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Review Article

Novel approaches of treatment *via* ocusert drug delivery

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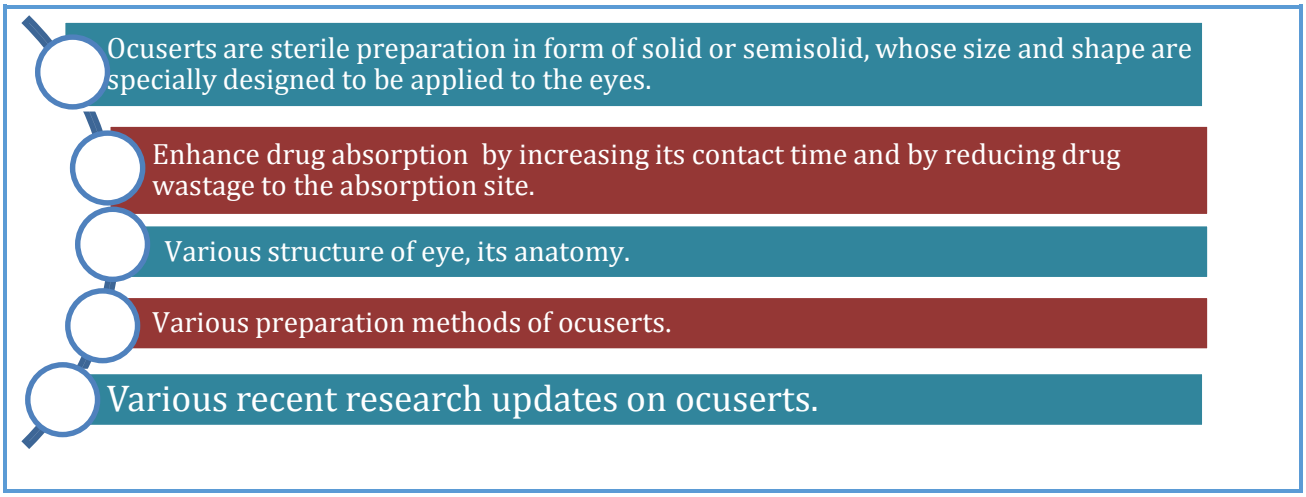
ABSTRACT

Ocuserts or ophthalmic inserts are "Sterile preparation in the form of solid or semisolid, whose size and shape are specially designed to be applied to the eyes". The most frequently used dosage forms (ophthalmic solutions and suspensions) are compromised in their effectiveness by several limitations, leading to poor ocular bioavailability. By utilization of the principles of the controlled release as embodied by ocular inserts offers an irritable approach to the problem of prolonging pre-corneal drug residence times. The controlled ocular drug delivery systems increased the efficiency of the drug by enhancing absorption increasing contact time of drug and by reducing drug wastage to the absorption site. Ocuserts were prepared using the solvent casting method. The article discusses about the various structure of the eye, its anatomy with an explanatory diagram. Also, various mechanisms of drug diffusion into an eye with special attention to biological/clinical performances, and potential applications and developments were discussed.

Graphical Abstract



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Introduction

In developing a drug delivery strategy, issue of absorption, distribution, metabolism, elimination (ADME) must be considered [1]. The eye presents unique opportunities and perspective when it comes to the delivery of pharmaceuticals. Ophthalmic drug delivery is one of the most interesting and challenging endeavours facing the pharmaceutical scientists [2]. Treatment of various diseases like dryness, conjunctiva, eye flu etc. can be done by topical administration of a drug to the eye. The protective mechanism of the eye such as blinking, baseline, draining decreases the bioavailability of drug and also help to remove rapidly foreign substances like bacteria's, dust particles as well as drugs from the upper surface of the eye. There are many eye diseases which can be affected to the eye and also eye vision. The importance of the route of administration can be appreciated because the drug enters the systemic circulation by avoiding the hepatic first-pass effect [3].

The main problem with Ocuserts is eye irritation (drug particle size and particle shape) which induces lacrimation i.e. tear to turn over, overflow on to lids, and due to pharmacokinetics responses like non-specific binding, metabolism and a different mechanism like diffusion, dissolution and erosion the conventional dosage form are less advantageous.

A major ophthalmic disorder affects the posterior segment, including the retina and lens, as well as the anterior segment which includes cornea, conjunctiva and sclera. Most important posterior segment disorders are diabetic retinopathy, vitreoretinopathy, macular holes and degeneration and miscellaneous disorders. The most important disorder of the lens is cataract and most important disorders of the cornea are refractive disorders such as the sequelae of redial keratotomy, dry eye, ulcerative conjunctivitis and wound healing and the consequences sjogren's syndrome [4].

Ocuserts are flexible, flat insoluble devices consist of two layers, enclosing a reservoir, used commercially to deliver a suitable amount of drug. All the ocuserts consist of three components namely, a centre drug reservoir which consists of incorporated in the polymer, the rate controlling membrane which ensures the controlled release of the drug from the reservoir, and outer annular ring meant for easy handling and proper insertion shown in Figure 1.

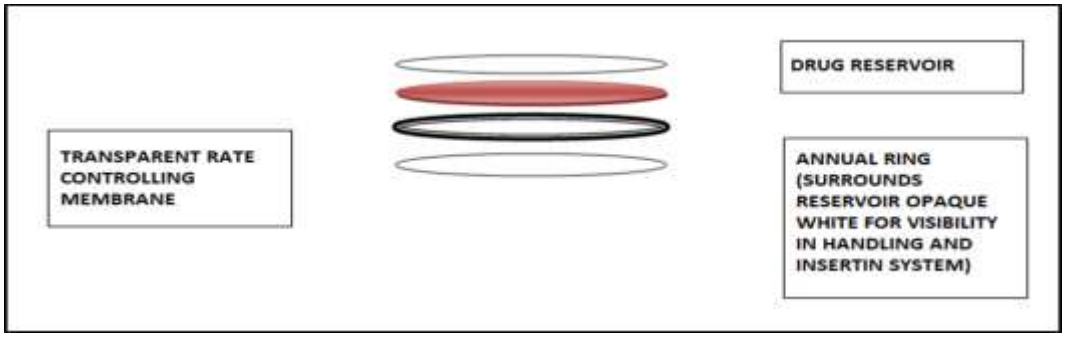

Figure 1. Schematic diagram for ocular inserts

Eye Structure

Anatomy of eye [5–8]

Eye is an essential part of human body which is about an inch in diameter. Eye is specialised for sight through an arrangement of multiple

tissues that functions to focus, transmit, and detect incoming light. The front part of the eye includes the iris, cornea, pupil, sclera, and conjunctiva (a thin layer of a tissue covering the front of the eye, except the cornea). Figure 2 represents the schematic diagram of the eye structure and various ocular barriers. The primary physiologic blockage against the instilled drugs is the tear film. Corneal region is the main site for drug transportation to the anterior chamber (I). The retinal pigment epithelium and the retinal capillary endothelium are the main barriers for systemically administered drugs (II). Intravitreal injection is an invasive strategy to reach the vitreous (III) [9].

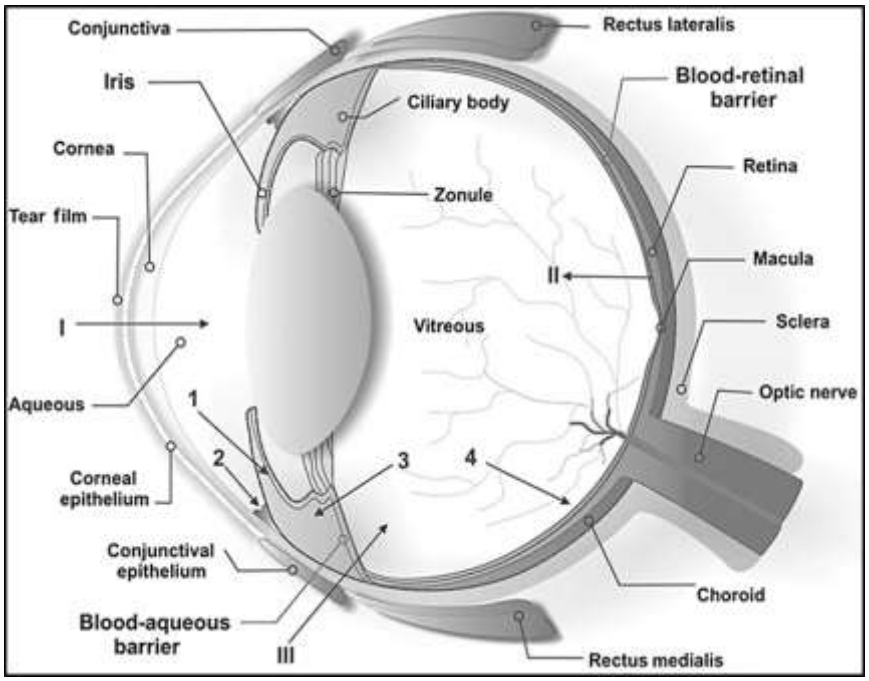

Figure 2. Structure of an eye

Sclera

The sclera is known as the white part of the eye. It is tough, opaque tissue that serves as the eye's protective layer. The moment of an eye is controlled by six different muscles which are attached around the eye ball. Optic nerve is connected at the backside of the black part. In children's, the sclera is thin and more translucent, allowing the underlying tissue to show through and give it bluish cast. Sclera tends to become yellow as age increases.

Aqueous humour

The aqueous humor is a jelly- like substance located in the anterior chamber of the eye.

Choroid

It absorbs unused radiation. It nourished the black part of the eye and composed of blood vessels. The choroid layer is located behind the retina muscle and connects with the ciliary muscle towards the front of the eye and is attached to the edge of the optic nerve at the black part of the eye. The biconvex lens is situated just behind the pupil. The chamber behind the lens is filled with vitreous humor, a gelatinous substance.

Ciliary Muscle

The ring- shaped muscle is attached to iris. Concentration and relaxation of the ciliary muscle controls the shape. Ciliary muscle contracts the lens to improve the focus of closer object.

Optic Nerve

The pair of the nerve that transmits visual coded information from retina to brain is known as cranial nerve II. Each nerve contains around one million fiberres, transmitting information from the rod and cone cells of the retina.

Pupil

The dark circular opening is at the center of the iris of an eye, and varies in size to regulate the amount of light reaching the retina. It appears black because light ray entering the pupil is either absorbed after diffusion reflections within the eye that mostly miss exiting the narrow pupil. As the size of iris increases or decreases, the size of the pupil decreases or increases subsequently.

Retina

It is a light-sensitive layer of tissue which is the third and inner coat of the eye. The retina contains photosensitive elements (rods and cones) that convert the light and detect into nerve impulse and send to the brain by the help of optic nerve.

Cornea

The cornea is an optically transparent tissue that fetches image to the black of the eye and covers about $1/6^{th}$ of the total surface area of eye-ball. The cornea is considered the main pathway for the permeation of drug into the eye. It is 0.5 mm thick in the central region, increases to approx. 0.7 mm at the periphery and composition of five layers.

- The Epithelium.
- The Bowman's Membrane.
- The Descemet's Membrane.
- The Corneal Endothelium.
- The Stroma

Conjunctiva

It helps in the maintenance and formation of the pre-corneal tear film and in the protection of eye. Human conjunctiva is 5-20% more permeable to the drugs than the cornea. It is made up of thin mucous membrane that lies in the posterior surface of the eyelids and an outer region of the cornea.

Composition of tear

The secretion of clear fluid contains numerous salts, glucose, other organic compounds 0.7% proteins and enzymes lysosomes.

- Water: 98.2%
- Solids: 1.8%
- Organic elements: (Proteins:0.67%,Sugar: 0.65%, NaCl: 0.66%,NPN: 0.05%)
- Urea: 0.03%
- Other mineral elements sodium, potassium and ammonia: 0.79%.

Common eye infection

Bacteria's are the major microbes which causes a large number of eye infection. In additional fungus, virus and protozoans also causes an eye infection. The most commonly eye infections are mentioned below [10–12].

- Conjunctivitis
- Cataract
- Keratitis
- Blepharitis

- Glaucoma
- Ititis

Mechanism of drug release [13]

The mechanism of controlled drug release into the eye is as follows:

A. Diffusion
B. Osmosis
C. Bio-erosion

Diffusion

The drug was released progressively at a controlled rate through the membrane into the tear fluid. The controlled release can be further managed by gradual dissolution of the solid dispersed drug within this matrix as a result of inward diffusion of an aqueous solution. The release of drug can take place via diffusion through the pores. If the inserts is formed of the solid non-erodible body with pores and disperses drug. *Urquhart* developed pilocarpine ocusert as ocular therapeutic systems [14]. This was the first rate-controlled, rate specified pharmaceutical product that provides predictable, time-independent concentrations of drug in the target sites. The near-constant drug concentration in ocular tissues markedly improves the selectivity of action of pilocarpine. This novelistic delivery system avoids miosis, myopia and reduces intraocular pressure (IOP) in glaucoma patients that are major drug related side effects. Pilo-20 and Pilo- 40 are commercially available ocusert that consists of pilocarpine alginate as a reservoir enclosed from both sides by thin ethylene-vinyl acetate (EVA) membranes. The former delivers the drug at a rate of 20 μg/h for 7 days, and the latter at a rate of 40 μg/h for 7 days.

Osmosis

Osmosis is dependent upon the degree of reduction of the free energy of one solvent over that of another. In the osmosis mechanism, the inserts comprises a transverse impermeable elastic membrane divides the interior of the insert into a compartment I and compartment II. The compartment one is obligated by a semi-permeable membrane and the impermeable elastic membrane and the compartment II is bounded by an impermeable membrane and provides a reservoir for the drug which is in liquid or gel form. When the insert is placed in the aqueous environment of an eye, water diffuses into the compartment I and stretches the elastic membrane to expand the first compartment and gets in the contract the second compartment so that the drug is forced through the drug release aperture.

Bio-erosion

The arrangement of the functional unit of a body of an insert is constituted from a matrix of bio-erodible material in which the drug is dispersed. When insert comes in contact with tear fluid it results in controlled and sustained release of the drug by bio-erosion of the matrix. The drug may be dispersed uniformly throughout the matrix but it is assumed a more controlled release is obtained if the drug superficially concentrated in the matrix.

Absorption of drug in the eye

Tropical administration of drug formulation is the most common route of ocular drug delivery; the drug is absorbed at sites:

A. Corneal
B. Non-corneal routes

Maximum absorption of the drug is done through the cornea, which then transfers to aqueous humor. The non-corneal route involves absorption across the sclera and conjunctiva, this route is not productive as it restricts the entry of the drug into the intraocular tissues.

Physiochemical properties of drug

Para-cellular or trans-cellular pathway is the main route for the drug to penetrate across the corneal epithelium. Para-cellular pathway involves the passive diffusion through the intracellular space (Hydrophilic drugs). The trans-cellular pathway involves the partitioning of the drug to cells (Lipophilic drugs). Passive diffusion is the main permeation mechanism for both types of pathways.

Ophthalmic inserts

These are sterile preparations with a solid or a semisolid consistency, and whose size and shape are specially intended for ophthalmic application. The inserts are placed in less frequency and lower fornix. The ophthalmic inserts are used to increase the contact time between the preparation and the conjunctiva tissue to ensure a sustained release suited to tropical or systemic administration or treatment. These are composed of polymer supporting with or without drugs; these are latter being incorporated as a dispersion or a solution in the polymeric support. The typical pulse entry of a drug release behaviour observed with eye drops, suspensions and ointments is replaced by more controlled, sustained and continuous drug delivery applying a controlled release ocular drug delivery system. In the recent time polymer based delivery devices are adding a further dimension to tropical drug delivery thereby promoting the use of polymers such as fibrin fabricated and collagen into erodible inserts for placement on the opening end of the eye. Principle of controlled release as embodied by ocular inserts offers an attractive approach to the problem of prolonging pre-corneal drug resident times. Ocular inserts also offers the potential advantage of improving patient compliance by reducing the dosing frequency.

Controlled ocular drug delivery system

Controlled release drug delivery system can be a major advantage towards solving the problems pertaining to targeting of a drug and improving the bioavailability of the ocuserts. Desideratum of controlled drug delivery is:

- Improving bioavailability by increasing corneal contact time of the drug.
- To serve controlled and sustained drug delivery.
- The loss to other tissue besides cornea is disallowed as to maintain better conditioning to delivery system in eye.
- To minimise the side issues produced by conventional systems.
- To give targeting within the ocular globes so as to put off the loss of drugs.
- To improve the therapeutic performance of the drug and patient comfort and compliances over conventional drug delivery system.
- To obstacle the protective barrier like lacrimation, drainage and deflection of exogenous chemicals into the systemic circulation by the conjunctiva

Favorable circumstances of ocular inserts [15]

1. Increased visual habitation, henceforth a drawn-out medication action and a higher bioavailability as for standard vehicles.
2. Possibility of discharging medications at a moderate, consistent rate.
3. Accurate dosing (in spite of eye drops that can be dishonourably ingrained by the patient and are incompletely lost after organization, each embed can be made to contain an exact dosage which is completely held at the organization site).
4. Reduction of systemic retention (which happens uninhibitedly with eye drops by

means of the naso-lacrimal channel and nasal mucosa).
5. Better patient consistence, coming about because of a decreased recurrence of organization and a lower occurrence of visual and systemic reactions.
6. Possibility of focusing on inward visual tissues through non-corneal (conjunctival scleral) courses.
7. Increased time span of usability concerning fluid arrangements.
8. Exclusion of additives, therefore decreasing the danger of affectability responses.
9. Possibility of joining different novel concoction/innovative methodologies.

Detriments of ocular insert [16]

1. A capital detriment of visual supplements lives in their strength, in the way that they are felt by the (frequently oversensitive) patients as an unessential body in the eye.
2. Their development around the eye, in uncommon examples, the basic evacuation is made more troublesome by undesirable relocation of the additions to upper fornix.
3. The intermittent unintentional misfortune amid rest or while rubbing the eyes.
4. Their impedance with vision.
5. Difficult arrangement of the visual supplements (and evacuation, for insoluble sorts).

Research updates

Ebtsam MA et al (2017)

formulated dorzolamide HCL and timolol maleate ocuserts to increase the patient compliance by providing controlled drugs release through polymeric matrix. Ocuserts were prepared by a solvent-casting method using different polymers Eudragit S100, Ethyl Cellulose and Hydroxy propyl methyl cellulose (HPMC) in various ratios. The prepared ocuserts were evaluated for their weight, thickness, drug content uniformity, surface pH, Swelling Index (SI) and folding endurance, *in-vitro* drug release studies *and in-vivo* tests were done to study the release profile and estimate the safety of the incorporated drugs in rabbits' eyes [17].

Shukr M et al (2014)

developed ocular inserts of lidocaine HCl to provide a sufficient level of anesthetic. Ocuserts were formulated using HPMC and PVA in different ratios with lidocaine HCl alone and lidocaine HCl β-cyclodextrins complex. Drug-polymer interactions were studied by Fourier transform infrared (FT-IR) spectroscopic studies. The prepared ocular inserts were characterized for weight variation, ocusert thickness, folding endurance, moisture absorption, drug content, surface pH, *In-vitro* and *In-vivo* drug release studies. The results of in vivo study showed that the addition of β-cyclodextrins in F7 significantly increase the drug content in the aqueous humor when compared with F3 ocuserts containing lidocaine HCl alone [18].

Ahad AH et al (2011)

developed ocuserts of Fluconazole *β*-CD (beta-cyclodextrin) complex and evaluated both *in vitro* and *in vivo*. The release rate was controlled by using various polymers such as HPMC K_4M, ethyl cellulose and dibutyl Phthalate was used as permeability enhancer. Drug-polymer interactions were studied by Fourier transformer infrared spectroscopic studies. The formulated ocuserts were tested for the different physicochemical parameter of *in vitro* drug release and *in vivo* permeation studies in rabbits. The formulated ocuserts were found to have acceptable physical

characters, diameter, thickness, folding endurance, uniformity in weight, less moisture absorption and controlled release of drug both *in vitro* and *in vivo* [19].

Upadhyaya N et al (2011)

developed ocular drug delivery system for Levofloxacin; fluoroquinolone (or quinolone) anti-infective by the solvent casting technique using different polymers such as Poly vinyl pyrrolidone K30 and Chitosan at various proportions and Hydroxy Propyl Methyl Cellulose (15 cps) combinations using PEG-400 as a plasticizer. The prepared ocuserts were evaluated for their physicochemical parameters. It was also observed that with increasing the proportion of PVP rate of release of Levofloxacin also increases. *In vitro* release studies and stability studies showed that ocular inserts formulation could be a promising once-a-day controlled release formulation [20].

Sarath CC et al (2010)

developed an ocular insert of Ciprofloxacin -β CD Complex and evaluated for sustained ocular delivery of the drug. The conventional/traditional method of ophthalmic administration resulted in poor availability & therapeutic response due to rapid precorneal elimination of the drug also it requires frequent instillation of medication into the eye, hence leads to poor patient compliance. Developed ocular ocuserts was evaluated for various parameters such as physical characters, thickness and diameter, weight variation, folding endurance, percentage moisture absorption, stability studies, microbiological studies and in vitro release studies [21].

Sankar AK et al (2006)

formulated diclofenac sodium-loaded ophthalmic inserts using sodium CMC (4%) and Methylcellulose (1%) established controlled zero order *in vivo* release showing no symptoms of inflammation and irritation [22].

Baeyens et al (1998)

Formulated and evaluated ocular inserts of gentamicin and dexamethasone. This new drug delivery system ensured the concomitant release of both drugs for the first 10 h of treatment and it was followed by gentamicin release to maintain levels above minimum inhibitory concentration for 50 h [23].

Preparation methods of ocusert [24]

Dissolvable casting method

In this method, numbers of clusters are prepared to utilize diverse proportions of medication and polymer. The polymer is broken up in refined water. A plasticizer is added to this arrangement under mixing conditions. The measured measure of medication was added to above arrangement and mixed to get a uniform scattering. After legitimate blending the throwing arrangement was poured in clean glass petridish and secured with an altered pipe to permit moderate and uniform dissipation at room temperature for 48 h. The dried movies were cut by stopper borer into round bits containing the drug. The visual supplements were then put away in a hermetically sealed holder (desiccator) under the surrounding condition.

Glass substrate technique

1% w/w polymer for instance chitosan was absorbed 1%v/v acetic corrosive answer for 24hrs, to get an unmistakable arrangement of chitosan in the acidic corrosive arrangement. The arrangement was separated through a muslin fabric to evacuate undissolved bit of the polymer (chitin). Required amount of

medication βCD complex was added and vortexed for 15minutes to break down the complex in chitosan arrangement. 1%w/v propylene glycol (plasticizer) was added to it and blended well with stirrer. The thick arrangement was kept aside for 30 min for finish ejection of air pockets. The rate controlling movies were readied. The movies were thrown by emptying arrangement into the focal point of leveled glass shape and allowing it to dry at room temperature for 24 h. In the wake of drying, movies were cut into ocuserts of craved size so that each contains measure up to amount of the medication. At that point, the framework was sandwiched between the rate controlling layers utilizing non-poisonous, non-aggravating, water-insoluble gum. They were wrapped in aluminium foil and were placed in a desiccator.

Melt extrusion technique

Firstly, the drug and polymer were sieved through mesh no. 60, weighed and blended geometrically. The plasticizer was added and blended. The blend was then placed in the barrel of Melt Flow Rate apparatus and thus extruded. The extrudates were cutted into an appropriate size and packed in polyethylene lined aluminium foil, heat sealed and finally they were sterilized by the gamma radiations.
Currently investigated ocular inserts containing antiglaucoma, antibacterial, anti-inflammatory or anti-viral drugs for ocular delivery are presented in Table 1.

Table 1. Research updates on ocular insert

Drug	Class of drug	Dosage form	Bases/polymers	References
Pilocarpine nitrate	Mitotic agent	Ocular inserts	Collagen	25
Pilocarpine nitrate	Mitotic agent	Ocular inserts	Mixtures of sodium salts of hyaluronic acid	26
Pilocarpine	Mitotic agent	Biodegradable inserts	PVMMA	27
Pilocarpine 20 µg/h and 40µg/h release	Mitotic agent	Insoluble insert	Ethylene vinyl acetate; alginate	28
Timolol 0.5%	Anti-glaucoma agent	Soluble insert	Hydroxypropylcellulose/ eudragit R/eudragit S	29
Gentamicin 11%	Anti-bacterial	Soluble insert	Collagen	30
Idoxuridine	Anti-viral	Bioerodible insert	Polypeptide	31
Levofloxacin	Anti-bacterial	Ocular inserts	Polyethylene oxide (PEO), Hydroxypropyl cellulose (HPC) and ethyl cellulose (EC)	32

Conclusion

The site specific drug delivery to ocular region is a challenging task. Due to certain drawbacks associated with the conventional formulations different carrier systems for ocular drug delivery was introduced. The major focus area in ocular drug delivery has been on the design of systems to increase the residence

time of topically applied drugs in the conjunctival sac. Controlled ocular drug delivery system increases the efficiency of the drug by minimizing its wastage and by increasing absorption by enhancing contact time of drug to the absorbing surface. They reduce dosing frequency and thus improve patient compliance. They also reduce the dose and drug related adverse effects. The commercial failure of the inserts was accredited to the psychological factors including the unwillingness of ophthalmologists and patients to abandon the traditional semi-solid and liquid dosage form, to price factors and to occasional therapeutic failures (e.g., unnoticed expulsion from the eye, membrane rupture). The prolonged, constant-rate release pattern achievable by inserts of the ocuserts can be considered as the most desirable condition for long term therapy, both because of efficacy as well as the reduction of ocular and systemic side-effects. Although at this time the advantages of solid ocular dosage forms are understood and appreciated, marketing strategies prevent their further commercialization, unless, of course, their potential use could be extended to applications other than long-term glaucoma or trachoma treatment, or short term medication after ocular surgery. Nevertheless, recent research suggests a renewed interest based on the efficacy of sub-conjunctival and intra-vitreal drug delivery devices.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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