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Patented Technologies In Ocular Drug Delivery System: An Overview

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ABSTRACT

Eye is a window to the outside world and hence it becomes an important part of our body. Various diseases occurring in the eye cavity are difficult to treat. Some diseases require continuous use of medicine and other requires surgery. Lacrisert, Vitrasert, Mydriaser, Prosert etc. are patented technologies useful in the treatment of eye disorders. In this article brief description of various patented technologies such as Eyegiene kit, Ophtha coils, Versidoser, Microneedle, Implantable MEMS ocular drug delivery system, Ocuseal liquid bandage, Filter paper strips is given.

Keywords: Ocular drug delivery, Lacrisert, Vitrasert, Microneedle, Mydriaser.

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INTRODUCTION

Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientist. The anatomy, physiology, and biochemistry of the eye render this organ highly impervious to foreign substances.¹

Advantages of Ocular Drug Delivery^{1,2}

- No need of trained personnel as the application of drug is without needle and hence self medication is possible.
- Good penetration of hydrophilic low molecular weight drugs can be obtained through the eye.
- Rapid absorption and fast onset of action due to large absorption surface area and high vascularisation.
- Avoidance of hepatic first pass metabolism and thus potential for dose reduction compared to oral cavity.
- To provide targeting within the ocular globe so as to prevent the loss to the other ocular tissue.
- To provide comfort, better patient compliance to the patient and to improve therapeutic performance of the drug.
- To provide better housing of delivery system.

Disadvantages of Ocular Drug Delivery^{1,2}

- Low absorption of drug due to limited permeability of cornea.
- A major portion of the administered dose drains into the lacrimal duct and thus can cause unwanted systemic side effects.
- Rapid elimination of the drug through the eye due to blinking and tear flow resulting in short duration of therapeutic effect, hence, frequent dosing is required.

A considerable amount of effort has been made in ophthalmic drug delivery since the 1970's. The various approaches attempted in the early stages can be divided into two main categories; bioavailability improvement and controlled release drug delivery. The latter was attempted by various types of inserts and nanoparticles. After initial investigations, some approaches were dropped quickly, whereas others were highly successful and led to marketed products.¹⁻³

ANATOMY AND PHYSIOLOGY OF THE HUMAN EYE⁴⁻⁶

Human eye is nothing but the organ through which we can see the world. The eye is divided into two segments viz. anterior and posterior segments of the eye. Cornea, ciliary body, iris, lens and

aqueous humour are present in the anterior segment of the eye. The cornea acts as barrier to drug delivery to eye due its components. The cornea consists of the epithelium (0.1mm in thickness) a highly lipophilic layer consists of 56 cell layers is a tight junction of cells acts as barrier for aqueous drugs. Beneath cornea the stroma is present which covers 90% of the cornea is a highly hydrophilic layer acts as a barrier for lipophilic drugs. Then endothelium layer is present which hydrates the surface of eye. Aqueous humour and vitreous humour are present in the eye the former hydrates the eye and later provides shape and support.

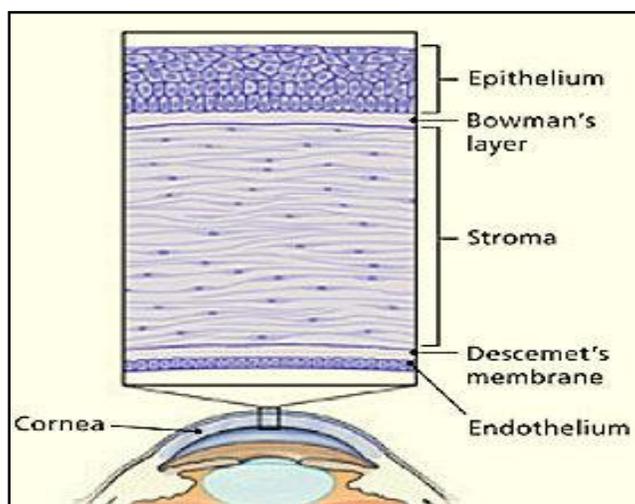


Figure.1: Anatomy of Eye

In this article we will discuss some patented technologies in the ophthalmology.

Lacrisert^{7, 8, 10}

The Lacrisert insert is a sterile, translucent, rod shaped pellet of hydroxypropyl cellulose without preservative and is commercially available. The product is inserted into the inferior cul-de-sac of the eye of the patients with dry eye states. The insert acts to stabilize and thicken the precorneal tear film and to delay its breakup. This device is designed as a sustained release artificial tear insert for the treatment of dry eye disorders. Inserts are typically placed in the eye once or twice daily. Following administration, the inserts soften and slowly dissolve. It was developed by Merck, sharp and Dohme in 1981.

Also Surodex1 and Posurdex1 (Allergan, USA) are the biodegradable implants in clinical Phase III studies. They are nearly identical poly lactic-co-glycolic acid (PLGA) implants with different doses of dexamethasone (60 mg for Surodex1 and 700 mg for Posurdex 1). Surodex1 was meant for the treatment of postoperative inflammation after filtering surgery on eyes with glaucoma placed underneath the scleral flap during the operation. Nevertheless, no further development of the implant is currently undertaken. Posurdex1 is designed for the treatment of macular edema

due to retinal vein occlusion, diabetic macular edema and uveitis by sustained release of dexamethasone over a month after intravitreal placement.

Vitrasert⁷⁻⁹

It is an ocular implant for delivering ganciclovir for the treatment of cytomegalovirus. This implant was developed under Vitrasert Dr. Smith This implant delivers the drug directly to the retina for over 5 months. It is useful for patients with AIDS associated cytomegalovirus retinitis. The device was prepared by coating a ganciclovir pellet with PVA. The pellet was then coated with ethylene vinyl acetate except on its top surface, and again coated with PVA. It is surgically implanted into the pars plana and attached to the sclera by a suture. The device lasted 4-5 months.

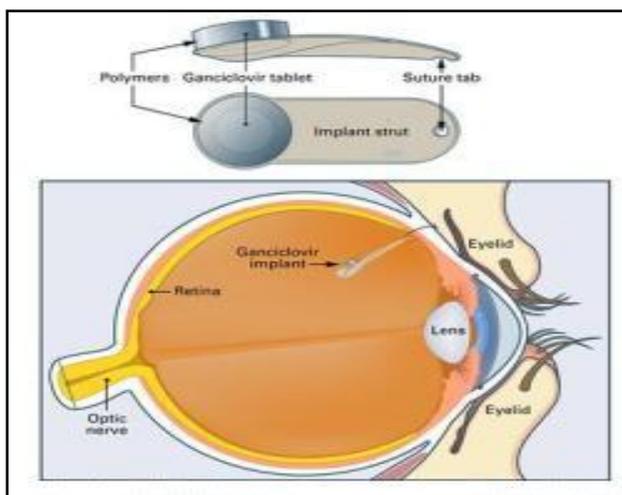


Figure.2: Vitrasert

Retisert⁷⁻⁹

The Retisert implant was also developed under Dr. Smith, using the same technology as Vitrasert. They developed an intraocular sustained release steroid implant capable of maintaining anti inflammatory intravitreal drug levels for periods of up to 3 years from single implantation.

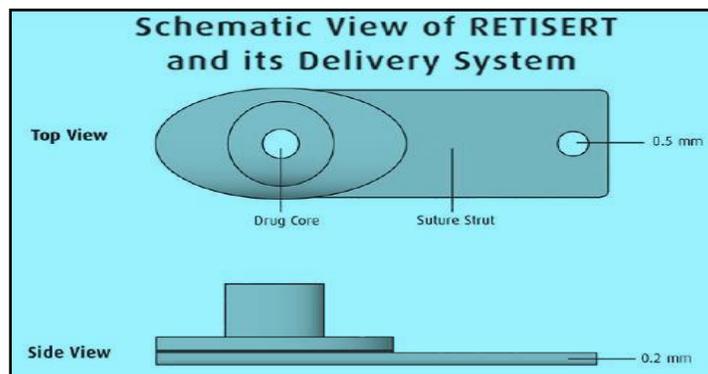


Figure.3: Retisert

This device was approved by the FDA in 2005 based on GMP production, release and stability; on GLP animal studies in multiple species demonstrating absence of toxicity, efficacy in models of inflammatory disease, and pharmacokinetics; and on two phase three studies in patients with uveitis.

Plexis^{8,9}

Is an innovative proprietary platform technology for sustained release of drug given by injection. This platform may be used for the depot delivery of a broad range of drugs. Auritec's Plexis technology combines a membrane based, diffusion driven release mechanism with drug particle sizing large enough to allow high drug loading, but small enough to be injected. Conceptually, they have developed an injectable depot made up of thousands of biodegradable mini Norplants. In this technology drug pellets are coated with semi-permeable polymers and injected into muscle tissue. Water then diffuses through the polymer and dissolves the drug core, creating a saturated solution inside the drug implant and essentially sink conditions outside the implant. This concentration gradient drives a constant release of the drug from the drug implant, as long as there is some drug core remaining to maintain a saturated solution. The period of release can be tuned by altering the permeability of the polymer coating.

The basis for their Plexis patents is the use of large crystals or amorphous particles of required dimensions, which are then appropriately coated. Large crystals or amorphous particles have three principal advantages for sustained release delivery: they dissolve slowly, enabling delivery systems to be developed based on dissolution; they can be manufactured simply and reproducibly; and they can be coated with conventional spray coating technologies, rather than relying on coacervation techniques for encapsulation. This will allow for greater drug loading.

Durasite¹¹

Insite Vision's DuraSite and DuraSite 2 platforms are sustained delivery technologies using a synthetic polymer based formulation designed to extend the residence time of a drug relative to conventional topical therapies. InSite Vision has issued US patent No. 8,501,800 on the company's DuraSite 2 next generation enhanced drug delivery system. DuraSite 2 has the potential to significantly increase efficacy and reduce dosing requirements for topically delivered ophthalmic drugs. Based on its ability to significantly improve drug retention and penetration into the tissues of the eye, Durasite and DuraSite 2 enable topical delivery of a solution, gel or suspension and can be customized for delivering a wide variety of potential drug candidates. This platform is currently leveraged in two commercial products for the treatment of bacterial eye infections, AzaSite and Besivance.

Microneedle¹²

A goal of ophthalmology researchers is to deliver medication to the back of the eye in a selective and minimally invasive way. An Emory Eye Center scientist and two fellow researchers have investigated opportunities and have recently been awarded a U.S. patent for application of microneedle technology. Filed for in 2007 and awarded in April 2011, the patent (US 7,918,814) was awarded to Henry F. Edelhauser, Emory Eye Center's former director of research, along with Mark Prausnitz, professor of chemical and biomedical engineering at the Georgia Institute of technology, and Ninghao Jiang. Because of its smaller size than the currently used intravitreal needles there may be less discomfort for the patients. Many patients with age related macular degeneration have injections on a regular basis. In the future, the same microneedle technology may be used to inject medication directly into the eye for many other ocular conditions, such as glaucoma, eliminating the need to put drops in the eyes every day a real chore for some patients. This hollow tubed microneedle can serve as a route for targeted drug delivery for retinal disease using an array of delivery suspensions such as microbeads and microbubbles.

Systane Lid Wipes¹³

Systane Lid Wipes Eyelid Cleansing Wipes offer a gentle wipe as part of a daily regimen recommended by eye care professionals, removing debris and eye makeup that can cause eye irritation. These premium premoistened eyelid cleansing wipes are hypoallergenic, non-irritating and soothing. And because each wipe is individually packaged, Systane Lid Wipes can be taken anywhere and remain sterile until use. It contains purified water USP, PEG-200 Hydrogenated Glyceryl Palmate, Disodium Laureth Sulfosuccinate, Cocoamido Propyl amine oxide, PEG-80 glyceryl cocoate, benzyl alcohol and edentate disodium.

Uses: as eye makeup remover and eyelid cleanser.

Eye mask¹⁴

US patent no. US D681086 S by Bruce Christie et al. explains the design of ocular mask. Akriti's new hot or Cold gel mask, Gel Eye Shield and Gel eye patch offer a unique and very effective solution to common eye fatigue. It will relieve tired, puffy eyes and soothe sinuses. The gel eye products provide refreshing relief, reduces stress, eliminate fatigue and muscle tension. The gel eye shield should be used to protect any soft tissue during healing to reduce swelling. An advantage of using the Gel Eye shield is the elimination of gauze used between the shield and the incision, which prevents the gauze sticking to the healing area.

Systane gel drops¹⁵

Systane Gel Drops is specially formulated to provide extra protection against the symptoms of

severe dry eye. This is designed to create a stronger, gel like bandage on the eye, Systane Gel Drops can be used in combination with other eye drops like Systane Balance or Systane Ultra Lubricant Eye Drops for extra relief, when needed. Two out of three patients agree that Systane Gel Drops is easier to use than their previous nighttime product, with long lasting relief of dry eye symptoms. This provides the convenience of a drop with the protection of a gel. It contains polyethylene glycol and propylene glycol.

Uses: for the temporary relief of burning and irritation due to dryness of the eye.

Systane balance lubricant eye drops¹⁵

This offers extended dry eye relief designed specifically for patients with dry eye associated with meibomian gland dysfunction a common cause of dry eye. The unique formulation of Systane Balance, with the LipiTech system and the demulcent, provide prolonged lipid layer restoration for longer lasting protection from dry eye. This patented formula helps restore a crucial component of tears that locks in moisture to relieve dry eye symptoms associated with meibomian gland dysfunction. It contains propylene glycol.

EyeGiene kit¹⁶

The EyeGiene Kit and the refills were invented by an American Ophthalmologist to improve the care of patients suffering from inflamed eyelids, and tired and dry eyes, this novel product is now made widely available through Akriti. The EyeGiene system is a simple device for application warming therapy to the eyes in conjunction with the MG Expressor Kit. Once activated, the unique source of heat, referred to as the temperature control module rapidly produces the intended warmth for several minutes. In addition to the general positive sensation, the warmth is known to improve the flow of natural oils in the glands in the eyelids that are critical for normal eyelid and tear film function. EyeGiene is designed for comfort and ease of use. The material in contact with the skin is safe and convenient.

Ocular drug delivery device¹⁷

It is a patented technology whose publication number is WO 2005020907 A2. In this technology an ocular device for insertion into an eye is provided. This device includes a body having an anterior surface and a posterior surface for placement on one of superior sclera and inferior sclera of the eye. The posterior surface is defined by a base curve that is substantially identical to a radius of curvature of the one of the superior sclera and inferior sclera of the eye. In one embodiment, the ocular device serves as an ocular drug delivery device and contains an active pharmaceutical agent, a lubricant, etc. the ocular device of this invention have been designed to be stable in the eye and therefore well retained over a prolonged period of time. Also the ocular

device is designed to provide the patients with levels of comfort and tolerance which is not achieved with ocular inserts. And hence can be used to deliver therapeutic agents to the eyes via continuous treatment for extended periods of time.

The device may be fitted and removed by the ophthalmic technician, nurse or doctor, as well as by patients themselves. The ocular device has a radius of about 11mm to about 13 mm. the ocular device of the present invention with a length of up to 35 mm may remain on the upper sclera and one with a length of up to 25 mm may remain on the lower sclera without causing discomfort. The length of the device of this invention is conveniently from 8 to 35 mm for use on the inferior sclera to suit the eyes of different infants, children and adults. The width of the device is preferably from about 1.0mm to 14 mm to suit the eyes of different sizes such as those of infants, children and adults. The volume of the device can range from about 70 μ l to 400 μ l and is preferably from about 100 μ l to about 200 μ l for adults. Infants and children under age five may require a device with a volume below 100 μ l.

Prosert^{17, 19}

It is an ophthalmic placebo insert which is insoluble, sterile and biocompatible. This system can contain one or several active components and allow its releasing in programmed or controlled way. Prosert is constituted of a matrix able to contain one or several active components, surrounded by a dialysant membrane of a changeable thickness which allows the releasing controlled by the tears. The entirety has the shape of a small oblong cylinder (reservoir) with rounded forms. When PROSERT is inserted in the cul-de-sac, the tears enter into the device and saturate the mesh net intended to contain the active component. When the osmotic equilibrium is achieved the active component is released through the dialysant membrane and then is spread in the conjunctiva. The releasing curve has an ascending phase up to achieve the equilibrium and then its stable; the releasing of the active component is done at constant speed.

Mydriaserit^{18, 19}

In the preparation for cataract surgery the pupil of the eye has to be dilated, in order for the surgeon to gain access to the lens of the eye. Usually this is done with several different types of eye drops that are placed into the eye every 15 min for the first hour until surgery time which makes patients uncomfortable. The pharmaceutical company in France Thea Have produced a commercial preparation called Mydriaserit. It is the first application of PROSERT technology is a mydriatic called MYDRIASERT that received its marketing authorization application. It is an insoluble ophthalmic insert, gradually releasing two well known active ingredients: phenylephrine and tropicamide. It is indicated in presurgical mydriasis. Mydriaserit, a new

insoluble ocular insert, ensures a regular and slow in vivo release of the drug. This release allows the mydriasis to be obtained quickly and to be maintained during surgery.

Versidoser Drug Delivery System²⁰

This system is under development by Mystic pharmaceuticals Inc., holds the near term potential for setting a new standard for effective front of the eye drug delivery. The VersiDoser platform utilizes aseptic unit dose packaging combined with novel multidose delivery devices that dispenses the drug into the eye in a predictable and consistent manner irrespective of the orientation of the device and the eye. These devices are capable of self administered precision dosing in the 12-15 μ l range and provides automatic dose counters, ease of use and therapeutic benefits for elderly and pediatric patient compliance.

OcuSeal liquid ocular bandage²¹

OcuSeal is a fully synthetic product which is developed to provide a protective hydrogel film barrier while stabilizing ocular wounds. It is designed to promote healing by protecting corneal incision from eyelid trauma.

Advantages:

- It reduce the risk of leakage and infection
- It is transparent having minimal effect on vision
- Ease pain
- Promote healing by protective corneal incisions from eyelid trauma
- Fully degrade within three days
- Easy application
- Time saving

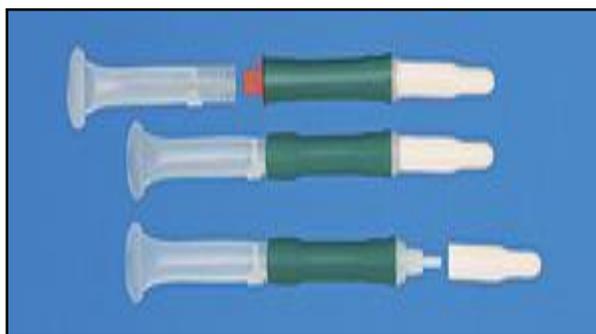


Figure. 4: OcuSeal liquid ocular bandage

Filter paper strips^{22, 23}

Fluorescent ophthalmic strips are used for a wide variety of purposes by ophthalmologists, optometrists, and opticians throughout Europe to color the tears of the eye. In the majority of

European countries Fluorescein is considered a medical device but it has recently been recognized that this conflicts with the EU legislation as clarified by the medical devices guidance document (Meddev guidance). This guidance describes fluorescein as an in-vivo diagnostic agent, and as such, considers Fluorescein to be medicinal product. Sodium fluorescein and rose Bengal dyes are commercially available as drug impregnated filter paper strips. These dyes are used diagnostically to disclose corneal injuries and infections such as herpes simplex and dry eye disorders.

Uses of Fluorescein:

- Assessment of the tear break-up time
- Contact lens fitting
- Application tonometry
- Assessment of the cornea

Ophtha coils²⁴

It can be placed in the lower conjunctival fornix, where it releases its drug. The device consists of a metal coil, coated with a hydrogel. The drug is entrapped in the hydrogel coating. The device is non biodegradable to prevent disintegration of the device or leakage of the drug and hence the device has to remove after the drug is released. Release of drug is by diffusion into the tear fluid. The coil can potentially serve as an alternative to the administration of drugs to the eye via eye drops.

Implantable MEMS Ocular Drug Delivery System^{25, 26}

MEMS technology is described to introduce drug continuously or periodically over a period of time into the eye. The device can be passive (mechanically operated) or active (electrically operated). Features of device include a refillable drug reservoir, a drug delivery tube, and a variety of flow valving and regulating elements. An electrically powered device can also include a micro pump for drug delivery and provide programmable dosing controlled by microelectronics. The provisional patent has been issued to the Ellis Meng et al. for the MEMS ocular drug delivery system.

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