Advances in Clinical Optometry: Ophthalmic Drug Therapy and Drug Delivery System

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ABSTRACT

***Background*:** Ocular drug delivery system refers to the approaches, formulations and technologies, for transporting a pharmaceutical compound in the eye in order to safely achieve the desired therapeutic effect. The conventional topical eye drop solutions, emulsions, suspensions and ointments, although being the most convenient and patient compliant route/system of drug administration, can hardly maintain therapeutic drug levels for a long duration in target tissues. Some other drug delivery systems which are also relatively new, in terms of widespread adoption include sustained-release implants and inserts.

***Objective*:** Since medications in general constantly require modifications in chemical constituents, formulation and also in their delivery systems for improved efficacy, novel, safe and patient compliant formulations such as suspensions and implants, and drug delivery devices/technologies such as contact lenses and eye drop dispensers capable of delivering and maintaining consistent drug levels in target tissues are continually being developed; enhancing ocular bioavailability of therapeutics through micro dosing and sustained drug release.

***Methods*:** This was basically peer reviewed by the researchers after searching through literatures objectively to bridge the missing gaps.

***Result*:** Most of the over-the-counter (OTC) drugs do not require the USA Food and Drug Administration (US-FDA) approval, provided they meet the basic requirements but this review discovers that there are a few approved novel ones that have outstanding therapeutic indices that can be used for better management of the eye patients.

***Conclusion*:** Optometrists and other eye care practitioners should therefore take advantage of these novel drugs to improve their practices for better patient management outcomes.

Keywords: Advances in clinical optometry, Ophthalmic drug delivery system, Ophthalmic drug therapy Optometrists and therapeutic effect.

1.0 INTRODUCTION

Ocular drug delivery system refers to the approaches, formulations and technologies, for transporting a pharmaceutical compound in the eye in order to safely achieve the desired therapeutic effect. The conventional topical eye drop solutions, emulsions, suspensions and ointments, although being the most convenient and patient compliant route/system of drug administration, can hardly maintain therapeutic drug levels for a long duration in target tissues. Some other drug delivery systems which are also relatively new, in terms of widespread adoption include sustained-release implants and inserts. Ocular drug delivery remains one of the most challenging tasks for pharmaceutical scientists partly because the unique structure of the eye restricts the entry of drug molecules at the required site of action. Drug delivery to the eye can be broadly classified into anterior and posterior segments. About 90% of marketed ophthalmic formulations are developed for drug delivery to the anterior segment of the eye via the topical route and involves the conventional dosage forms, such as solutions (62.4%), suspensions (8.7%), and ointments (17.4%) [3]. Less than 5% of the topically administered drug enters the eye [12, 22]. The remaining 95% either encounter the corneal epithelial barrier or is washed off from the eye by other mechanisms such as lacrimation, tear dilution and tear turnover, resulting in poor retention time, decreased permeability across the corneal epithelium, and consequently, low ocular bioavailability of drugs [5].Other factors that determine the topically applied drug concentration are the volume of the instilled drug solution and the patient's age. Larger instilled volumes easily pass into the nose from the nasolacrimal duct while smaller volumes are easily eliminated from the lacrimal sac [18] hence, the need to review the topic as regards advances in clinical optometry.

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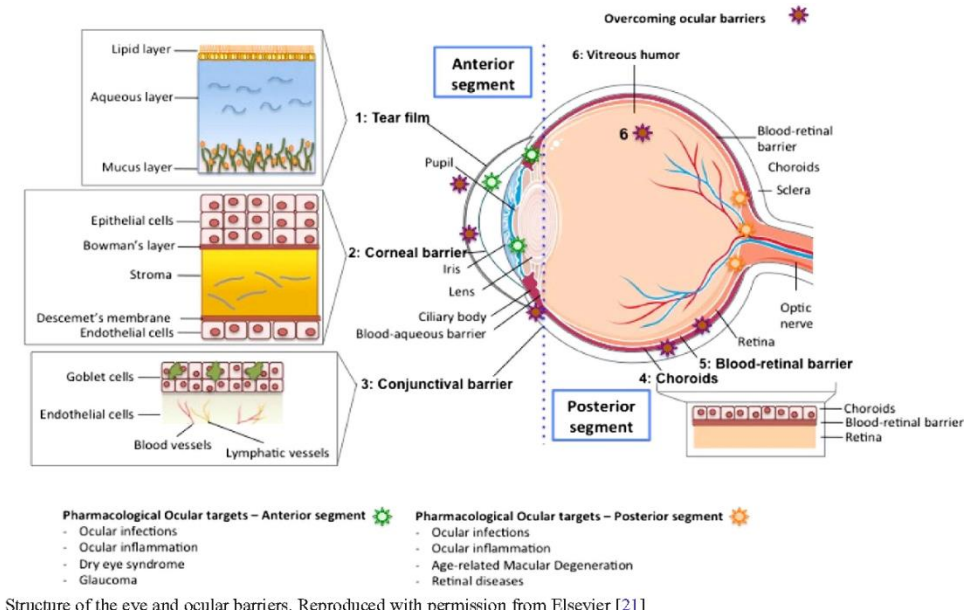


Structure of the eye and ocular barriers. Reproduced with permission from Elsevier [21]

Figure 1: Showing structure of the eye and ocular barriers[27]. Copyright 2015, Elsevier.

1.1 Some Anterior Segment Drug Delivery Barriers

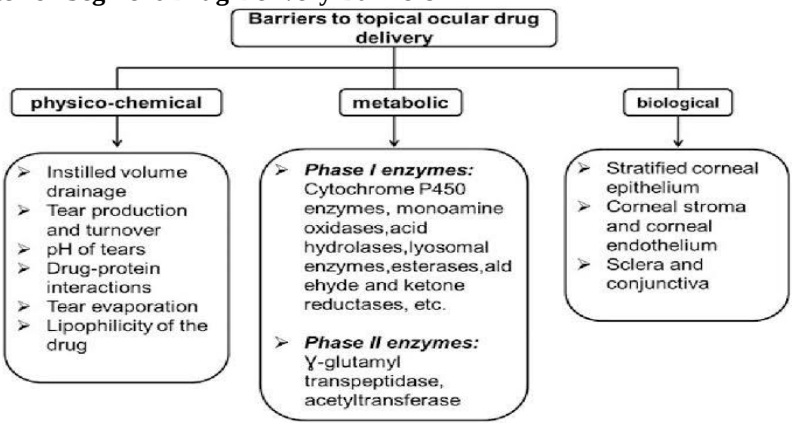


Figure 2: Showing summary of barriers to topical ocular drug delivery[38]

1.1.1 Epithelial Tight Junction

The corneal epithelium forms the primary barrier to topical drug absorption. It is stratified, consisting of a basal layer of columnar cells, two to three layers of wing cells and one to two outer layers of squamous cells [19]. Superficial cells are surrounded by intercellular tight junctions (*zonulaoccludens*) (which are composed of anastomotic strands) that confer resistance to the paracellular drug absorption [13].

1.1.2 Reflex Blinking

While a regular eyedropper delivers an average of about 50µL of the topical formulation [23], an eye can transiently contain about 30µL, and the rest is lost either by reflex blinking (about 5 to 7 blinks/min) [12] or nasolacrimal drainage, significantly decreasing the quantity of drug available for therapeutic action[12].

1.1.3 Tear turnover

With a volume of about 7µL to10µL, the tear film turns over at the average rate of about 1.3µL/min in humans [23]. The increase in volume of cul-de-sac following topical administration leads to reflex blinking and increased tear secretion; hence, rapid drug loss from the precorneal area (Lee and Robinson, 1979) [20] (due to tear turnover and nasolacrimal drainage) until the tear volume in the conjunctiva cul-de-sac returns to a normal range (7µL to 9 µL) [12].

1.1.4 Nasolacrimal Drainage

This pathway includes the puncta, canaliculi, lacrimal sac, and nasolacrimal duct. Following topical application, the eye drop solution mixes with lacrimal fluid and approximately half of the drug flows into the upper canaliculus and the rest into the lower canaliculus of the lacrimal sac. This flow continues into the nasolacrimal duct, and from there, drains into the nose [6]. Owing to the constant production of lacrimal fluid, the contact time of the drug with ocular tissues is approximately 1 to 2 min [3].

1.1.5 Efflux Pumps

The efflux proteins either restrict or enhance drug absorption depending on their cellular localization, and are located either on the apical or basolateral cell membranes [21]. Two major efflux pumps are responsible for drug resistance: The P-glycoprotein (which is responsible for preventing entry of amphipathic compounds in normal and cancer tissues); and the Multidrug Resistant Protein (MRP) (which is known to efflux organic anions and conjugated compounds) [22, 32].

1.2 Conventional Ocular Drug Delivery Systems

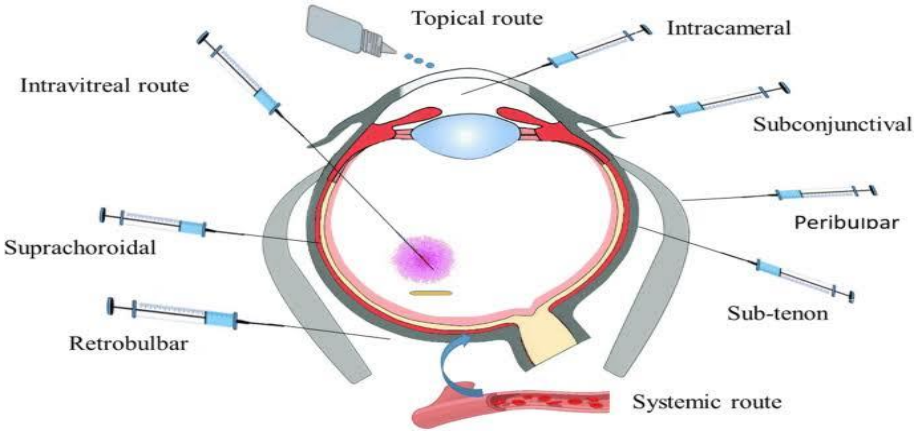


Figure 3: Showing popular routes of ophthalmic drug delivery (Gaballa et al., 2021)[11].

1.2.1 Topical liquid/solution eye drops

Topical drops have been attributed the most convenient, safe, patient-compliant and non-invasive mode of Ocular drug administration [36]. An eye drop solution stays only about less than 5 minutes on the ocular surface following topical administration (McDonald, 2019). To improve drug contact time, permeation and ocular bioavailability, various additives may be added to topical eye drops thus: viscosity enhancers (e.g. hydroxymethyl cellulose and polyvinyl alcohol) [36]; permeation enhancers (e.g. also includes some preservatives such as benzalkonium chloride, ethylene diaminetetraacetic acid, sodium salt); and cyclodextrins.

Viscosity enhancers improve formulation viscosity thereby improving precorneal residence time and bioavailability while permeation enhancers modify the corneal integrity to improve corneal uptake. Viscosity enhancers and cyclodextrins suffer from the disadvantage of precorneal loss, and care should be taken in the selection of penetration enhancers due to the high sensitivity of ocular tissues [36].

1.2.2 Emulsions

Emulsions have the advantage of improving both solubility and bioavailability of drugs[21]. Two types of emulsions widely employed in ophthalmic drug formulations are: oil in water (o/w) and water in oil (w/o) emulsion systems. The o/w emulsion is more common and widely preferred over w/o system in ophthalmic drug delivery due to less irritation and better ocular tolerance of o/w emulsion [36, 37].

1.2.3 Suspensions

Suspensions are usually insoluble in aqueous solvents, and consist of a suitable suspending and dispersing agent. Suspension particles improve drug contact time and duration of action relative to drug solution by retaining in precorneal pocket. While larger sized particles are retained for longer time and slow drug dissolution, smaller sized particles replenish the drug absorbed into ocular tissues from precorneal pocket. Hence, duration of drug action for suspensions is dependent on particle size [25].

1.2.4 Ointments

Ointment formulations also help to improve ocular bioavailability and sustain the drug release. Ointments used in ophthalmic practice are made up of a mixture of semisolid and paraffin, a solid hydrocarbon that has a melting point at 34°C (which is the physiological ocular temperature). The choice of hydrocarbon is always dependent on biocompatibility [25].

2.0 Advances in Ophthalmic Drug Therapy and Drug Delivery System

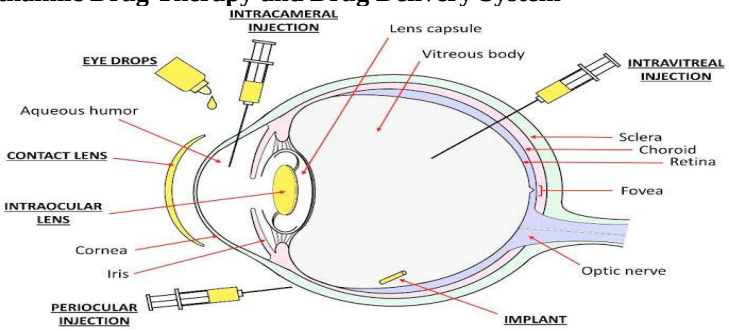


Figure 4: Showing both popular and novel ophthalmic drug delivery routes (https://google.com/)

2.1 Topical ophthalmic drug delivery Route

- Presbyopia treatment drops: Vuity™ -via miosis
- Xelpros (Benzalkonium Chloride free latanoprost);
- Rho-kinase Inhibitors for Glaucoma and Ocular hypertension: Rhopressa (netasurdil ophthalmic solution 0.02%), Roklatan (netasurdil/latanoprost.)
- Neurotrophic Keratitis: Oxervate (Cenegermin, DompÃ©)

Other ophthalmic drug delivery routes/vehicles

- Antimicrobial coatings for contact lenses
- Microdosing –Eyenovia'sOptejet eye dropper.
- Bimatoprost sustained release implant (Durysta);
- Dexamethasone plugs: Dextenza;
- Post Operative inflammation: Eyepoint'sDexycu –neo intracameral dexamethasone suspensions 9%

2.1.1 Presbyopia Treament Drops (Vuity™)

Figure 5: Showing Vuity™ (Pilocarpine HCl, 1.25%) Eye drop (https://www.empr.com/drug/vuity/)

The FDA has approved the use of Pilocarpine HCl 1.25% for the treatment of presbyopia. This formulation like regular miotics contracts the pupil size in a pin-hole camera effect thereby increasing dept of focus and improving near vision [14].

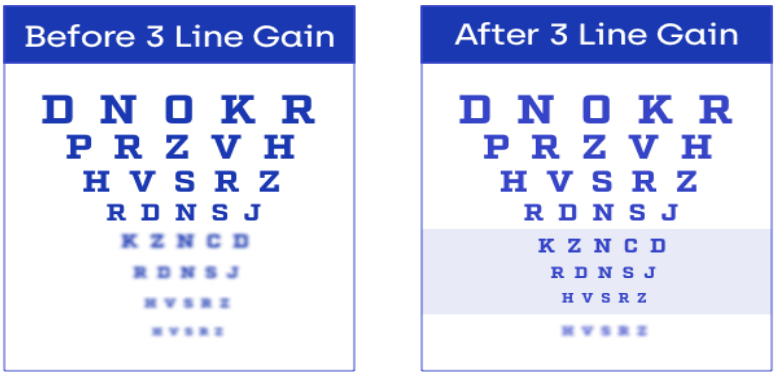


Figure 6: Illustrating improvement in near visual acuity following instillation of Vuity™ Eye drop (https://vuity.com).

This formulation is commercially available as Vuity™ and unlike regular miotics is capable of adjusting to the tear film pH to between 3.5 and 5.5, is administered once daily and begins acting after about 15 minutes, improves near vision up to 6 hours (up to 3 line gain) and intermediate vision up to 10 hours (Harrison, 2021), without losing up to one line in distance visual acuity (https://vuity.com). It contains 0.0075% benzalkonium chloride (BaK) as preservative, other inactive ingredients, and hydrochloric acid and/or sodium hydroxide for the pH adjustment (Harrison, 2021).

Unlike other miotics initially used for presbyopia control which were usually instilled in one eye to preserve vision in dim light in the other eye, Vuity™ can be instilled in both eyes. It also has reduced stinging and side effects [15]. Side effects include headache and eye redness. It is to be used with caution when performing activates with poor lighting e.g. driving at night (https://vuity.com).

2.1.2 Rho-Khinase (Rock) Inhibitors For Glaucoma And Ocular Hypertension (Rhopressa and Roklatan)

Figure 7: Showing the Rho-kinase inhibitor Eye drops (Samaniego, 2020).

The FDA has approved two new glaucoma medications classified as rho-kinase inhibitors. They are Aerie's Rhopressa (netasurdil ophthalmic solution 0.02%)[29,30].
These ROCK inhibitors directly decrease resistance to the conventional outflow of aqueous humour, thereby significantly lowering intraocular pressure (IOP). The rho-associated protein kinase (ROCK) has been found to be directly involved in regulation of contractile properties, fibrotic activity and permeability of the trabecular meshwork and Schlemm's canal tissues, thereby influencing extracellular matrix production[16,31].

Figure 8: Showing the Rhopressa Eye drop (https://m.indiamart.com/)

Figure 9: Showing the Rocklatan Eye drop (https://pharmacy.amazon.com/)

Rhopressa is usually instilled in the affected eye, one drop, once a day in the evening, and is indicated in open angle glaucoma as well as in ocular hypertension. Possible side effects include eye discomfort, redness, tearing corneal staining, eyelid redness and temporary blurry vision. There is risk of increased side effects if used more often than once daily.

Rocklatan is also usually instilled in the affected eye, one drop, once a day in the evening, and is indicated in open angle glaucoma as well as in ocular hypertension. It has been shown to maintain reduced IOP by approximately 37% from baseline. Possible side effects include increased iris and eyelid pigmentation and thickening and elongation of eye lashes among others. Risk of increased side effects if used more often than once daily ("Rocklatan 0.02%-0.005% Eye Drops," 2022; https://rocklatan.com).

2.1.3 Microdosing: Eyenovia's Optejet Eye Dropper.

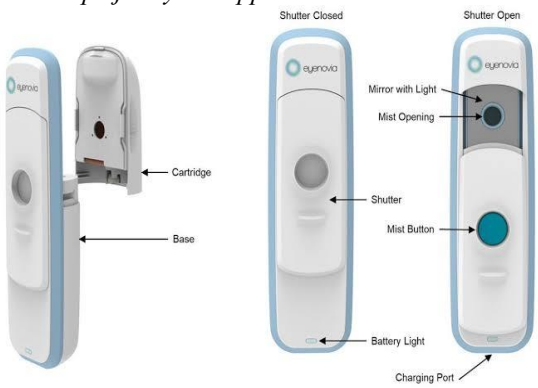


Figure 10: Showing labeled Component parts of the Optejet eye dropper[10]. Copyright Eyenovia, Inc.

Using the new Eyenovia Inc. Optejet® Dispenser, eye drops can now be administered in smaller/mirco doses, minimizing the risk of dose-related side and adverse effects[15].This device is capable of delivering eye drops at approximately 1/5th the drug volume of a conventional eye dropper with high precision very conveniently.

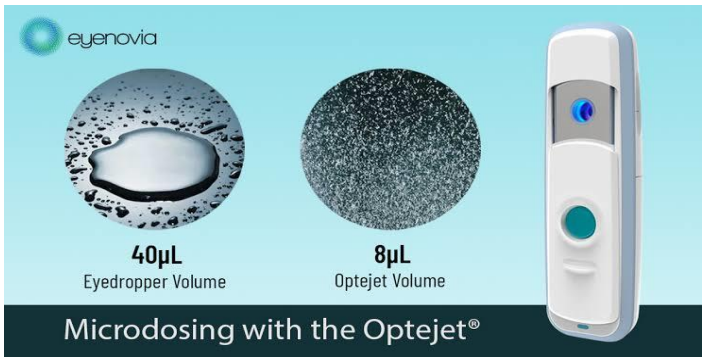


Figure 11: Illustrating topical microdosing with the Optejet in comparison to a conventional eye dropper (https://twitter.com/eyenovia)

Its benefits also include fast delivery, reduced patient-chair time allowing more patients to be care for; >95% successful drug delivery on first attempt; includes a MAP™ (Microdose array Print) technology which makes it usable while seated or standing; administers doses horizontally with less impact force on ocular surface unlike traditional eyedroppers that work with gravity and patient in a reclining position; 80% less exposure to drug and preservative toxicity and less drug overflow. It also includes the smart monitoring feature which enables synchronization with smart devices for dose monitoring, setting reminders for dose refill, and also dose tracking[26].

a.  b. 

Figure 12: Showing less need for reclining and higher degree of accuracy upon first trial using the optejet (a) (McKinney, 2021) as against conventional eye dropper (b) (https://google.com)

2.1.4 Bimatoprost Sustained-Release Implant (Bimsr) [Approved on March 5, 2020]

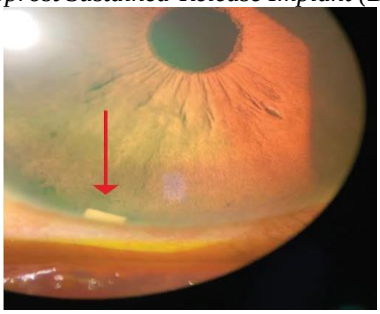
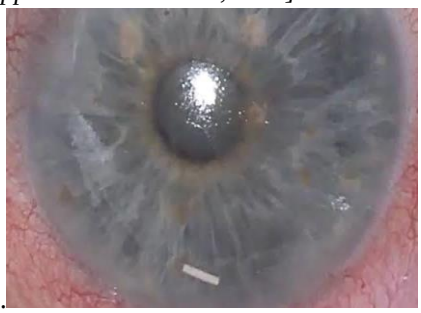
a.  b. 

Figure 13: Clinical images (a)[33,7]

This drug is described as the only FDA approved sustained-release intracameral implant at the time. It is produced by Allergan PLC and has proven capable of reducing IOP from baseline by about 30% over a period of 12 months following its injection into the eye[15,35]. It is biodegradable and a single dose can last up to 4 – 6 months. It is believed to increase matrix metalloproteinase expression which causes reorganization of the extracellular matrix to permit greater aqueous outflow, decreasing episcleral venous pressure. It is commercially available as Allergan's Durysta™ and indicated in open angle glaucoma as well as ocular hypertension[2].

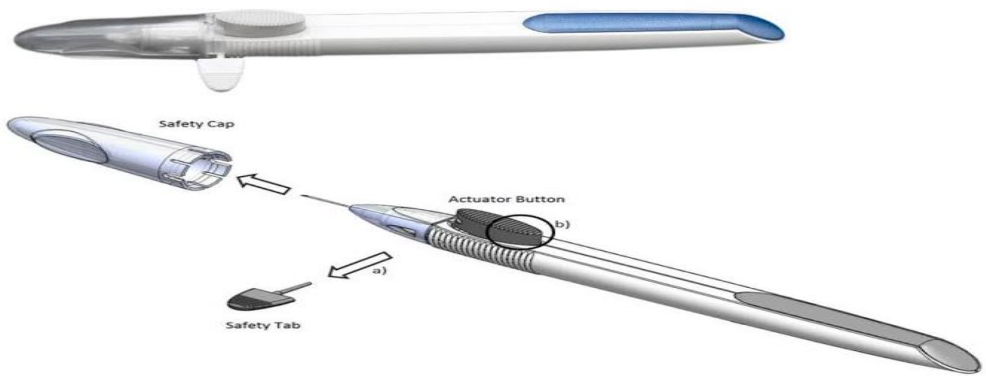


Figure 14: Images showing the Durysta Injector and its labeled parts [4].

Use of this SR implant eliminates the problem of drop/dosage adherence, reduces ocular surface and periocular side effects following usage of topical drops by targeting main site of action of prostaglandin class and reducing exposure to off-target tissues (it also reduces daily treatment burden of patients using topical drops [35]. Adverse effects following bimatoprost SR intracameral implant include corneal endothelial cell loss with repeated BimSR administration as against single dose [35]. *2.1.5*

2.1.5Dexamethasone Plugs (Dextenza)

Figure 15: Showing Dextenza insert packaging (https://www.dextenza.com)

Dextenza is a 0.4mg Dexamethasone ophthalmic intracanalicular insert formulated for adult use and indicated for ocular itching associated with allergic conjunctivitis. It is inserted via the lower punctum into the lower canaliculus and it delivers steady 0.4mg for up to 30 days after insertion[24]. It is completely resorbable and requires no removal. If removal is necessary, saline irrigation or manual expression may be done to remove it[15,24].

a. b.

Figure 16: Schematic diagrams illustrating (a) Dextenza insertion (https://www.dextenza.com) and (b) its brief pharmacokinetics (Wagle, 2020).

About 1 – 10% of patients experience increased IOP (9%), reduced VA (2%), eye pain (1%), corneal oedema (1%), conjunctival hyperaemia (1%), cystoids macular oedema (1%), and headache (1%) as adverse effect following its use; while side effects are same as with regular steroid use[24].It is contraindicated in active eye infection. Renewal of medication should be made only after proper examination and assessment by a qualified eye doctor [24].

2.1.6 Post-Operative Inflammation (Dexycu)

Figure 17: Showing Dexycu packaging [17]

DEXYCU® (Dexamethasone intraocular suspension 9%) was the first and only FDA approved single-dose, sustained-release steroid administered via intracameral route for the treatment of post-operative inflammation following cataract surgery. It is produced by EyePoint Pharmaceuticals, Inc. [9]

As with normal steroids, they may increase IOP, delay wound healing, exacerbate infection, and induce posterior subcapsular cataracts as side effects, and also cause corneal oedema and iritis as adverse reactions [9, 8].

A modified technique for administering this drug allows for consistency, visibility and monitoring of the drug volume and location, prevents migration of the drug into the anterior chamber, and also decreases the likelihood of iatrogenic iritis. This technique involves injecting it into the peripheral anterior lens capsule, as opposed to the initial technique of injecting directly into the posterior chamber [34].

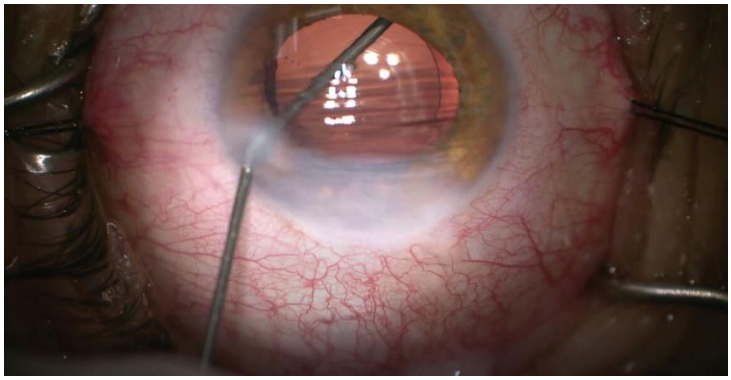


Figure 18: Showing intracapsular administration of Dexycu (Singh, 2021) [24].

3.0 CONCLUSION

Tremendous effort, no doubts, is being put into ocular research toward the development of safer patient-compliant ophthalmic drug delivery strategies. Only few of these are already commercially available and are applied clinically. Newer ocular drug delivery devices are gaining wider acceptance and adoption because they are continually proving capable of minimizing drug induced toxicity and vision loss, sustaining drug release, improving specificity, and helping to minimize dose frequency. With the current pace of ongoing researches in ocular therapeutics, topical drop formulations with the above properties which may be good alternatives to invasive modes of drug administration even to the eye's posterior segment (such as periocular and intravitreal injection) might also be developed in the nearest future.

3.1 Recommendations

1) We recommend that ocular therapeutics in Optometric practice be reviewed very often through Continuous Professional Development (CPD) programmes and seminars for better patient management outcomes;
2) Clinical Optometrists and other eye care practitioners should be able to recommend the use of, and also administer these novel drug delivery systems to patients where indicated;
3) Individual practitioners and eye care facilities should procure and adopt these novel technologies and also be willing to venture into eye health as well as academic research using them in order to generate more data for comparative assessment of efficacy;
4) The government at all levels, private individuals, Non-governmental Organizations (NGO) as well as other corporate bodies should pull resources together so as to procure these novel ophthalmic drugs and drug delivery systems for greater efficiency at all levels of eye and healthcare service delivery;
5) Adequate policies encouraging import duty waivers, grants and subsidies should be enacted by the government so as to encourage and create enabling environment for investors in the eye and healthcare industry.

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Conflict of Interest

The authors declare no conflict of interest.

Contribution of the Authors
Both authors contributed significantly and equally.

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