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Review Article

Overview of current technologies in ocuserts for the treatment of ophthalmic diseases

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ABSTRACT

Ocular drug delivery is one of the most fascinating and challenging tasks facing the Pharmaceutical researchers. One of the major barriers of ocular medication is to obtain and maintain a therapeutic level at the site of action for prolonged period of time. The development of newer, more sensitive diagnostic techniques and therapeutic agents renders urgency to the development of maximum successful and advanced ocular drug delivery systems. The main objective of the present review was to describe different technologies used for the preparation of ocuserts and importance of ocuserts in the treatment of ophthalmic diseases. Different categories of drugs used for the treatment of ophthalmic diseases such as anti-viral, anti-biotics, anti-glaucoma, anti-bacterial and anti-fungal drugs. Methods involved in the preparation of ocuserts like solvent casting method, film casting and kneading method. Finally concluded that the present review gives the full description about ocular drug delivery system for the treatment of ophthalmic disease in effective manner.

Keywords: Ocuserts; kneading method; Glaucoma; cul-de-sac; film casting method; conjunctivitis; Keratitis.

INTRODUCTION

Topical application of ophthalmically active drugs is the most prescribed route of administration for treatment of various ocular disorders. It is generally agreed that the intraocular bioavailability of topically applied drugs is extremely poor. This is mainly due to drainage of the excess fluid by the nasolachrymal duct as well as dilution and elimination of the solution by tear turnover. (Tanwar, Y. S., 2007) frequent administration, massive and unpredictable doses. Those factors required to formulate a controller release ocular drug delivery system which maintains a steady state drug release. (Sankar, V., 2006).

The advantage of ocular inserts, which are solid devices placed in the cul-de-sac of the eye in comparison with liquid formulations are numerous. Because of the prolonged retention of the devices and a controlled release, the effective drug concentration in the eye can be ensured over an extended time period. Dosing of the drug is also more accurate and the risk of systemic side-effects is decreased. Furthermore, solid devices have an increased shelf life and the presence of additives such as preservatives is not required. Occular delivery systems like inserts, biodegradable polymeric systems, and collagen shields are being developed in order to attain better ocular bioavailability and sustained action of ocular drugs (Ramkanth, S., 2009).

A basic concept in ophthalmic review and development is that the therapeutic efficacy of an ophthalmic drug can be greatly improved by prolonging its contact with the corneal surface. Ophthalmic inserts offer many advantages over conventional dosages forms, like increased ocular residence, possibility of releasing drug at a slow and constant rate, accurate dosing, exclusion of preservatives and increased shelf life. Design, construction and technology of ocular insert in a controlled and sustained ocular delivery device are gaining rapid improvement to overcome this constraint (Hitesh, B., 2009).

Physiology of the eye

The eye is a spherical structure with a wall consisting of 3 layers: the outer sclera, the middle choroid layer and the inner retina. The sclera is a tough fibrous coating that protects the inner layers. It is white except for the transparent at the front, the cornea, which allows light to enter the eye.

The choroid layer, situated inside the sclera, contains many blood vessels and is modified at the front of the eye as the pigmented iris. The biconvex lens is situated just behind the pupil. The chamber behind the lens is filled with vitreous humor, a gelatinous substance occupying 80% of the eyeball. The anterior and posterior chambers are situated between the cornea and iris, and iris and lens, respectively and filled with aqueous humor. At the back of the eye is the light-detecting retina.

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Cornea and Its Layers

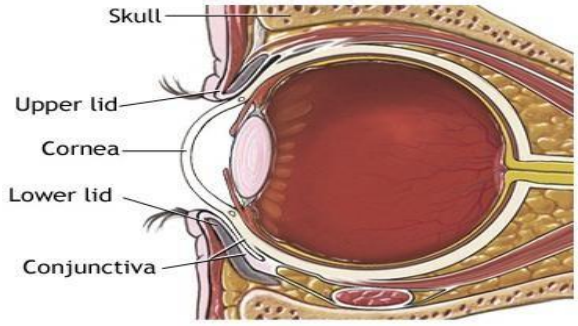

Figure 1: Structure of cornea and its layers

The cornea is an optically transparent tissue that conveys images to the back of the eye and covers about 1/6th of the total surface area of the eyeball. It is an auricular tissue to which nutrients and oxygen are supplied via bathing with lachrymal fluid and aqueous humor as well as from blood vessels that line the junction between the cornea and sclera. The cornea is considered to be the main pathway for the permeation of drugs into the eye. It is approximately 0. 5mm thick in the central region, increasing to approximately 0. 7mm at the periphery and composed of 5 layers (Rather, KS, 2009).

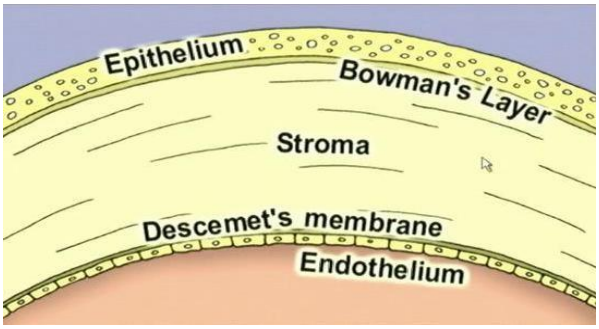

Figure 2: Internal structure of corneal layers

- The epithelium is squamous stratified, consisting of 56 layers of cells (increasing to 8-10 layers at the periphery), has a total thickness of around 50-100µm and a turnover of about one cell layer per day. The tight junctions and hydrophobic domains in this layer make it the most important barrier to drug delivery.
- The Bowman's membrane is a cellular homogenous sheet, about 8-14µm thick. This is positioned between the basement membrane of the epithelium and the stroma.
- The stroma, or substantial propria, accounts for around 90% of the corneal thickness. It contains approximately 85% water, and about 200-250 collage nous lamellae that are super imposed on to one another and run parallel to the surface. The lamellae provide physical strength while permitting optical transparency. The stroma has a relatively open structure and will normally allow the diffusion of hydrophilic solutes.
- The Descemet's membrane, which is secreted by the endothelium, lies between the stroma and the endothelium.
- The corneal endothelium is responsible for maintaining normal corneal hydration and consists of a single layer of flattened hexagonal cells 5µm high and 20µm wide. The endothelium is in direct contact with the anterior chamber and is subject to a passive influx of water from the aqueous humor towards the stroma.
- For a drug to cross the cornea effectively, it has to have both hydrophilic and lipophilic properties, and be sufficiently small to pass through tight junctions.

Conjunctiva

Conjunctiva of the eyelids and globe is a thin and transparent membrane, which is involved in the formation and maintenance of the tear film. In addition, conjunctiva or episclera has a rich supply of capillaries and lymphatic's; therefore, administrated drugs in the conjunctival or episclera space may be cleared through blood and lymph. The conjunctival blood vessels do not form a tight junction barrier, which means drug molecules can enter into the blood circulation by pinocytosis or convective transport through paracellular pores in the vascular endothelial layer. The conjunctival lymphatics act as an efflux system for the efficient elimination from the conjunctival space. The human conjunctiva is between 2 and 30 times more permeable to drugs than the cornea and it has been proposed that loss by this route (Noriyukikuno, 2011).

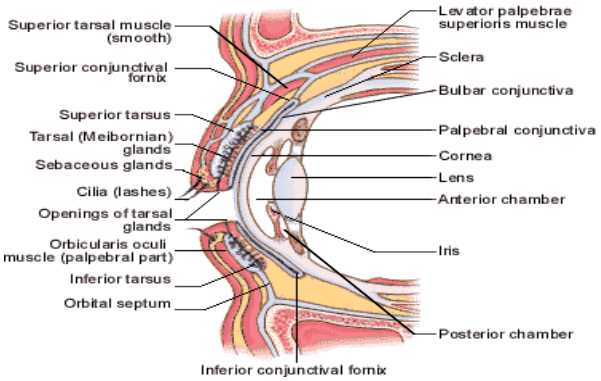

Figure 3: Structure and parts of conjunctiva

Nasolachrymal Drainage System

Nasolachrymal drainage is the major route of precorneal disposition for drug applied to the eye. The drug dose 75% is introduced in to the precorneal area is lost to the nasolachrymal drainage system within 5min following each eye drop instillation because of this nasolachrymal drainage (Chine, Yie. W., 2007).

The nasolachrymal drainage systems consist of three parts: the secretary system, the distributive system and the excretory system. The secretary system consists of basic secretors that are stimulated by blinking and

temperature change-due to tear evaporation and reflex secretors that have an efferent parasympathetic nerve supply and secrete in response to physical or emotional stimulation (Noriyukikuno, 2011).

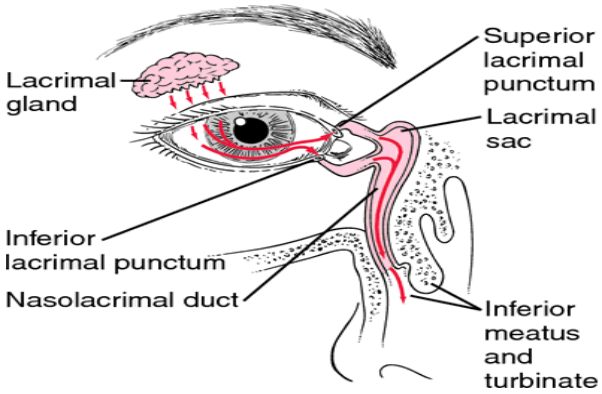

Figure 4: Nasolachrymal drainage system

The distributive system consists of the eyelids and the tear meniscus around the lid edges of the open eye, which spread tear over the occular surface by blinking, thus preventing dry areas from developing.

The excretory part consists of the lachrymal puncta the superior, inferior and common canaliculi the lachrymal sac; and the nasolachrymal duct. In humans, the two puncta are the openings of the lachrymal canaliculi and are situated on an elevated area known as the lachrymal papilla.

The cul-de-sac of the eye normally holds around 7-9µl of tears but can retain up to 20-30µl if care is taken not to blink. The normal tear flow rate is 1µl min^{-1} and the pH is maintained at 6. 5-7. 6.

Ophthalmic Disorders

Conditions treated by the typical application of drugs include:

Conjunctivitis: It is a condition where redness of the eye and the presence of a foreign body sensation are evident. Caused by bacterial and viral infection, pollen and other allergens, smoke and pollutants (Venkata Ratnam, G., 2011).

Keratitis: The condition in which patients have a decreased vision, ocular pain, red eye, and often a cloudy/opaque cornea. Keratitis is mainly caused by bacteria, viruses, fungi, protozoa and parasites.

Glaucoma: Glaucoma is a group of disease of the eye characterized by damage to the ganglion cells and the optic nerve. These effects may lead to various degrees of loss of vision and blindness. Increased intraocular pressure (IOP) remains the most important risk factor for the development of glaucoma (Notham Gooch, 2012).

Dry eye syndrome: the inadequate wetting of the ocular surface.

Iritis (anterior verities) :-commonly has an acute onset with the patient suffering pain and inflammation of the eye.

Other conditions include the ophthalmic complications of Rosacea, blepharitis (inflammation of the lid margins) and Chalazia (Meibomian cysts of the eyelid).

Drugs used in ophthalmic diseases

Different categories of drugs used for the treatment of ophthalmic diseases such as anti-viral, anti-biotic, anti-glaucoma, anti-bacterial and anti-fungal drugs.

OCCUSERTS

Ophthalmic inserts are defined as sterile preparations, with a solid or a semi solid consistency, Whose size & shape are especially designed for ophthalmic application. They are essentially composed of a polymeric support containing drug (s), the latter being incorporated as dispersion or a solution in the polymeric support. The inserts can be used for topical or systemic therapy (Sarath chandran, C., 2010).

Table 1: Drugs used in ophthalmic diseases

Anti-viral	Anti-bacterial druga	Anti-glaucoma	Anti-fungal drug
Acyclovir Gancyclovir Didanosine Zalcitabin Stavudine	Ciprofloxacin Sulfonamide Chliramphenicol Pefloxacin Levofloxacin	Pilocarpine	Floconazole

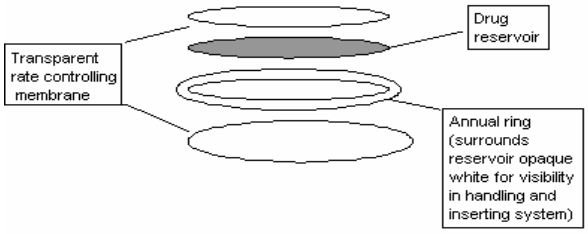

Figure 5: Structure of ocuserts

Recent trends for ocuserts

Membrane-bound ocular inserts (biodegradable and non –biodegradable), for example, ocuserts, Alzacorp.

Mucoadhesives dosage forms (ocular films or sheath, optha coil, HEMA hydrogel, Dispersion, polymer rods, poly sulfone capillary fiber).

Filter paper strips (drugs-impregnated filter paper strips for staining agent-sodium fluorescent, lissamine green, and rose Bengal).

Collagen shields, cyclodextrin-based system, ophthalmic rods (artificial tear inserts, e. g., lacriserts) (Anith kumara, 2010)

Soft contact lenses, implants, flexible coils, and cotton pledgets (drug presoaked hydrogel type, polymeric gels).

Nano particles (Microspheres, Nanosuspension, Amphiphilogels, Noisome, Liposome, Dendrimersand Quantum dots).

Ocular Iontophoresis and pumps.

Chemical delivery systems vesicular systems (Davis, J. L., 2004).

Application of Ocular Inserts

Ocular therapy generally include glaucoma, artificial tears and anticancer drug for intraocular malignancies.

The best application of diffusion therapy in the eye is the ocuserts, developed by Alza Corporation.

The unit is placed in the eye and resides in the lower cul-de-sac jest below the carnea device itself remains in the eye the drug is released in to the tear film.

Application of sustained release of artificial tears artificial tears are administered for the treatment of dry eye by topical application of eye drops ex-hydroxyl Propyl cellulose.

Delivery of drug to the eye which has proven successful is that of pro drug administration ex-phenyl ephrine pivalate (Dr Javed Ali-Dr. R. k. khar-Dr. alka ahuja., 2004).

Increased ocular residence, hence a prolonged drug activity and a higher bioavailability with respect to standard vehicles; Possibility of releasing drugs at a slow, constant rate; Accurate dosing Reduction of systemic absorption, Better patient compliance, resulting from a reduced frequency of administration and a lower incidence of visual and systemic side-effects.

Possibility of targeting internal ocular tissues through non-corneal (conjunctival scleral) routes; Increased shelf life with respect to aqueous solutions; Exclusion of preservatives, thus reducing the risk of sensitivity reactions; Possibility of incorporating various novel chemical/technological approaches (Karthikeyan., 2008).

TYPES OF OCCUSERTS

1) Insoluble inserts

a) Diffusion based

b) Osmotic based

c) Soft contact lenses

2) Soluble inserts

3) Bioerodible insets

The foreign-body sensation, presents a challenge to overcome the discomfort leads to poor-patient compliance, excessive lachrymator that accompanies irritation, dilutes the drug and causes reduction in its concentration. A properly designed ocular inserts will minimize the sensation caused by its insertation (Rather, K. S., 2009).

1) Comfort

2) Lack of explosion

3) Ease of handling with insertion

4) Non-interference with vision and oxygen Permeability.

5) Reproducibility of release kinetics

6) Sterility

7) Stability

8) Ease of manufacture

9) Applicability to variety of drugs.

Insoluble ophthalmic inserts

The insoluble inserts have been classified into three

Groups

i. Diffusion systems

ii. Osmotic systems

iii. Hydrophilic contact lenses.

The first two classes include a reservoir in contact with the inner surface of the rate controller and supplying drug thereto. The reservoir contains a liquid, a gel, a colloid, a semisolid, a solid matrix or a carrier-containing drug homogeneously or heterogeneously dispersed or dissolved therein. Carriers can be made of hydrophobic, hydrophilic, organic, inorganic, naturally occurring or synthetic material.

Diffusion inserts

Ocuserts system is a novel ocular drug delivery system based on porous membrane. The release of drug from diffusion inserts/Ocuserts is based on a diffusion release mechanism. It consists of a central reservoir of drug enclosed in specially designed micro porous membrane allowing the drug to diffuse from the reservoir at a precisely determined rate (Deivasigamani karthikeyan. 2008).

The drug release from such a system is controlled by the lachrymal fluid permeating through the membrane until a sufficient internal pressure is reached to drive the drug out of the reservoir. The drug delivery rate is controlled by diffusion through the membrane, which one can be controlled.

Osmotic inserts

The osmotic inserts are generally compared of a central part surrounded by a peripheral part. The first cen-

tral part can be composed of a single reservoir or of two distinct compartments.

In the Osmosis mechanism, the insert comprises a transverse impermeable elastic membrane dividing the interior of the insert into a first compartment and a second compartment; the first compartment is bounded by a semi-permeable membrane and the impermeable elastic membrane, and the second compartment is bounded by an impermeable material and the elastic membrane. There is a drug release aperture in the impermeable wall of the insert. The first compartment contains a solute which cannot pass through the semipermeable membrane and the second compartment provides a reservoir for the drug which again is in liquid or gel form (Darougar., 1999).

The tear fluid diffuse into peripheral deposits through the semi permeable polymeric membrane wets them and induces their dissolution. The solubilizer deposits generate a hydrostatic pressure against the polymer matrix causing its rupture under the form of apertures. Drug is then released through these apertures from the deposits near the surface of the device which is against the eye, by the sole hydrostatic pressure.

Soft contact lenses

These are shaped structure made up of a covalently cross linked hydrophilic or hydrophobic polymer that forms a three-dimensional network When a hydrophilic contact lens is soaked in a drug solution, it absorbs the drug, but does not give a delivery as precise as that provided by other non-soluble ophthalmic systems. The drug release from such a systemic generally very rapid at the beginning and then declines exponentially with time. The release rate can be decreased by incorporating the drug homogeneously during the manufacture or by adding a hydrophobic component. Contact lenses have certainly good prospects as ophthalmic drug delivery systems.

Soluble Ophthalmic inserts

Soluble inserts is a oldest class ophthalmic inserts. They have a great advantage of being entirely soluble so that they do not need to be removed from the site of application.

Soluble inserts are a sterile thin film of oval shape weighting 15 - 16mg. after introduction in the inferior cul-de –sac where wetted by the tear film. it softens in 10-15 seconds during 10 -15 min the film turns in to a viscous polymer mass. Thereafter in 30-60min it becomes a polymer solution (N. K. Jain., 2007).

Types

a) Based on natural polymers e. g. collagen.

b) Based on synthetic or semi synthetic polymers.

Soluble ophthalmic inserts

The soluble inserts offer the additional advantage of being of a generally simple design, of being based on products well adapted for ophthalmic use and easily processed by conventional methods. The main advantage is decreased release rate, but still controlled by diffusion. The release rate, J, is derived from Fick's law yields the following expression,

$$J = \frac{AdkCS}{L}$$

When A - Surface are of the membrane.

K – Diffusion coefficient of the drug

L – Membrane thickness

CS – Drug solubility in water

D – Diffusion coefficient of the Ocuserts membrane.

The other factors affecting drug release from these

Ocuserts include

- Penetration of the inclusion.
- Swelling of the matrix.
- Dissolution of the drug and the polymers.

Biodegradable ophthalmic inserts

These inserts are formed by bio-erodible polymers. Which undergo hydrolysis of chemical bonds and hence dissolution. The great advantage of these bioerodible polymers is the possibility of modulating their erosion rate by modifying their final structure during synthesis and by addition of anionic or cationic surfactants (Punch, PI., 1985).

Methods for preparation of Ocuserts

Solvent casting technique

In this method using different ratios of drug and polymer a no of batch are prepared. The polymer is dissolved in distilled water a plasticizer is added to this solution under stirring condition. The weighed amount of drug was added to above solution and stirred to get a uniform dispersion. After proper mixing the casting solution was poured in clean glass Petridis and covered with an inverted funnel to allow slow and uniform evaporation at room temperature for 48 hour. The dried film thus obtained were cut by cork borer in to circular pieces of definite size containing drug. the ocular inserts were then stored in a sir tight container under ambient condition (Renu kalyanwat., 2011).

Film casting technique

Weighed quantities of the drug and polymers were solubilizer in DCM (Dichloromethane) with continuous mixing. The solutions were then sonicated for few seconds to remove the air. Polymeric drug solutions were poured on to Teflon coated Petri dish. The matrix films were dried constantly under the ambient conditions. In

all the films plasticizers are incorporated (Hitesh, B., 2009).

EVALUATION OF OCUSERTS

Weight uniformity

Each film was weighed individually and then the average weight of films taken as the weight of the film (Dipti, H., 2011).

Thickness

Film thickness was measured by a screw gauge at three different points on the film.

Folding Endurance

Folding endurance of the film was determined by repeatedly folding the inserts at the same place till it breaks (Dipti, H., 2011).

Percentage Moisture loss

The ocuserts were pre weighed accurately and kept in desiccators containing anhydrous calcium chloride. After 3 days, the films were taken out and weight (N. Updhyaya, 2011)

$$Percentage\ moisture\ loss\ = \frac{Initial\ weight - Final\ weigh}{Initial\ weight} \times 100$$

Percentage Moisture Absorption

The ocuserts were pre weighed accurately and kept in desiccators containing 100ml of saturated solution of aluminum chloride. After 3 days, the films were taken out and weighed (N. Updhyaya., 2011)

$$Percentage\ moisture\ absorption = \frac{Final\ weigh - Initial\ weight}{Initial\ weight} \times 100$$

Water vapor transmission

The vials of equal diameter were used as transmission cells were washed and dried. About 1gm of fused calcium chloride was taken in the cells and the films were fixed over the brim with the help of solvent. Then, the cells were weighed accurately and kept in closed desiccators containing saturated solution of potassium chloride (200 ml) and the cells taken out and weighed after 3rd day of storage. Then, the water vapors transmitted were calculated by the following formula.

WVT Rate = --WL/S

W- Gm of water transmitted

L- Thickness of film

S- Exposed surface area of film

Surface pH Determination

Inserts were left to swell for 5 hours on agar plate prepared by dissolving 2% (m/v) agar in warm simulated tear fluid (STF; sodium chloride: 0. 670 g, sodium bicarbonate: 0. 200 g, calcium chloride. 2H2O: 0. 008 g, and purified water q. s. 100 g (3)) of pH 7. 2 under stirring and then pouring the solution into Petri dish till gelling at room temperature. The surface pH was measured by means of a pH paper placed on the surface of swollen patch.

Swelling index

Swelling of the polymer depends on the concentration of the polymer, ionic strength and the presence of water. To determine the swelling index of prepared ocular inserts, initial weight of insert was taken, and then placed in agar gel plate (2% *m/v* agar in STF, pH 7. 2) and incubated at 37±1°C. For five hours, insert was removed from plate after every one hour, surface water was removed with help of filter paper, and insert was reweighed. Swelling index was calculated.

Swelling Index (Sw) %= [wt - w0/wt] ×100

(Sw) % = Equilibrium percent swelling

Wt = Weight of swollen insert after time t.

W0 = Original weight of insert at zero time

Ocular Irritation

The potential ocular irritation and/or damaging effects of the ocuserts under test were evaluated by observing them for any redness, inflammation, or increased tear production. Formulation was tested on five rabbits by placing the inserts in the cul-de-sac of the left eye. Both eyes of the rabbits under test were examined for any signs of irritation before treatment and were observed up to 12 hours (Hindustan Abdul Ahad., 2011)

Microbiological studies

Ocular inserts were evaluated microbiologically for controlled drug release for a period of 7 Days. Melted nutrient agar medium was taken and inoculated with 4-5 loops full of test Microorganism from the provided culture. The inoculated medium was poured into a sterile Petridis and allowed to solidify. A sterile ocular insert was placed carefully on the semisolid Medium. The petri dish was incubated in inverted position for 24 hours at 37±0. 5°C. After Incubation, observed for the zone of inhibition. The zone of inhibition was recorded. The ocuserts was then transferred to a fresh, similarly prepared plate. The same procedure was repeated for 7 Days, i. e., by transferring the same insert to a fresh Petridis at an interval of 24 hour

Sterility testing

The sterility test was carried out using by direct inoculation of the culture media with the product to be examined. Sealed package was opened using aseptic precautions and the inserts were placed in the culture medium. Then the inserts were incubated in soya-bean casein digest medium (pH 7. 3) at 35 ±0. 5 0C for 14 days.

Drug content uniformity

Drug content was estimated by triturating ocular inserts in 20 ml of phosphate buffer pH. 7. 2 With the

Table 2: Marketed available Ophthalmic Occuserts

S. no	Name of drug	Brand name	Category	Treatment of diseases
1	Diclofenac Sodium (Ramkanth, S., 2009).	VOLTAREN	NACID	Inhibition of intraoperative miosis and post operative inflammation in cataract surgery
2	Levofloxacin (Hitesh, B., 2009).	QUIXIN	Anti - bacterial.	bacterial conjunctivitis
3	Natamycin (A. Rajasekaran., 2010)	NATACYN	Anti-fungal	conjunctivitis and keratitis
4	Pilocarpine (Pei Fei Lee, Yeong Tai Shen., 1975)	OCUSERT PILO	Anti-glaucoma	Glaucoma
5	Acyclovir (S. Shanmugan., 2011)	BETOPTICS	Anti- viral	Conjunctivitis

help of a mortar and pestle. The solution was filtered and one ml of the solution was withdrawn, diluted and measured by a UV-Visible Spectrophotometer (Balasubramanian., 2006).

***In vitro* drug release studies**

In vitro drug release study was carried out by using biochambered donor- receptor compartment model. The commercial semi permeable egg membrane, presoaked overnight in the freshly prepared dissolution medium (STF pH7. 2), and was tied to one end of a cylinder (open at both the sides) which acted as donor compartment (Saisivam., 1999). The ocular insert was placed inside the donor compartment in contact with the semi-permeable membrane. The donor compartment was attached to a stand and suspended in 25 ml of the dissolution medium maintained at 37±1°C in the way that touches the receptor medium surface. The dissolution medium was stirred at a low speed using magnetic stirrer. The aliquots of 5 ml were withdrawn at regular intervals of specified time intervals and replaced by an equal volume of dissolution medium every time. The samples were analyzed on UV spectrophotometry.

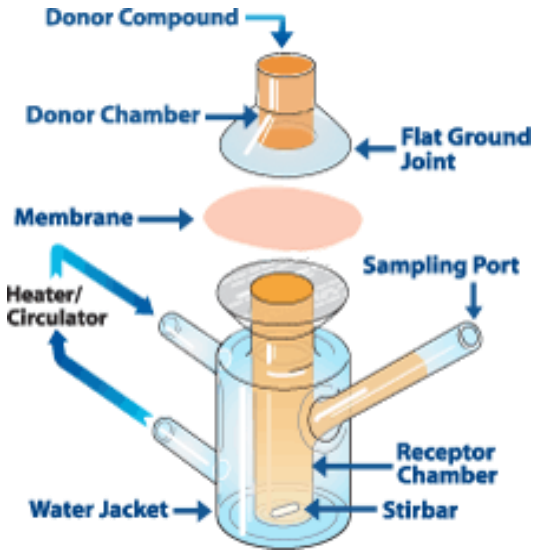

Figure 6: Biochambered donor- receptor compartment model

Stability studies

The inserts were stored in amber colored glass bottles at three different temperatures of 4°C, Room temperature and 40°C for a period of two months. The samples were withdrawn after 7, 15, 30 and 60 days and analyzed for physical appearance, drug content and sterility. The optimized formulation was packed in aluminum foil. It was then stored at 40°C / 75 % RH according to ICH. Samples were withdrawn after three months and evaluated for change in drug release pattern (Hindustan Abdul Ahad., 2011)

CONCLUSION

The ocuserts have wide variety of advantages to treat ophthalmic disease. Finally concluded that the present review work has been reveals that the ophthalmic disease and their treatment by using ocuserts**.**

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