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REVIEW ARTICLE

PROMISING IMPLICATION OF OCUSERTS IN OCULAR DISEASE

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ABSTRACT

Ocular route of 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 exquisitely impervious to foreign substances. The challenge to the formulator is to circumvent the protective barriers of the eye without causing permanent tissue damage In spite of extensive pharmacological and clinical data pointing to the usefulness and advantages of solid devices for topical drug delivery to the eye, liquid, and to a smaller extent, gel-type preparations appear to enjoy the continued interest of manufacturers and ophthalmologists. The main purpose of preparing ocular insert is to increase ocular bioavailability of drug. Ocular inserts maintain the drug concentration within a desired range. Fewer administrations are required so they increase patient compliance. In the present update, the advantages, disadvantages and requirement for success of ocular inserts, and examine the few inserts which are available on the market or are being developed by pharmaceutical companies for drug delivery. In this review, we have focused on the present era of ocuserts helps in treating eye diseases.

Key Words: Ocuserts, Eye Diseases, New advanced ocusert system

INTRODUCTION:

The eye as a portal for drug delivery is generally used for local therapy against systemic therapy in order to avoid the risk of eye damage from high blood concentrations of the drug, which is not intended. The unique anatomy, physiology and biochemistry of the eye render this organ impervious to foreign substances, thus presenting a constant challenge to the formulator to circumvent the protective barriers of the eye without causing permanent tissue damage[1].

"Ophthalmic disorder" refers to physiologic abnormalities of the eye. They may involve the retina, the vitreous humor, lens, cornea, sclera or other portions of the eye, or physiologic abnormalities which adversely affect the eye, such as inadequate tear production. Major ophthalmic disorders affect the posterior segment, including the retina and lens, as well as the anterior segment which includes the cornea, conjunctiva and sclera. Among the most important posterior segment disorders are macular holes and degeneration, retinal tears, diabetic retinopathy, vitreoretinopathy and miscellaneous disorders. The most important disorder of the lens is cataract. The most important disorders of the cornea are refractive disorders such as the sequelae of radial keratotomy, dry eye, viral conjunctivitis, ulcerative conjunctivitis and wound healing (such as corneal epithelial wounds) and the consequences of Sjogren's syndrome[2].

A major problem being faced in ocular therapeutics is the attainment of an optimal concentration at the site of action. Poor bioavailability of drugs from ocular dosage forms is mainly due to the tear production, nonproductive absorption, transient residence time, and impermeability of corneal epithelium. In addition to this, drugs that are hydrophobic or unstable at the pH comfortable in eye cannot be formulated as eye drops. Because of limitations of bioavailability pertaining to ocular route, there are many potent drugs, which still need to be studied for their therapeutic potential by topical ocular route. Novel drug delivery systems could be some effective means of exploring the potential of such drugs[3].

Ocuserts[4] are defined as sterile preparations with a solid or semisolid consistency, whose size & shape are especially designed for ophthalmic application. Generally, all types of ocuserts consists of three components namely, a central drug reservoir in which the drug is incorporated in a polymer, rate controlling membrane which ensures the controlled release of medicament from the drug reservoir, and an outer annular ring meant for easy handling and proper insertion shown in figure no. 1. Ocuserts increases corneal contact time, prolongs duration of action, improves bioavailability, reduces the frequency of administration and thus achieves better patient compliance. Uniform ocular drug level eliminates systemic side effects and provides undisturbed sleep due to extended drug activity throughout the night. It is also possible to administer the drug to inflamed eye due to

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sustained release of the medicament from ocusert. Furthermore, ocuserts are advantageous in saving time to the healthcare professionals. The efficacy of any ophthalmic drug[5] depends on the rate and extent to which the drug reaches aqueous humour and ultimately to the interior segment or to target tissues for providing expected therapeutic response.

The zero order kinetics[6] characteristics a sustained release type of delivery system whereby the drug is held in a reservoir and is released into the tear film at constant rate to provide a constant concentration in the corner which provides greatly improved compliance

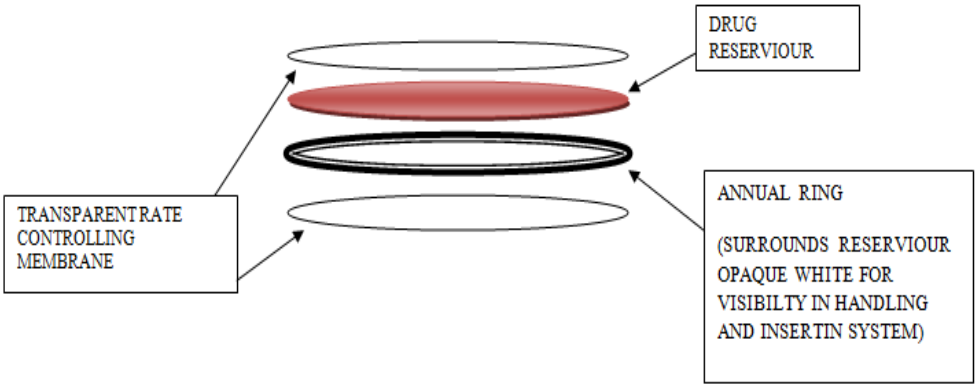

Figure 1: Schematic diagram of ocular insert

OCUSERTS USING IN VARIOUS EYE DISEASES:

1. Glaucoma[7]: Glaucoma refers to a group of eye conditions that lead to damage to the optic nerve. This nerve carries visual information from the eye to the brain.In most cases, damage to the optic nerve is due to increased pressure in the eye, also known as intraocular pressure (IOP).

Medication available but having side effects: Ophthalmic pilocarpine is used to treat glaucoma, a condition in which increased pressure in the eye can lead to gradual loss of vision. Pilocarpine is in a class of medications called miotics. It works by allowing excess fluid to drain from eye[8].

The amount of the drug administered in pilocarpine eye drops is substantially in excess of that needed for IOP control. The need to avoid this problem and the inconvenience of administering drops are leading to the development of a variety of alternative methods for drug delivery to the eye[9]. Pilocarpine needs to be administer four times a day which do not provide a constant therapeutic effect of the medication while leading the side effects of blurred or fluctuating vision and also not been tolerated by patients under the age of 40 and leeds to the fluctuation of intraocular pressure.

Other Side Effects[10]:

1. **Prostaglandin Analogs:** possible changes in eye color and eyelid skin, stinging, blurred vision, eye redness, itching, burning.
2. **Beta Blockers:** low blood pressure, reduced pulse rate, fatigue, shortness of breath; rarely: reduced libido, depression.
3. **Alpha Agonists:** burning or stinging, fatigue, headache, drowsiness, dry mouth and nose, relatively higher likelihood of allergic reaction.
4. **Carbonic Anhydrase Inhibitors:** in eye drop form: stinging, burning, eye discomfort; in pill form: tingling hands and feet, stomach upset, memory problems, depression, frequent urination.

New advanced ocusert system

Ocular inserts of Timolol maleate: Controlled release of timolol maleate ocusert avoids the pulse-entry with which side-effects are associated. These systems can be based on any of several different mechanisms, and include both erodible and nonerodible matrices, wafers. Timolol maleate was the first β-blocker to be used as an anti-glaucoma agent and to date remains as the standard because none of the newer beta blockers were found to be more effective. Timolol maleate has the longest record of safety and efficacy to lower IOP and is administered via eye drops one or more times per day [11]. They lengthen the extent of drug action by enhancement of corneal absorption.

Pilocarpine ocusert: A matrix-dispersed pilocarpine soluble insert avoids some of the problems of administration of pilocarpine by drops. It has shown an effective lowering of the IOP with a duration of at least 24 hours.The insert is, in effect, a device for prolonging the contact time of the dispersed drug with the corneal tear film. It is therefore analogous to the use of agents which increase tear film viscosity, such as methylcellulose and polyvinyl alcohol[12], without the disadvantage inherent in the removal of a drug-soaked carrier such as the cotton pled-get. Since there is a limit to the effectiveness of increasing viscosity on drug

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penetration, the duration of effect seen with these inserts can be attributed to prolonged release with the slow dissolution of the device[13].

2. Herpes Simplex Eye Disease: The most common herpes simplex eye disease caused is an infection of the cornea, which can potentially threaten sight. The infection varies in duration, severity and response to treatment, depending in part on which of several different strains of HSV type I caused the original infection. It can be considered a "cold sore" or "fever blister" of the eye14.Herpes simplex keratitis (HSK) remains a common cause of unilateral corneal disease[15].

Medication available but having side effects: Acyclovir, an antiviral is effective against human Herpes Simplex viruses, commercially available as a 3 % w/w eye ointment to be applied 5 times a day in the eye. The poor therapeutic response exhibited by conventional ophthalmic ointments due to rapid precorneal elimination of the drug[16].

New advanced ocusert system

Acyclovir ocular inserts: They were prepared using solvent casting method said promising formulation would be able to offer benefits such as increase residence time, prolonged drug release, reduction in frequency of administration and thereby may help to improve the patient compliance[17].

3. Eye Allergies: Eye allergies often are hereditary, and occur due to processes associated with other types of allergic responses. When an allergic reaction takes place, your eyes may be overreacting to a substance perceived as harmful, even though it may not be. These substances are called allergens[18].

For example, dust that is harmless to most people can cause excessive production of tears and mucus in eyes of overly sensitive, allergic individuals.

Medication available but having side effects: The disadvantage with Systane eye drops, use in eye allergies, especially with the gel formula, is that when first applied the eyes, people may experience a blurry vision for about 20 to 30 seconds. It can also cause a little feeling of burning and stinging sensations around the eyes but not to the point that it will cause redness and further irritations to the eyes. Additionally, although it s a very rare case, at the initial application of the Systane eye drops, some people may experience pain in the eyes, changes in vision orientation and swelling and irritation.

Blurred vision, headache, and increased tear production; swelling of the cornea and iris; temporary burning, irritation, pain, redness, stinging, or swelling of the eye are the side effects.

New advanced ocusert system: Ketorolac tromethamine ocuserts were prepared using different polymers such as hydroxy propyl methylcellulose, ethyl cellulose, methylcellulose and polyvinyl pyrrolidone in different proportions[19].

4. Blepharitis[20]: An infection of lid tructures (usually by staphylococcus aureus) with concomitant seborrhoea, rosacea, a dry eye and abnormalities in lipid secretions.

Medication available but having side effects: The poor bioavailability and therapeutic response exhibited by Ofloxacin conventional ophthalmic solutions due to rapid pre-corneal elimination of the drug[21].

New advanced ocusert system: Ocular inserts were prepared with prolonged release of drug and minimum swelling within cul-de-sac using Ofloxacin[21].

5. Ocular Hypertension:

The term ocular hypertension usually refers to any situation in which the pressure inside the eye, called intraocular pressure, is higher than normal. Eye pressure is measured in millimeters of mercury (mm Hg). Normal eye pressure ranges from 10-21 mm Hg. Ocular hypertension is an eye pressure of greater than 21 mm Hg[22].

Medication available but having side effects: Medication for ocular hypertension having side effects shown in table 1.

Table 1: Medication available but having side effects[23]:

Medication	Mechanism	Dosage form	Adverse effects
Pilocarpine	Muscarinic Agonist	Eye Drops	
Timolol	B-Receptor Antagonist		Bradycardia Bronchoconstriction
Acetazolamide	Carbonic Anhydrase Inhibitor	Systemic Administration	Diuresis, Loss Of Appetite Tingling Neutropenia
Clonidine	A2-Receptoe Agonist	Eye Drops	
Ecothiopate	Choline Esterase Inhibitor	Eye Drops	Muscle spasm Systemic effect
Cartelol	B- Receptor Antagonist	Eye Drops	Bradycardia Bronchoconstriction
Dorzolamide	Carbonic Anhydrase Inhibitor	Eye Drops	Bitter taste Burning sensation
Apraclonidine	A- 2 Agonist	Eye Drops	
Lanatoprost	Prostaglandin Analogue	Eye Drops	Ocular pigmentation

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New advanced ocusert system

Pilocarpine ocusert system for sustained control of ocular hypertension: A number of excellent drugs are available that are effective in reducing IOP. These drugs are typically applied as eye drops. However, patient adherence can be poor, thus reducing the clinical efficacy of the drugs. Several novel delivery systems designed to address the issue of adherence and to ensure consistent reduction of IOP are currently under development. A pilocarpine-containing, polymermembrane unit (Ocusert) was evaluated in 29 patients with open-angle glaucoma.Their potential is dependent on developing suitable delivery systems that can provide the drugs in a sustained, local manner to the retina and optic nerve. Drug delivery systems have the potential to improve patient adherence, reduce side effects, increase efficacy, and ultimately, preserve sight for glaucoma patients[24].

6. Herpes Simplex Keratitis:

Herpes Simplex keratitis (HSK) is a viral infection that if left untreated can have devastating ocular consequences[25]. The keratitis caused by the herpes simplex virus (HSV) typically presents as a unilateral "red eye" with a variable degree of pain or ocular irritation. Photophobia and epiphora are common; however, vision may or may not be affected, depending upon the location and extent of the corneal lesion. You may see a vesicular skin rash and follicular conjunctivitis with the initial infection, but these are less common with recurrent HSV. A more common sign is secondary uveitis[26].

Medication available but having side effects[27]: Adverse events associated with the use of ganciclovir ophthalmic gel may include, but are not limited to, the following:

1. Blurred Vision
2. Eye Irritation
3. Punctate Keratitis
4. Conjunctival Hyperemia

New advanced ocusert system

Idoxuridine ocular insert therapy:use in treatment of herpes simplex keratitis[28]: Therapy of acute herpes simplex keratitis in rabbits with idoxuridine-releasing ocular inserts showed that an application rate of 30µg/hr gave significantly better results than conventional treatment with idoxuridine drops and ointment while exposing the eye to 40% less drug. Delivery rates lower than this were equal or not as effective as drop and ointment therapy and rates up to 100µg/hr did not produce significantly better results than rates of 30µg/hr. Serial viral cultures demonstrated the persistence of virus beyond the period of clinical resolution of disease in all treatment groups, indicating that therapy should be continued longer than apparent resolution of disease.

7. Dry Eye Syndrome:

Dry eye is a disorder of the tear film due to tear deficiency or excessive tear evaporation which causes damage to the interpalpebral ocular surface (i.e. exposed eye surface) and is associated with symptoms of ocular discomfort. This definition of dry eyes was adopted by the National Eye Institute workshop on dry eyes[57].

The eye becomes dry either because there is not enough tears being produced or because there is abnormally high rate of evaporation of tears.

New advanced ocusert system

Hydroxypropyl cellulose ophthalmic inserts for treatment of dry eye[29]: There are various treatment modalities for dry eye syndrome available to eye care professionals, which can be used as monotherapy or in combination. There is evidence to suggest that with proper use and adequate patient education, hydroxypropyl cellulose ophthalmic inserts are an effective and safe treatment choice for dry eye syndrome. Most patients showed significant improvement in ocular symptoms and clinical signs, and many patients continued using hydroxypropyl cellulose ophthalmic inserts for several years alone or in conjunction with other dry eye therapies. There was no significant worsening in symptoms or any major long-term side effects of the medication. The inserts may be particularly helpful in patients who cannot tolerate preservatives or immunosuppressant drops, do not want to instill multiple artificial tears throughout the day, or still have an insufficient tear film despite other therapies. However, it is worth noting that several of the studies excluded patients with meibomian gland disease or blepharitis. It remains to be seen if the inserts help patients with evaporative aqueous tear loss due to meibomian gland dysfunction or blepharitis. One would think that both of these disease groups would benefit from using the inserts because there is often overlap of patients who also have dry eye syndrome. Nonetheless, hydroxypropyl cellulose ophthalmic inserts can be used effectively as monotherapy, or in conjunction with other therapies, and should be considered in the treatment of dry eye syndrome.

8. Conjunctivitis:

Conjunctivitis is the inflammation of the conjunctiva (the membrane that lines the eyelids and covers the exposed surface of the eyeball).Conjunctivitis can be caused by allergies, bacteria, viruses, chemicals, or underlying health conditions. The eyes are susceptible to infection because they are not sterile. They rely on lysozyme (an enzyme found in the tears) to destroy bacteria. Bacteria line the surface of the eyelids (all the way down into the shaft of the eyelashes), which makes the conjunctiva predisposed to germs and conjunctivitis[30].

Medication available but having side effects Moxifloxacin hydrochloride ophthalmic solution used. Serious side effects are not expected to occur during treatment with this medication. Some eye burning, stinging, irritation, itching, dryness, redness, tearing; or blurred vision may occur[31].

New advanced ocusert system

Polymeric Controlled Release Natamycin Ocular Inserts: Ocular drug delivery system for Natamycin; a polyene antibiotic is highly useful for the treatment of conjunctivitis and keratitis. Natamycin, a polyene antibiotic is highly useful for the treatment of fungal blepharitis, conjunctivitis and keratitis. Natamycin when formulated as eye drops suffered the disadvantage of instillation of the dye drops for every 3-4 h and hence maximized patient non compliance, leading to ineffective therapy[32].

9. Corneal Ulcers:

A corneal ulcer is an erosion or open sore on the surface of the cornea. The cornea is the transparent area at the front part of the eye that serves as a window through which we see. It also refracts light and offers protection to other parts of the eye. If the cornea becomes inflamed due to infection or injury, an ulcer may develop. A corneal ulcer is a serious condition that must be treated promptly to avoid lasting vision problems[33].

Medication available but having side effects Treatment for corneal ulcers needs to be aggressive, as some ulcers lead to vision loss and blindness. Treatment usually involves antibiotics as well as antiviral or antifungal medications. Steroid eye drops may also be given to reduce inflammation but having side effects like White precipitate and ocular discomfort (stinging and burning may occur upon application). For e.g. In patients with corneal ulcer or frequent administration of the drug, white precipitates have been observed, which resolved spontaneously with continued application The precipitate does not preclude continued use of CILOXAN Eye drops or CILOXAN Eye ointment, nor does it adversely affect the clinical course of the ulcer or the recovery process[34].

New advanced ocusert system

Ocular inserts of Ofloxacin[35]: Ocular inserts of ofloxacin were prepared with objectives of reducing the frequency of administration, obtaining controlled release and greater therapeutic efficacy in the treatment of corneal ulcers.

Ofloxacin ocular inserts were prepared to overcome the problem of the excretion and low retention time into the eye. The prepared ocular inserts show the more retention time and less excretion through the eye secretions. The ocular inserts prepared were smooth and passed all the evaluation tests. Formulations show a maximum cumulative percentage drug release of 91.27 % at the end of 24 hours. Ocuserts formulated also passed the test for sterility. They showed zero-order release of the drug in the *in vitro* and *in vivo* release studies. The drug in the films was found to be active against selected microorganisms as was proved by microbial efficacy studies. A high correlation coefficient was found between *in vitro* and *in vivo* release rate studies. Shelf-life of the product was found to be more than one year[36].

Table number 2: Research Work on Ocular Insert:

S.No	Drug	Dosage form	Category of drug	Polymers / Bases	Reference
1.	Dexamethasone	Ocular Insert	Anti-Inflammatory	Cellulose Acetate Phthalate, Eudragit RS. 100 And RL 100	37
2.	Pilocarpine Nitrate	Ocular Insert	Miotic Agent	Collagen	38
3.	Pilocarpine Nitrate	Ocular Insert	Miotic Agent	Mixtures Of Sodium Salts Of Hyaluronic Acid	39
4.	Tropicamide	Ocular Insert	Mydriatic Agent	Mixtures Of Sodium Salts Of Hyaluronic Acid	39
5.	Timolol Maleate	Ocular Insert	Anti-Glaucoma Agent	Alkyl Monoesters Of Poly Vinyl Methyl Ether-Maleic Anhydride (PVM - MA)	40
6.	Ciprofloxacin Hydrochloride	Ocular Insert	Anti-Infective Agent	Hydroxy Propyl Methyl Cellulose, Methyl Cellulose, Ethyl Cellulose And Polyvinyl Pyrrolidone	41
7.	Ketorolac Tromethamine	Ocular Inserts	Anti-Inflammatory	Hydroxy Propyl Methyl Cellulose, Polyvinyl Pyrrolidone, Methyl Cellulose And Ethyl Cellulose	42
8.	Natamycin	Ocular Inserts	A Polyene Antibiotic Is Highly Useful For The Treatment Of Conjunctivitis And Keratitis	Eudragit L-100, Eudragit S-100, Eudragit RL-100, Hydroxy Propyl Methyl Cellulose Phthalate And Cellulose Acetate Phthalate	43

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9.	Acyclovir	Ocular Inserts	An Antiviral Is Effective Against Human Herpes Simplex Viruses	Hydroxypropylmethylcellulose, Polyvinylalcohol And Eudragit	44
10.	Levofloxacin	Ocular Inserts	Antibacterial	Polyethylene Oxide , Sodium Alginate And Ethyl Cellulose	45
11.	Diclofenac Sodium	Ocular Inserts	Non- steroidal, Anti-Inflammatory	Methyl Cellulose (MC), Sodium Carboxymethyl Cellulose (SCMC) Alone And In Combination.	46
12.	Fluconazole	Ocular Inserts	Antifungal	Fluconazole Was Made Complex With B-CD, And The Release Rate Was Controlled By HPMC K4M And Ethyl Cellulose Polymers	47
13.	Flurbiprofen Sodium	Ocular Inserts	Non- steroidal Anti-Inflammatory	Hydroxy Propyl Methyl Cellulose.	48
14.	Azithromycin	Ocular Inserts	Antibacterial	Carbopol, And Hydroxypropyl Methylcellulose (HPMC)	49
15.	Dorsolamide HCL	Ocular Inserts	Carbonic Anhydrase Inhibitor	Hydrophilic Polymer PVP K 30	50
16.	Phenylephrine	Ocular Inserts	Mydriatic	Gellan Gum	51
17.	Pefloxacin	Ocular Inserts	Antibiotic	Hydroxypropyl Methylcellulose (HPMC)	52
18.	Brimonidine Tartarate	Ocular Inserts	Intraocular Pressure Lowering Agent	Polyvinylpyrrolidone K-90	53
19.	Moxifloxacin Hydrochloride	Ocular Inserts	Antibacterials	Gelatin	54
20.	Gatifloxacin Sesquehydrate	Ocular Inserts	Antibacterials	Polyvinyl Alcohol And Polyvinyl Pyrrolidone.	55
21.	Ofloxacin	Ocular Inserts	Antibacterials	Hydroxy Propyl Methyl Cellulose, Methyl Cellulose, Poly Vinyl Pyrrolidone And Poly Vinyl Alcohol	56

CONCLUSION

The limitations of existing medical therapies for ocular disorders include low drug bioavailability, no specificity, side effects, and poor treatment adherence to therapy. These limitations may be overcome through the use of sustained-release intraocular drug delivery systems. In the area of topical ocular administration, important efforts concern the design and the conception of new ophthalmic drug delivery systems able to prolong the residence time. The use of inserts, which are solid devices to be placed in the cul-the-sac or on the cornea represents one of the possibilities to reach increased residence time. These solid ophthalmic devices present the advantage of avoiding a pulsed release due to multiple applications.

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