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Review

The Concept of Ophthalmic Inserts as Drug Delivery Systems: An Insight

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Abstract: Ophthalmic drug delivery is an extremely interesting and highly challenging endeavor facing pharmaceutical scientists. As an isolated organ, it is difficult to study the eye from a drug delivery point of view. The anatomy, physiology, and biochemistry of the eye render this organ exquisitely impervious to foreign substances. In recent scenarios, most eye diseases are treated with topical application of eye drops. However, these conventional eye drops have two major problems. One is it needs frequent administration and another is the formation of crystalline deposits on the cornea due to its pH-dependent solubility which is very low. Also, conventional drug delivery systems such as solutions, emulsions, and eye drops deliver the appropriate amount of drug but due to barriers such as lacrimal drainage, tear flow, etc. cause the drug to drain from the ocular surface. To provide the solution to the above problems many novel formulations have been developed. Ocular insert is one of them. Ocular inserts are defined as sterile, thin, multilayered, drug-impregnated, solid, or semisolid consistency devices placed into the cul-de-sac or conjunctival sac, whose size and shape are specially designed for ophthalmic application. They are made of various techniques that make them soluble, erodible, and insoluble. The review study emphasizes on advantages of ocular inserts over conventional dosage forms. The study includes the physiology of the eye and various preparation, and evaluation methods of ocular inserts.

Keywords: Conventional, Cul-de-sac, Eye, Ocular drug delivery, Ocular inserts, Novel

Introduction

Topical application of drugs to the eye is the well-established route of administration for the treatment of various eye diseases like dryness, conjunctiva, eye flu, etc. (Dhanapal and Ratna 2012). For illness of the eye, topical administration is usually ideal over systemic administration, before reaching the anatomical barrier of the cornea, any drug molecule administered by the ocular route that crosses the precorneal barriers. The protective mechanisms of the eye such as blinking, baseline and reflex lacrimation, and drainage decrease the bioavailability of drugs and also help to remove rapidly foreign substances like dust particles and bacteria, including drugs from the surface of the eye. There are most commonly available ophthalmic preparations such as drops and ointments about 70% of the eye dosage formulations in the market. But these preparations when instilled into the eye are rapidly drained away from the ocular surface due to blinking tear flow and lachrymal nasal drainage of the eye. With conventional ophthalmic solution normal dropper is used which delivers about 50-75µl per drop and a portion of these drops rapidly drain until the eye is back to normal i.e., with a resident volume of 7µl. Due to this drug loss in front of the eye, very small drugs are available to enter the cornea and inner tissue of the eye. Actual corneal permeability of the drug is relatively low and very small corneal contact time (about 1-2

min) in humans for an instilled solution is usually less than 10%. Therefore, only a small amount of the drug actually penetrates the cornea and reaches intraocular tissue.

1. Anatomy of the Human Eye

The adult eyeball is often referred to as a spherical globe, with its largest diameter being 24 mm anteroposteriorly (Sharma et al. 1974). Sclera is a white outer protective coat i.e. white of the eye. The cornea is the transparent, curved structure at the front of the eye and has poor penetration of drugs. Iris is a colored part of the eye. The pupil is the black part of the eye in the middle of the iris. The lenses are transparent discs immediately behind the iris and pupil. Aqueous humor is the transparent fluid that circulates behind the cornea and in front of the lenses. Vitreous is the material (like transparent jelly) that fills the eyeball between the lens and retina. The retina is a light-sensitive layer of millions of nerve cells that line the back of the eyeball (Fig. 1). Choroid is a large network of blood vessels that transport oxygen and other nutrients to the retinal pigment cells (Kurade et al. 2015).

The eyes are constantly cleansed and lubricated by the lacrimal apparatus which consists of four structures: lacrimal glands, lacrimal canals, lacrimal sac, and nasolacrimal duct. The lacrimal fluid secreted by the lacrimal glands is emptied on the surface of the conjunctiva of the upper eyelid at a turnover rate of 16% per minute. It washes over the eyeball and is swept up by the blinking action of the eyelids.

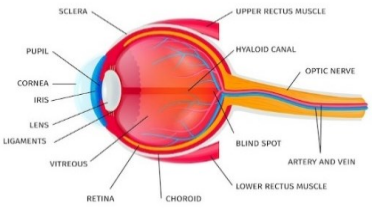

Fig. 1. Basic anatomy of the human eye.

2. Disorders of the Human Eye

Cataract

The term cataract refers to any cloudiness or opacity of the normally transparent crystalline lens of the eye. A cataract may or may not cause a loss of vision, depending on the size of the opacity, its density, and its location. Severe cataracts are a major cause of treatable blindness throughout the world.

Conjunctivitis

Conjunctivitis is an inflammation of the conjunctiva, the transparent mucous membrane lining the inside of the eyelids, and the white of the eyeball. Normally the white, or sclera, is clearly visible through the conjunctiva, but when the conjunctiva is inflamed, its normally invisible blood vessels become engorged, making the eye appear red. Conjunctivitis may be caused by many types of infectious agents, such as viruses or bacteria, as well as by toxic, chemical, and allergenic irritants.

Macular Degeneration

Macular degeneration, also called “age-related macular degeneration” (AMD), is the most common cause of blindness and vision impairment among the elderly. AMD damages the macula, a small part of the eye's light-sensitive retina (the layer of tissue that sends signals for vision to the brain). Because the macula is responsible for seeing sharp details directly in the center of the field of vision, damage caused by AMD may interfere with a person's ability to see straight ahead (necessary for driving and distance viewing, like TV watching) and for fine, detailed vision (newsprint reading, sewing, crafts, and repairs).

Night Blindness

Impairment of the vision in dim light is called night blindness, or nyctalopia. It may be due to vitamin A deficiency because that vitamin plays a major role in the cells of the eye sensitive to dim light. Night blindness is also a manifestation of various eye disorders such as glaucoma and optic nerve disease. It is often the earliest symptom of retinitis pigmentosa, a chronic and progressive inflammation of the retina.

Keratoconjunctivitis Sicca (KCS)

Dry eye syndrome, also known as Keratoconjunctivitis Sicca (KCS), is a disorder of the tear film that occurs due to tear deficiency or excessive tear evaporation; it causes damage to the interpalpebral ocular surface and is associated with a variety of symptoms reflecting ocular discomfort.

Dry eye symptoms may be a manifestation of a systemic disease; therefore, timely detection may lead to the recognition of a life-threatening

condition. Also, patients with dry eye are prone to potentially blinding infections, such as bacterial keratitis, and also at an increased risk of complications following common procedures such as laser refractive surgery.

3. Types of Ophthalmic Dosage Forms

Ophthalmic Solutions

The solution in the form of eye drops is one of the most frequent dosage forms used in the eye. The drug in the solution remains active as it enters the eye surface after passing through the cornea or conjunctiva. The main disadvantage of solutions is their less retention time in the eye, reduced bioavailability as 75% of the solution is removed through nasolacrimal fluid, unsteadiness of the drug, and a need for preservatives. The demerits of the eye can be shortened by using a viscosity-enhancing agent in the solution as it increases the retention time.

Ophthalmic Suspensions

Suspensions may be defined as a dosage form containing small divided insoluble drug particles dispersed in an aqueous vehicle having a suspending and dispersing agent. The retention time of the suspension is longer in comparison to the solution because of the ability of the particle to remain in the cul-de-sac. The dissolution rate of particles of suspension is inversely proportional to the particle size. Therefore, for suspension, a suitable particle size should be selected for the delivery of the drug into the eye for better dissolution which would be less than 10μm (Gurtler and Gurney 1995).

Sol-gel System

It is a newer concept of producing a gel from solutions by increasing the amount of viscosity-enhancing agent in the solution. As a result, the viscosity of the drug solution increases which results in gels leading to increased contact time and bioavailability and less drainage from the cornea. Many concepts have been discovered for the formation of in-situ gels these systems show their activation by changes in pH, temperature, or by Ion activation. The viscous solution or gels may result in increased contact time in the eye surface for the absorption of the drug but it can irritate the eye (Gurtler and Gurney 1995).

Ophthalmic Ointments

Ophthalmic ointments are semi-solid dosage forms containing mineral oil and white petroleum jelly as the base whose concentration varies according to the consistency needed for the ointment and the melting temperature. Drug loading in ointments is greater than in the case of solution. Due to the high consistency and viscosity of ointments, it can affect the vision of the eye which is the main disadvantage of ointments. So its application is only limited to the nights before sleeping. Only moisture-sensitive drugs can be delivered by base ingredients due to their anhydrous nature. Ointments are mostly preferred by pediatric patients. The main advantages of ophthalmic ointments are greater contact time and increased absorption of total drug (Gurtler and Gurney 1995).

Ophthalmic Emulsions

Ophthalmic dosage forms have the advantage of delivering poorly water-soluble drugs. The emulsion consists of a phase oil phase or a non-aqueous phase in which the drug is dissolved or an aqueous phase which is made miscible using an emulsifying agent. The emulsion is of two types-o/w types or w/o type, out of which w/o type which water in the external phase is less irritating to the eye and can be bearable by the patient than o/w type emulsion (Kumar et al. 2011).

a. Ocular Inserts

Ophthalmic inserts are sterile preparations with a solid or a semisolid consistency, and whose size and shape are specially designed for ophthalmic application. Ocular inserts can overcome the disadvantages reported with traditional ophthalmic systems like eye drops, suspensions, and ointments. The composition of ocuserts includes polymeric support in which drug(s), are incorporated in the form of dispersion or a solution. For topical or systemic therapy in the eye, ocuserts can be used. The main purpose of the use of ophthalmic inserts is to enhance the retention time of the active form of the drug in the eye to ensure a sustained release suit. In comparison with other liquid formulations the ocuserts have numerous benefits Because of the prolonged retention time of the device and a controlled release, an efficient concentration of drug in the eye can achieved for an extended time. Dosing frequency can also be reduced and the risk of systemic adverse effects is decreased.

b. Classification of Ophthalmic Inserts

Depending on solubility ophthalmic inserts are classified as below:

Insoluble Inserts

This category of inserts includes diffusion and osmotic systems in which a drug reservoir is placed between the rate-controlling polymers to supply the drug in a controlled manner. In the reservoir system, the drug is dispersed or dissolved in a polymer in the form of a liquid, a gel, a colloid, a semisolid, or a solid matrix. The polymer that is used as a carrier may be hydrophobic, hydrophilic, organic, inorganic, naturally occurring, or synthetic material in nature (Rathore et al. 2010, Bloomfield et al. 1978). In this drug release depends on diffusion or osmosis.

Soluble Inserts

This type of insert belongs to the oldest class of ocular inserts. The main advantage of these inserts is that as they are completely soluble there is no need for removal from the site of application. The therapeutic agents are preferably absorbed by soaking the insert in a solution containing the drug, drying and rehydrating it before use on the eye. The amount of drug loaded will depend upon the amount of binding agent, the concentration of the drug solution into which the composite is soaked, as well as the duration of soaking (Bloomfield et al. 1978).

Bio-erodible Inserts

The bio-erodible inserts consist of homogeneous dispersion of a drug with or without a coating of hydrophobic coating which is considerably not permeable to the drug. As the name indicates bio-erodible polymers are used in the formulation of these inserts. The bio-erodible materials that are suitable for ophthalmic use are poly (orthoesters) and poly (orthocarbonates), etc. The drug release of these systems depends on the contact of the device with tear fluid showing an apparent bioerosion of the matrix (Bloomfield et al. 1978). It is of three types SODI (Soluble Ocular Delivery Inserts), Lacrisertis, and mini disc.

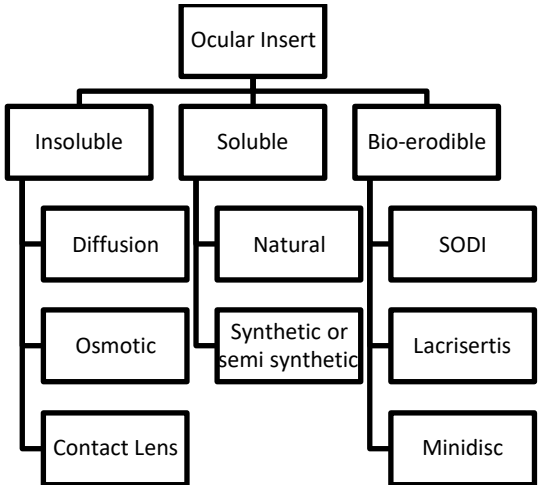

Fig. 2. Classification based on solubility ophthalmic inserts.

c. Mechanism of Drug Release

In the case of a controlled drug delivery system, the release of the drugs into the eye based on Diffusion, Osmosis, Bio-erosion

Diffusion

In this mechanism, the release of drugs through the membrane into the tear fluid occurs continuously in a controlled manner. Drug release takes place through diffusion into the pores. The controlled release can be regulated by the gradual dissolution of the solid dispersed drug within the matrix, due to which inward diffusion of an aqueous solution occurs. When the device is inserted into the eye, water from the tear fluid starts penetrating the matrix, then swelling of polymer with chain relaxation begins, and then drug diffusion takes place.

Osmosis

In osmosis, the insert is composed of a transverse elastic impermeable membrane. The interior parts of the inserts are divided into two compartments. In the first compartment, there is a solute that cannot cross the semi-permeable membrane and the second compartment supplies a reservoir for the drug which again is in liquid or gel form. When the insert comes into contact with the aqueous environment of the eye, water diffuses into the first compartment and enlarges the elastic membrane to open out the first compartment and contract the second compartment so that the drug is forced through the drug release (Dave et al. 2012).

Bio-erosion

In bio-erosion, the body of the insert is made from the matrix of a bio-erodible material in which the drug is present in a dispersed form. The contact of the insert with tear fluid results in the controlled release of the drug from the matrix, it may or may not be dispersed uniformly throughout the matrix, but the controlled release property of the drug can be achieved. These devices maintain constant surface geometry and that drug is poorly water-soluble.

d. **Advantages and Disadvantages of Ocular Insert**

The various advantages and disadvantages have been compiled in Table 1.

Table 1. Advantages and disadvantages of ocular insert. Source: Venkata et al. 2011, Karthikeyan et al. 2014.

Advantages	Disadvantages
Releasing of the drug slow and constant rate.	One of the main disadvantages of ocular inserts is their 'solidity', i.e., they are felt by the patients as an extraneous body in the eye. This may cause physical and psychological barriers to user acceptance and compliance.
Reduction of systemic absorption (which occurs freely with eye drops via the nasolacrimal duct and nasal mucosa)	Difficulty in the placement of ocular inserts.
Better patient compliance, resulting from a reduced frequency of administration and a lower incidence of visual and systemic side effects	Interference with the vision.
Increased shelf life for aqueous solutions	Unwanted migration of the insert to the upper fornix.
Increasing contact time and thus improving the bioavailability.	Leakage may occur
Increase ocular residence and prolong drug activity.	The occasional inadvertent loss during sleep or sometimes

e. Formulation Methods of Ocular Inserts (Ocuserts)

Solvent Casting Method

In this method number of batches are prepared of different ratios of drug and polymer. The polymer is dissolved in a suitable solvent. Into this solution plasticizer is added following continuous stirring and the accurately weighed amount of drug is added to the above solution and a uniform dispersion is obtained. The solution is transferred into a petri dish. The dried film was cut into definite sizes. The ocular inserts are stored in an airtight container (Dave et al. 2012, Karthikeyan et al. 2014).

Glass Substrate Technique

In this method the polymer like chitosan is soaked in 1%v/v Acetic acid solution for 24hrs, to get a clear solution. The solution is filtered. The required amount of drug is added and vortexed for 15 minutes to dissolve the complex in the polymer solution. A plasticizer is added to the above solution. The viscous solution is obtained and kept aside for 30 minutes until air bubbles are removed The rate-controlling films are formed and allowed to dry at room temperature for 24 hrs. The dried films are cut to form ocusert in definite shape and size Then, the matrix is sandwiched between the rate-controlling membranes using gum which is non-toxic, non-irritating, and water-insoluble. They are wrapped in aluminum foil separately and stored in a desiccator (Karthikeyan et al. 2014).

Melt Extrusion Technique

The drug and the polymer are passed through a sieve having a mesh size of 60#, weighed, and blended. In this mixture, the plasticizer is added. The blend is then discharged to the container of the Melt flow rate apparatus and extruded. The extrudate was cut into appropriate sizes and packed in polyethylene Aluminum foil, heat sealed, and sterilized by gamma radiation (Karthikeyan et al. 2014, Pandey et al. 2011).

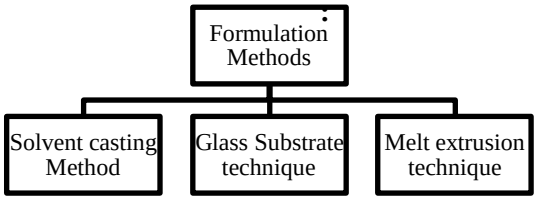

Fig. 3. Different formulation methods of Ocular Inserts (Ocuserts).

f. Evaluation Parameters of Ocuserts

Ocular inserts are evaluated based on various evaluation parameters like weight, thickness, content uniformity, percentage moisture loss, swelling index, percentage moisture absorption, in vivo drug release, in vitro drug release, surface pH, accelerated stability studies, folding endurance, etc.

Uniformity of Weight

All the prepared films are weighed separately and the weight of each film is noted. Then the average weight of the film is calculated. The standard deviation is calculated from the mean value (Karthikeyan et al. 2014).

Uniformity of Thickness

Thickness was determined by the use of Vernier-caliper/micro-meter gauze. Thickness was measured at five different points of each insert and the mean value was calculated (Born et al. 1997).

Percentage Moisture Absorption

This test is carried out to check the stability of ocular inserts. For the calculation of the percentage moisture absorption of the ocular inserts, the inserts are weighed and placed in desiccators containing 100 ml of saturated solution of aluminum chloride, and humidity is maintained at 79.5%. After three days' inserts were taken out and weighed properly. The percentage moisture absorption was calculated by using the formula (Abhilash et al. 2005):

$$\text{Percentage Moisture Absorption} = \text{Final Weight} - \frac{\text{Initial Weight}}{\text{Initial Weight}} \times 100$$

Swelling Index

A small amount of film is cut and weighed initially and then it is soaked in pH 7.4 tear fluid for 1 hour. After 1 hour, the film is reweighed. The swelling index is calculated by following formula (Abhilash et al. 2005, Mueller et al. 1956).

$$\text{Swelling Index} = \frac{\text{Initial Weight}}{\text{Final Weight}} \times 100$$

Drug Content Uniformity

A small amount of inserts is cut and dipped in 7 ml of tear fluid. Then it is taken in a centrifuge tube centrifuged for 15 min and analyzed in UV spectrometry. The concentration of a drug is calculated using a standard plot (Abhilash et al. 2005, Mueller et al. 1956).

Percentage Moisture Loss

This parameter checks the adherence of the film in the dry condition. Inserts were weighed and kept in a desiccator containing calcium chloride and after three days they were weighed again. Then by formula moisture loss was calculated (Abhilash et al. 2005):

$$\text{Percentage Moisture Loss} = \text{Initial Weight} - \frac{\text{Final Weight}}{\text{Initial Weight}} \times 100$$

Surface pH

Insert is placed in a closed Petri plate in distilled water for half an hour. After this, the swelling of the insert occurred. A swollen insert is then placed in a digital pH meter to determine surface pH (Abhilash et al. 2005, Mueller et al. 1956).

Folding Endurance

Folding endurance for ocular insert determined the number of folds that occurred in the film till its breakage. The folding endurance test was repeated using other sets of ocular inserts (Abhilash et al. 2005).

***In vitro* Diffusion Studies**

In vitro, drug release study of ocuserts is done by using Franz diffusion cell. It is an instrument used to study the permeability study of drugs. It consists of two compartments, one is the donor compartment in which dosage form i.e. ocusert is added and another is the receptor compartment which is filled with 7.4 tear fluid to simulate the tear fluid in the eye. Both compartments are separated by a membrane which may be semi semi-permeable dialysis membrane or egg membrane. The instrument is started, and RPM and temperature are adjusted. Ocusert is placed in the donor compartment and tear fluid in the receptor compartment. 1ml sample is withdrawn after a fixed time interval and after making a suitable dilution sample is analyzed in a UV spectrophotometer. The sample is withdrawn until a constant absorbance is not obtained. Drug release is calculated (Shafie and Rady 2012, Charoo et al. 2003).

Accelerated Stability Studies

In this study, ocuserts are placed in a square petri dish and film of them is taken out and kept at 3 different temperatures i.e. 400^{o}C, 500^{o}C, and 600^{o}C, and the time taken for the degradation is checked (Charoo et al. 2003).

g. Currently Available Ocular Inserts (Rathore et al. 2010)

S. No.	Name	Company	Uses
1.	Soluble ocular drug insert	Alza Corporation	Glaucoma, Dry eye treatment
2.	Collagen Shields	Bausch and Lomb Pharmaceuticals	Dry eye Syndrome
3.	Minidisc	Alza Corporation	Dry eye syndrome
4.	Lacrisert	Merck and Co. Inc	Dry eye syndrome
5.	Bioadhesive ophthalmic eye inserts	Sigma Aldrich Corporation	Treatment of Glaucoma
6.	Ocuserts	Alza Corporation	Dry eye syndrome

h. Conclusion

It's evident that drug delivery to the eye shows significant and important complications. Conventional dosage form needs frequent administration every 4 hours and formation of crystalline deposits on the cornea due to its pH-dependent solubility which is very low. The purpose of preparing an ocular insert is to increase the bioavailability of the drug. Inserts are available in different forms depending on their composition and applications. Ocuserts reduced the number of dose administrations thus improving patient compliance. It increases contact time and thus improves bioavailability. Systemic side effects can be decreased, hence reducing adverse effects. The use of preservatives is prohibited thus reducing the risk of sensitivity reactions (Lambert and Guilatt 2005, Lee and Robinson 1976). Ocular inserts are prepared with a different method and can be evaluated with different parameters. Ocuserts are novel approaches in the era of ocular drug delivery compliance with ethical standards.

References

1. Abhilash, A.S., Jayaprakash, S., Nagarajan, M., Dachinamoorthy, D. (2005). Design and evaluation of Timolol ocuserts. Indian J. Pharma Sci., 67(3), 311-314.
2. Bloomfield, S.E., Miyata, T., Dunn, M.W., Bueser, N., Stenzel, K.H., Rubin, A.L. (1978). Soluble gentamicin ophthalmic inserts as a delivery system. Arch. Ophthalmol., 96, 885-887.
3. Born, A.J., Tripathi, R.C., Tripathi, B.J. (1997). Wolff's anatomy of the eye and orbit, 8th ed. Chapman & Hall Medical, London, pp. 211–232.
4. Charoo, N.A., Kohli, K., Ali, A., Anwer, A. (2003). Ophthalmic delivery of Ciprofloxacin hydrochloride from different polymer formulations: *in vitro* and *in vivo* studies. Drug Dev. Ind. Pharm., 29(2), 215-221.
5. Chrai, S.S., Makoid, M.C., Erikson, S.P., Robinson J.R. (1974). Drop size and initial dosing frequency problems of topically applied ophthalmic drugs. J. Pharm. Sci., 64, 333.
6. Dave, V., Pareek, A., Yadav, S., Paliwal, S. (2012). Ocular drug delivery system- A technical note. World Journal of Pharmacy and Pharmaceutical Sciences, 1(3), 859-862.
7. Dhanapal, R., Ratna, J.V. (2012). Ocular drug delivery system –a review. International Journal of Innovative Drug Discovery, 2(1), 4-15.
8. Gurtler, F., Gurney, R. (1995). Patent literature review of ophthalmic inserts. Drug Dev. Ind. Pharm., 21, 1.
9. Jitendra, Sharma, P.K., Banik, A., Dixit, S.A. (2011). New Trend: Ocular Drug Delivery System. An Inter. J. of Pharma. Sci., 2(3), 1-22.
10. Karthikeyan, D., Bhowmick, M., Pandey, V. P., Nandhakumar, J., Sengottuvelu, S., Sonkar, S., Sivakumar, T. (2008). The concept of ocular inserts as drug delivery systems: An overview. Asian Journal of Pharmaceutics, 2(4).
11. Kumar, A., Malviya, R., Sharma, P.K. (2011). Recent Trends in Ocular Drug Delivery: A Short Review, European J. Applied Sci., 3(3), 86-92.
12. Kumari, A., Sharma, P. K., Garg, V. K., Garg, G. (2010). Ocular inserts—Advancement in therapy of eye diseases. Journal of Advanced Pharmaceutical Technology & Research, 1(3), 291-296.
13. Kurade, D.S., Joshi, D.G., Anita, B. (2015). A review on ocular drug delivery with new trends. International Journal of Advanced Research, 3(11), 629-642.
14. Lambert, G., Guilatt, R.L. (2005). Current ocular drug delivery challenges. Drug Dev. Report Industry Overview Deals, 33, 1-2.
15. Lee, V.H.L., Robinson, J.F. (1976). Review: Topical ocular drug delivery; recent developments and future challenges. J. Ocul. Pharmacol., 2, 67.
16. Mueller, W.H., Deardroff, D.L. (1956). Ophthalmic vehicles: The effect of methylcellulose on the penetration of Homatropine hydrobromide through the cornea. J. Am. Pharma. Assoc., 45, 334-341.
17. Pandey, P., Panwar, S.A., Dwivedi, P., Jain, P., Agarwal, A., Jain, D. (2011). Design and evaluation of ocular inserts for controlled drug delivery of Acyclovir. International Journal of Pharmaceutical & Biological Archives, 2(4), 1106-1110.
18. Rathore, K.S., Nema, R.K., Sisodia, S.S. (2010). Timolol maleate a gold standard drug in glaucoma used as ocular films and inserts: an overview. Int. J. Pharm. Sci. Rev. Res., 3.1, 23-9.
19. Shafie, Mohamad Ali Attia, Mai Ahmed Hassan Rady (2012). *In vitro* and *in vivo* evaluation of timolol maleate ocular inserts using different polymers. J. Clin. Exp. Ophthalmol., 3, 246.
20. Venkata, R.G., Madhavi, S., Rajesh, P. (2011). Ocular drug delivery: An update review. International Journal of Pharmacy and Biological Sciences, 1(3), 437-446.