a mass balance on the drug released into the ocular tear film. This model predicted that the *in vivo* release of cyclosporine A from PPs is approximately 1.5 µg/day with an ocular bioavailability of 64% [41].

In another study, PPs loaded with antibiotic moxifloxacin (MOX) were developed (Ocular Therapeutix, MA, USA) for extended delivery of the drug for the treatment of bacterial conjunctivitis. This PP comprises a dried polyethylene glycol hydrogel rod that is embedded with MOX-encapsulated microspheres that release drug for ten days. The PPs released MOX at a concentration greater than the target concentration of 250 ng/ml, which is the target minimum inhibitory concentration (MIC_{90}) up to ten days as calculated from mean tear fluid concentrations. However, the concentrations of MOX were below detectable limits at day 20 and day 30. A clinical study has reported that MOX-PPs were well tolerated, released and maintained MOX tear fluid concentrations at therapeutic levels above the MIC_{90} values for seven days for common susceptible conjunctivitis pathogens [42]. These studies clearly indicate the potential of PPs for controlled delivery of drugs to the eye.

Chee assessed the safety and feasibility of a MOX-loaded PP in cataract patients. After cataract surgery, MOX was inserted into the punctum and follow-up assessments were continued for 30 days. The study was conducted in two groups and each group consisted of ten cataract patients. It was observed that the retention of MP in the punctum was 95% to day ten in 19 patients and all plugs were absent at day 30 for both studies. MP was delivered and maintained drug concentration in the tear fluid at therapeutic levels (above 250 ng/ml) for seven days and

exhibited a favorable safety and tolerability profile. It was concluded that it might be a viable alternative to topical antibiotic drops for the treatment of bacterial conjunctivitis [42]. Ocular Therapeutix conducted a single-site, single-armed, single-dose study using a pool of ten patients and implanted a novel sustained drug delivery MOX-PP immediately following cataract surgery. The patients were evaluated over a ten-day period. The MOX-PP achieved 100% retention in all ten patients and drug levels were maintained well above MIC_{90} (2000 and 3000 ng/ml). Hence, the results demonstrated the sustained levels of MOX throughout the ten-day treatment period. Furthermore, there were no adverse events and ocular complaints outside the normal post-cataract symptoms [43].

Overall, drug-loaded PPs are potential devices for improved delivery of drugs to the ocular cavity. Drugs that have poor ocular bioavailability can be loaded into PPs with a desired release rate with significantly enhanced bioavailability. The polymeric composition of PPs can be modified to obtain the desired release rate of a drug based on requirements of the disease condition. Furthermore, a few studies have also reported combination of topical eye drops with PPs that has resulted in enhanced drug delivery to the eye [44]. This clearly indicates the overarching advantages of using PPs over conventional eye drop preparations that need frequent dosing.

Current challenges of using PPs

Although PPs have demonstrated their advantages as drug delivery vehicles for the treatment of DES, their use is associated with complications including mechanical conjunctivitis, plug extrusion, spontaneous distal migration, epiphora, corneal abrasion, suppurative canaliculitis, dacryocystitis and distal lachrymal system blockage [26,29]. In a study with silicone plugs (FCI

Ophthalmics) spontaneous loss happened in 14.7% after three months, 27.3% after one year and 36.8% after two years [45]. In another study involving the modified Freeman 'tapered-shaft' plug (Eagle Vision) and SoftPlug™ (OASIS Medical), it was reported that 47% spontaneous loss occurred at six months with the majority being lost in the initial three months of the study [24]. The reasons for PP extrusion were attributed to mucosal dissection by the plug edges leading to necrosed tissue and pyogenic granuloma formation [46]. Migration of the PP into the lacrimal drainage system is another major complication that could require surgical intervention for removal of the plug. The migrated plug can cause canaliculitis and dacryocystitis owing to a local inflammatory reaction triggered by allergens and debris attracted by the negatively charged surface of the silicone [47]. Complications such as punctal and proximal canalicular stenoses after plug extrusion or migration were reported in a frequency of 25.7% during a period of 32 months [46]. In a separate study, canalicular stenosis occurred in 14.3% after three months, 26.9% after one year and 34.2% after two years [45].

Epiphora, which is the production of excessive tears, is another complication associated with use of PPs. It was reported that mild epiphora occurs in up to 36% patients. Although most patients tolerate the epiphora, up to 5% request removal of the plugs [48]. Pyogenic granuloma leading to plug extrusion was reported to occur for the silicone plug and SmartPLUG™. In a study conducted in 404 patients with silicone PPs, pyogenic granuloma resulted in extrusion of 4.2% of all plugs inserted after a median time of 141 days. Furthermore, large plug size was considered to be the major risk factor leading to granuloma formation [47]. In a retrospective study of SmartPLUG™ with 28 patients, 64.3% had canaliculitis, dacryocystitis or conjunctivitis [49]. A more recent study with a total of 1026 patients receiving SmartPLUG™ was reported by Fezza *et al.* [50]. According to the published results, the average time to develop canaliculitis after

SmartPLUG™ insertion was 2.7 years with the lower left lid being the most common site, followed by the right lower, right upper and left upper lids. The study reported a total of 61 cases of SmartPLUG™-induced canaliculitis representing 6.0% canaliculitis rate [50]. Overall, based on results from clinical studies, the reasons for complications relating to PPs can be attributed to effects of design, sizing and method of insertion.

Concluding remarks

PPs offer a safe and effective treatment for the patients with aqueous deficient dry eye and/or for sustaining drug delivery to other conditions. The patients often benefit with symptomatic relief and clinically measurable improvements. Therefore, this therapeutic approach can improve the quality of life of many patients with severe conditions associated with the anterior segment of the eye (e.g. dry eye or other infections). Careful selection of the optimal plug size and continuous follow-up would be beneficial to maximize the success rate of the treatment. Based on the progress achieved so far and the number of therapies in the pipeline, the future of PP-based dry eye therapy or drug delivery seems optimistic. However, the experience and knowledge gained from previous clinical studies will be helpful in overcoming many of the current drawbacks, so that newer and effective PPs can be designed for simply blocking the puncta (for DES) and/or sustaining drug delivery to the anterior segment of the eye. It is too early to comment on PP application for posterior drug delivery. However, following successful demonstration of anterior drug delivery, technologies such as specialized nanoparticle loaded PPs can be sought for long-acting posterior drug delivery.

Conflicts of interest

The authors do not have any conflicts of interest to declare.

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Figure legends

Figure 1. Schematic illustration of punctum location (inset) and placement of punctual plugs (PPs) in the punctum of the eye.

Figure 2. Schematic representation of assorted designs of silicone-based punctual plugs (PPs), where each design has been claimed to provide a unique advantage to the dry eye syndrome (DES) patients. **(a)** PLUG1™ (CE marked) is a unique dual-lobed design that allows it to fit a wide range of punctum sizes. **(b)** SUPEREAGLE® (CE marked) design uses soft and low durometer silicone that claims to provide "super patient comfort". The tapered shaft and pivoting wide-flex nose design allows "super retention", available in three different sizes. **(c)** SUPERFLEX® is claimed to be a better fit design that is easier for insertion and provides greater patient comfort. This device is available in multiple sizes. **(d)** EAGLE FLEXPLUG™ is the only tapered shaft™ PP with contouring traction ribs. This design is claimed to provide the ultimate in flexibility, fixation and patient comfort. **(e)** EAGLEPLUG® is an easy to insert and remove design [51].

Figure 3. Schematic illustration of a punctal plug delivery device.

Table 1. List of different types of PPs that were fabricated in different shapes and from different biodegradable and nonbiodegradable polymeric materials

Highlights:

- Punctal plugs (PPs) are miniature medical devices that are used to block puncta to treat dry eye syndrome
- PPs are currently been investigated as sustained-release drug delivery devices
- Sustained-release PPs can be used to treat a range of anterior segment eye diseases
- Drug-loaded PPs showed improved ocular bioavailability when compared to eye drops
- PPs with nanoparticles can achieve drug delivery to the posterior segment of the eye

Figure 2

Figure 1 New

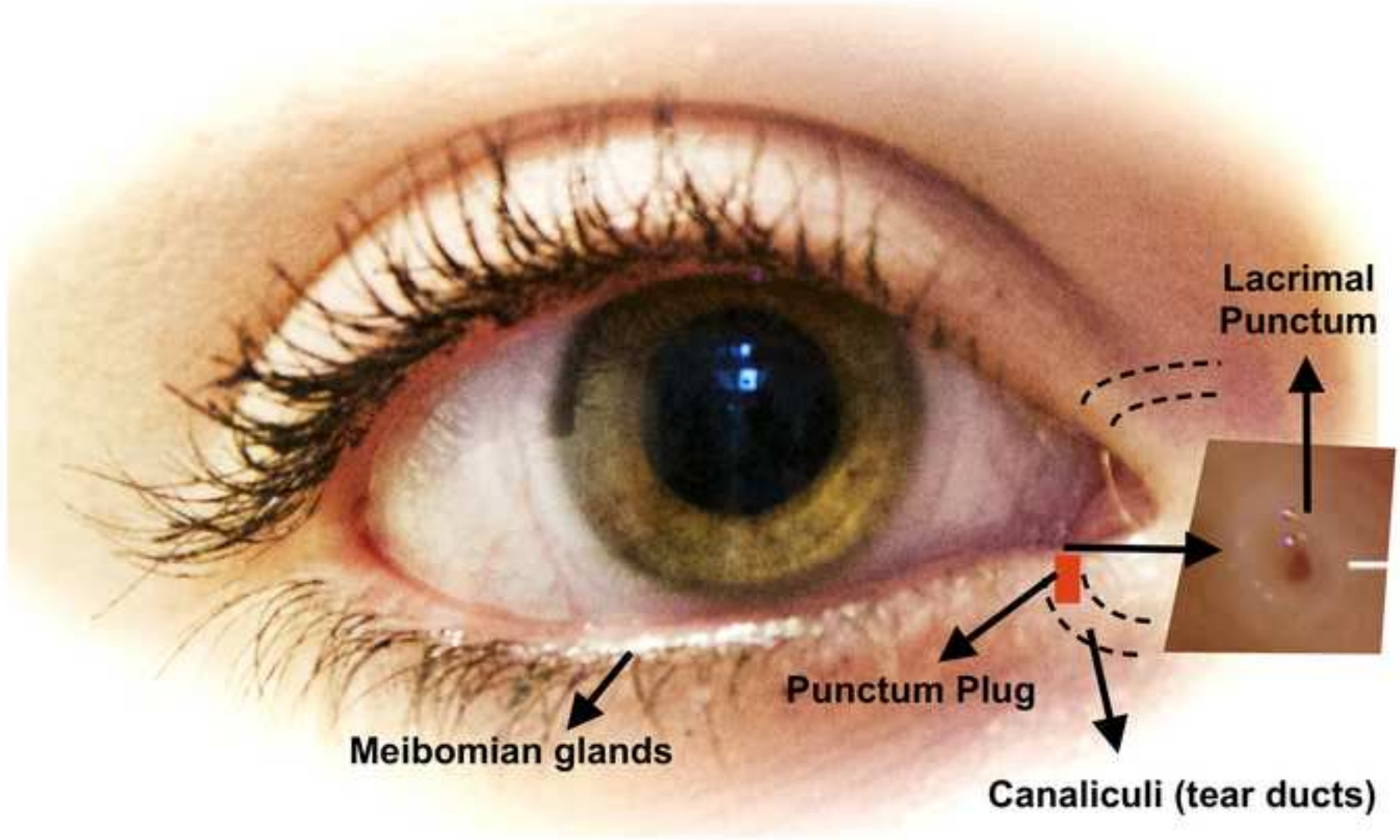
Lacrimal
Punctum
Punctum Plug
Meibomian glands
Canaliculi (tear ducts)

Figure 3 New

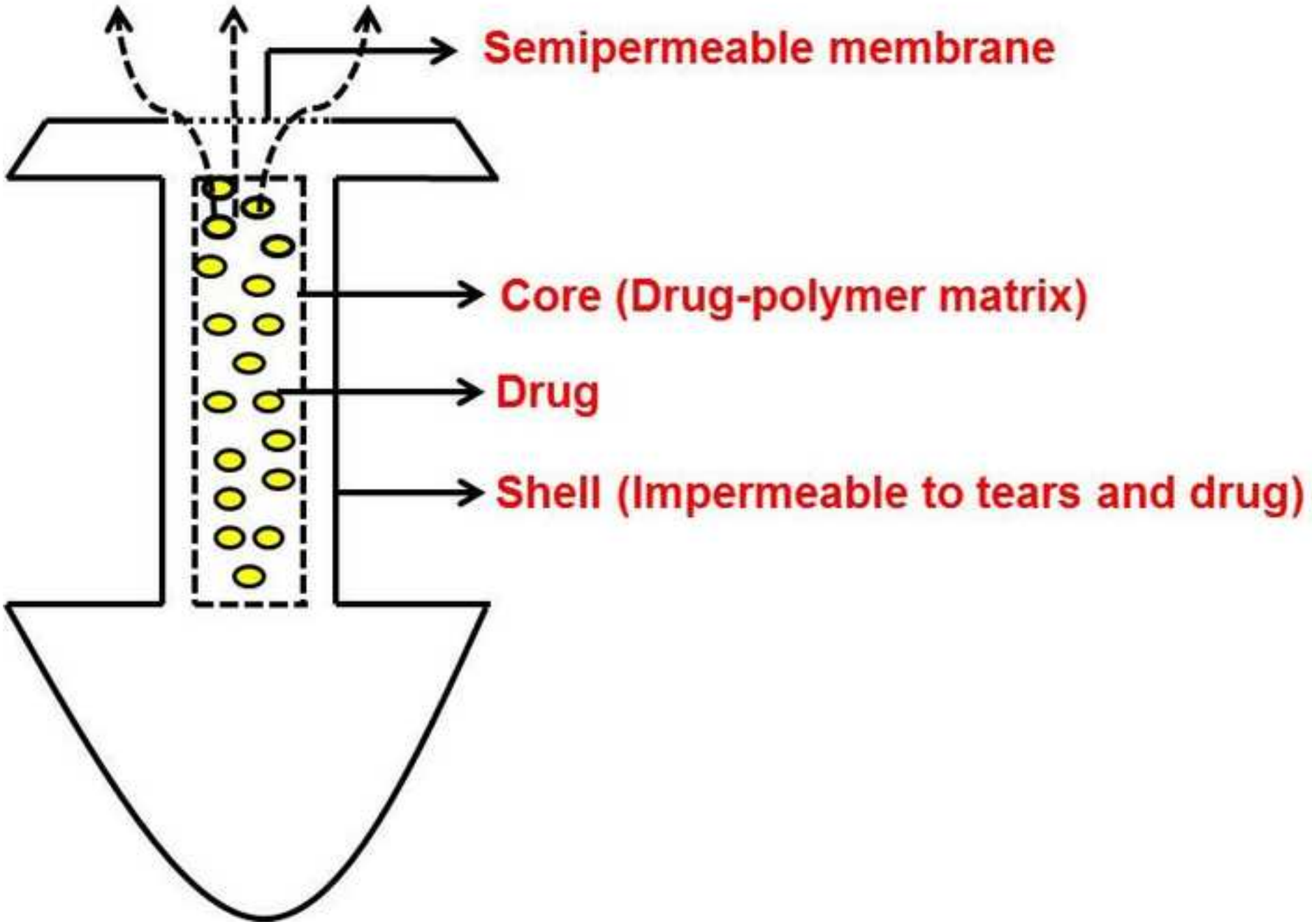
Semipermeable membrane
Core (Drug-polymer matrix)
Drug
Shell (Impermeable to tears and drug)

Table 1. List of different types of PPs that were fabricated in different shapes and from different biodegradable and non-biodegradable polymeric materials.

Brand	Design	Dimensions	Composition	Application	Ref
SOFT PLUG Collagen	Rod-shaped	2 x 0.2 mm, 2 x 0.3 mm and 2 x 0.4 mm	Collagen. Absorbable within 2-5 days	For short-term, diagnostic, and postsurgical occlusion.	[27]
SOFT PLUG Silicone Plugs	Pointed nose to allow easy insertion with large anchor with wide shelf firmly secures plug making dislocation.	0.4, 0.5 and 0.7 mm with 0.8 mm diameter	Medical grade Silicone	Control of tear drainage through the canaliculus	[27]
FORM Fit	Semi-rigid rod	0.3 x 2.5 mm 0.3 mm one size fits all	Polyvinyl pyrrolidinone (PVP) based Hydrogel.	Hydrates over a 10 min period. Upon contact with Tear fluid, the plug will slowly swell to approx. 3 times its initial size to completely fill the vertical canalicular cavity.	[27]
SOFT PLUG Extended Duration Plugs [http://oasismedical.com/dry-eye-products.html]	Rod-shaped design	2 x 0.2 mm, 2 x 0.3 mm, 2 x 0.4 mm, & 2 x 0.5 mm	Absorbable copolymer of glycolic acid and trimethylene carbonate and dyed with D&C Green Number 6.	Block tear drainage. Less than 3 months	[27]
Snug Plugs™	Preloaded in a stretched position, returning to their natural shape when released in the punctum	NA	Medical grade silicone	Dry eye	[28]
Ready-Set"	Collarette plugs	0.4 to 1.0 mm diameter	Medical grade silicone	Dry eye	[28]