RECENT TRENDS IN NOVEL OPHTHALMIC DRUG DELIVERY SYSTEM- A SHORT REVIEW

Anu Kaushik*
Research Scholar, Shri Jagdish Prasad Jhabarmal Tibrewala University, Rajasthan.

Corresponding Author: Anu Kaushik
Research Scholar, Shri Jagdish Prasad Jhabarmal Tibrewala University, Rajasthan.

Article Received on 01/06/2016  Article Revised on 22/06/2016  Article Accepted on 13/07/2016

ABSTRACT
Ophthalmic drug delivery is among the most interesting and challenging endeavors facing the pharmaceutical scientist. The anatomy, physiology, and biochemistry of the eye renders this organ more impervious to foreign substances. Their is significant challenge for the formulator to circumvent the protective barriers of the eye without causing permanent tissue damage. Development of newer, more sensitive diagnostic techniques and novel therapeutic agents continue to provide ocular delivery systems with high therapeutic efficacy. The major problem with the conventional dosage forms is the bioavailability of drug, which were improved ion last three decades by common method i.e. adding viscosity-enhancing agent or mucosalheive polymers into drug formulation. The specific aim for designing a therapeutic system is to achieve an optimal concentration of a drug at the active site for the appropriate duration.

KEYWORDS: Novel ophthalmic drug delivery system, conventional dosage form, in-situ gelforming system.

INTRODUCTION
The ophthalmic formulation such as solution, suspension and ointments, available in market show drawbacks such as increased precorneal elimination, high variability in efficiency and blurred vision. The goal of pharmacotherapeutics is to treat a disease in a consistent and predictable fashion. An assumption is made that a correlation exists between the concentration of a drug at its intended site of action and the resulting pharmacological effect. Ophthalmic solutions are available for multidose or single-dose administration in a wide variety of glass and plastic dropper bottles, which deliver drops with a volume between 25 and 70 µL. On administration of topically applied eye drops, removal from the eye is rapid because of tear production and the blinking processes occurs simultaneously. The precorneal volume is about 7 µL, but volumes up to 20 to 30 µL can be held in this area before spillage occurs. Instillation of volumes greater than this will result in simply spilling out onto the cheek or rapid loss with the tears through drainage into the nasolachrymal duct. Also, the instilled product is diluted by normal tear production, with tear production rates in man reported as 1 µL/min under resting conditions. In practice, the introduction of any eye drop product, but particularly products causing irritation, will stimulate the tear production rate and increase the rate of drug removal from the eye. The removal of material by dilution is also aided by the blink reflex where each blink pumps approximately 2 µL of tear fluid into the nasolachrymal duct. Therefore, only small amount of drug actually penetrates the cornea and reaches intraocular tissue. Because of these limitations, Controlled drug delivery to the eye is restricted imposed by the efficient protective mechanism. An ideal ophthalmic drug delivery must be able to release the drug in sustained manner and to remain in the area of front of the eye for prolonged period of time. The in-situ activated gel forming systems can be administered in drop form and create considerably few problems with vision so that it is most preferable type of drug delivery system. Further, In-situ gel systems provide better sustained release properties than drops. These type of dosage forms are used now a day in various type of eye disease like glaucoma, dry eye syndrome, eye infection etc. Ocular disposition and elimination of a therapeutic agent is dependent upon its physicochemical properties as well as the relevant ocular anatomy and physiology.  

Anatomy and Physiology of the eye
Eye is the organ of the sense of sight situated in the orbital cavity and it is supplied by the optic nerve (2nd cranial nerve). Eyeball is made up of two segments, an anterior part and posterior part. The posterior wall is lined by the light sensitive structure called retina. Eyebrows
The two eyebrows are arched structures which is placed horizontally over the superciliary ridge of the frontal bone, separated from each other by a smooth hairless prominent area known as glabella.
Eyelids
Eyelids protects the eyeball from foreign particles coming in contact with its surface and cutoff the light during sleep.

Fig.1 Human eye

Conjunctiva
It is a thin mucous membrane, which covers exposed part of the eye. After covering the anterior surface, the conjunctiva is reflected into the inner surface of the eyelids.\[13\]

Lacrimal apparatus
The lacrimal apparatus comprises of the structures concerned with the formation and drainage of tears. The nasolacrimal drainage system consists of mainly three parts: the secretory system, the distributive system and the excretory system.\[15\]

The eyeball
The eyeball comprises of three coats:\[12\]
- Outer (fibrous coat): sclera and cornea,
- Middle (vascular coat): choroid, ciliary body and iris,
- Inner (nervous coat): retina.

The outer fibrous coat
It is dense strong walls which protect the intraocular contents.

Cornea
The cornea is transparent, avascular, watchglass-like structure with a smooth shining surface.

Sclera
The sclera, or white of the eye forms the outermost layer of tissue of the posterior and lateral aspects of the eyeball and is continuous anteriorly with the transparent cornea.\[14\]

Iris
The iris works in the same manner as the pupil of the eye.\[16\]

Ciliary body
The Ciliary body is the anterior continuation of choroid consisting of ciliary muscle (smooth muscle fibres) and secretory epithelial cells.

Choroids
It is dark brown highly vascular layer situated in between sclera and retina. It supplies nutrition to the outer layers of retina.

The inner nervous coat (retina)
Retina, the innermost tunic of the eyeball, is a thin, delicate, transparent membrane. It is related with the visual functions.

Interior of eyeball
Interior of the eyeball contains, from anterior to posterior- the aqueous humour, lens and vitreous.

Aqueous humour
The anterior segment of eye, i.e. the space between the cornea and the lens, is divided into anterior and posterior chambers by the iris.

Vitreous humour
Behind the lens and filling the posterior segment (cavity) of the eyeball is the vitreous body (humour).

Lens
The lens is a transparent, biconvex, crystalline structure placed between the iris and the vitreous.\[12,14\]

Advantages of ocular drug delivery systems\[4-5\]
- Needle free drug application and easy convenience
- Low molecular weight drugs can be obtained through the eye.
- Possess Good penetration of hydrophilic
- By increasing the corneal contact time the ocular bioavailability of drug can be increased. This can be done by effective adherence to corneal surface.
- Avoiding hepatic first pass metabolism and so, potential for dose reduction compared to oral delivery.

CONVENTIONAL OPHTHALMIC DRUG DELIVERY SYSTEMS
Aqueous Solutions
Nowadays, majority of topical ophthalmic preparations are available in the form of aqueous solutions. Homogeneous Solution dosage form offers many advantages including the simplicity of large scale manufacture. However, eye drops do have the disadvantage of being rapidly drained from the eye, with corresponding loss of drug. The inclusion of viscosity-increasing agents in the formulation, such as hypromellose, hydroxyethylcellulose, polyvinyl alcohol, povidone, or dextran, is used to increase the tear...
viscosity, which decreases drainage, therefore prolonging preconstral retention of the drops in the eye. Various studies have shown that an increase in product viscosity increases the residence time in the eye, but there is a danger that high-viscosity products are not well tolerated in the eye.

**Suspensions**
Aqueous or oily suspension, eye drop formulations may be considered for drugs that are poorly water soluble, or due to poor aqueous drug stability. One advantage of ophthalmic suspensions is that they should prolong the residence time of drug particles in the eye, allowing time for dissolution in the tears and increase in ocular bioavailability. Some of the difficulties that a formulator should overcome during development of a suspension are non-homogeneity of the dosage form, settling, cake formation, aggregation of suspended particles, resuspending, effective preservation, and ease of manufacture.

**Ointments**
Eye ointments are sterile semisolid preparations intended for application to the conjunctiva. They are attractive because of their increased contact time and better bioavailability compared to the solutions.[1,6-7]

**Novel Ophthalmic Drug Delivery Systems**

**Ocular Inserts**
In 1975, the first controlled-release ophthalmic dosage form was marketed in the United States by Alza Corporation. Ocusert is an elliptical shaped membrane which is soft and flexible and designed to be placed in the cul-de-sac between the sclera and eyelid. They continuously release drug at a steady rate (20 and 40 μg/h) for 1 week.

**Liposomes**
It can increase the ocular bioavailability of certain drugs by increasing the association of the drug with the cornea by means of an increased lipophilic-liposomal bilayer interaction with the corneal epithelium. Several other potential advantages of using liposomes as drug carriers for ocular drug delivery have been reported. They accommodate both hydrophilic and lipophilic drugs, they are biocompatible and biodegradable, they will protect the encapsulated drug from metabolic degradation; and can act as a depot, releasing the drug slowly.[1]

**Microemulsions**
Microemulsions are dispersions of water and oil facilitated by a combination of surfactant and co-surfactant to reduce interfacial tension. These systems are characterized by higher thermodynamic stability, small droplet size (≈100 nm) and clear appearance. They possess low surface tension and therefore exhibit good wetting and spreading properties.

**Nanosuspensions**
This can be defined as sub-micron colloidal system which consists of poorly water-soluble drug, suspended in an appropriate dispersion medium stabilized by surfactants. Nanosuspensions consists of colloidal carriers like polymeric resins which are inert in nature. They help in enhancement of drug solubility and bioavailability. Unlike microemulsions, they are also popular because of their non irritant nature.[7,8]

**In-situ Hydrogel[1,7]**
Ophthalmic delivery systems developed containing polymers that undergo a phase change from liquid to semisolid as a result of changes in temperature, pH, or ionic strength in the tear film. These formulations are liquid formulation upon administration, but gel on contact with the eye to provide extended retention time. In situ gel formers also have the advantage of ease of administration, and improved patient compliance, because they can be instilled as a liquid drop.

**Advantages of hydrogels[9]**
- Sustained and prolonged action
- Dose of administration is decreased.
- Reduced side-effects.
- Patient compliance is improved.
- Drug targeting to specific site.
- Protecting mucosa from irritating drugs.
- Extensive first pass metabolism prevents Drug loss.
- Therapy having lower cost.

**Types of hydrogels[10-11]**

**a) Temperature induced in-situ gel systems**
Gelling of the solution can be triggered by change in temperature, thus sustaining the drug release. This is achieved by using a polymer that is a solution at room temperature (<25°C) and a gel at body temperature. Thermosetting polymer can be used for this type of gelling system and may be used up to 20-30%. An increase in concentration of poloxamer (Thermosetting polymer) increases contact time, increases elasticity of the gel and thus decreases the sol-gel transition temperature.

**b) pH induced in situ gel systems**
Gelling of the solution is triggered by a change in pH. At pH 4.4 the formulation is a free-running solution which undergoes coagulation when the pH is raised by the tear fluid to pH 7.4.

**c) Osmotically induced in situ gel systems**
Gelling of the solution may also be triggered by a change in ionic strength. It is assumed that the rate of gelation depend on the osmotic gradient across the surface of the gel. So, the osmolality of the solution might have an effect on the rate of the sol-gel transition occurring in the eye.

**Recent studies on ophthalmic drug delivery system**
- Abdul Malik PH et al.,[16]
Formulated in situ gelling system of Gatifloxacin using polymers i.e. carbopol 940 (0.1% to 0.5% w/v) and HPMC E4M (0.2% to 0.6% w/v) and evaluated its clarity, temperature, pH, tonicity, sterility, rheological behavior, in-vitro release, transcorneal permeation and ocular irritancy. The results demonstrated that the carbopol/ HPMC mixture may be used as an in situ gelling vehicle to enhance the ocular bioavailability of Gatifloxacin.

-**Abdul Hasansathali et al.,[18]**
  Developed Brimonidine tartrate niosomal in situ gels for glaucoma treatment. Poor bioavailability of drugs from ocular dosage form is mainly due to tear production, non productive absorption, transient residence time, impermeability of corneal epithelium. This could be corrected by the use of niosomal vesicular system. Niosomes were formulated by using different ratios of span series and cholesterol. Optimized batch of small unilamellar vesicles having size of about 50-100 nm had highest EE and showed prolonged drug release. Insitu gelling system of niosomal drops were formulated by using HPMC K 15 M and carbopol 940 to maintain the drug localization for extended period of time. The niosomal formulation was then transformed into gel when it instilled into the eye. All the gel formulations exhibited pseudo plastic rheological behavior and slow drug release pattern. Antiglaucoma activity of the prepared gel formulations showed more significant and sustained effect in reducing intra ocular pressure than marketed and niosomal drops.

-**Manas bhownik et al.,[20]**
  Formulated and evaluated the thermo-sensitive in-situ gels for in-vitro evaluation of ophthalmic delivery systems of ketorolac tromethamine (KT), using methylcellulose (MC) along with hydroxypropylmethyl cellulose (HPMC). The gel temperature of 1% MC solution was observed at 60°C. It was found that 6% oral rehydration salt without dextrose (ORS) was capable to reduce the gel temperature below physiological temperature. HPMC was added to increase viscosity and drug release time. The results showed a large increase in viscosity at 37°C with addition of HPMC have provided sustained release of the drug over a period of 4 hr.

-**Gilhotra Ritu Mehra et al.[22]**
  Formulated pilocarpine in-situ gelling solution by using alginate along with novel bioadhesive tamarind gum and chitosan as bioadhesive agents. The formulations were tested for drug content uniformity, bioadhesive strength, gelation and in vitro release study. Further in-vivo miotic test was carried for all formulations. It was found that the formulations were satisfactory in terms of content uniformity, bioadhesion and gelation. The tamarind gum based formulation showed best slow drug release profile compared to the other formulations. This was about 25 % in initial hour and about 80 % during 12 h.

-**Shivan and Swamy et al.[24]**
  Formulated a novel in situ gum based ophthalmic drug delivery system of Linezolid by using Hydroxypropyl guar (HPG) and xanthum (XG) as gums with the combination of hydroxyethyl cellulose (HEC), carbopol (CP), and sodium alginate as viscosity enhancing agents. Suitable concentrations of buffering agents were used to adjust the pH to 7.4. All the formulations were sterilized and evaluated for clarity, pH measurement, gelling capacity, drug content estimation, rheological study, in-vitro diffusion study, antibacterial activity, isotonicity testing, eye irritation testing. The developed formulations exhibited sustained release of drug from formulation over a period of 6hr thus increasing residence time of the drug.

-**Weisan pan et al.[25]**
  Formulated an ophthalmic delivery system of an antibacterial agent, gatifloxacin, based on ion-activated in situ gelation technique. Alginate (Kelton®) was used as the gelling agent in combination with HPMC (Methocel E50Lv) which acted as a viscosity-enhancing agent. The rheological behaviors of all formulations were not affected by the incorporation of gatifloxacin. Both in vitro release studies and in vivo pre-corneal retention studies indicated that the alginate/HPMC solution retained the drug better than the alginate or HPMC E50Lv solutions alone. These results concluded that the alginate/HPMC mixture could be used as an in situ gelling vehicle to enhance ocular bioavailability and patient compliance.

-**A.H. El-Kamel et al.[26]**
  Formulated Pluronic F127 (PF127) based formulations of timolol maleate (TM) aimed at enhancing its ocular bioavailability. The effect of isotonicity agents and PF127 concentrations on the rheological properties of the prepared formulations was examined. The viscosity and the ability of PF127 gels to deliver TM, in vitro, in absence and presence of various viscosity enhancing agents were evaluated. At the used concentration, some of the examined isotonicity agents had effect on the viscosity of TM gel. However, the viscosity of gel increased as the PF127 concentrations increased. The slowest drug release was obtained from 15% PF127 formulations containing 3% methylcellulose. In vivo study showed that ocular bioavailability of TM, measured in albino rabbits, increased by 2.5 and 2.4 fold for 25% PF127 gel formulation and 15% PF127 containing 3% methylcellulose, respectively, compared with 0.5% TM aqueous solution.

-**Srividya et al.[27]**
  Formulated an ophthalmic delivery system of an antibacterial agent, ofloxacin, based on the concept of pH-triggered in-situ gelation. Polycrylic acid (Carbopol 940) were used as the gelling agent in combination with hydroxypropylmethylcellulose (Methocel E50LV). The developed formulation was therapeutically efficacious, stable, and non-irritant and provided sustained release of the drug over an 8-h period.
S. Miyazaki et al.[28] Formulated the thermoreversible in-situ gels by aqueous solutions of an enzyme-degraded xyloglucan polysaccharide and evaluated as sustained release vehicles for the ocular delivery of pilocarpine hydrochloride. In-vitro release of pilocarpine from gels formed by warming xyloglucan sols (1.0, 1.5 and 2.0% w/w) to 34 °C followed root-time kinetics over a period of 6 hr. The miotic responses in rabbit following administration of xyloglucan sols were compared with those from in situ gelling pluronic F127 sols and from an aqueous buffer solution containing the same drug concentration. Sustained release of pilocarpine was observed with all gels, the duration of miotic response increasing with increase of xyloglucan concentration. The degree of enhancement of miotic response following sustained release of pilocarpine from the 1.5% w/w xyloglucan gel was similar to that from a 25% w/w Pluronic F127 gel.

CONCLUSION
It can be concluded that ocular drug delivery system act as unique carrier system for many pharmaceuticals. Ophthalmic delivery based formulations can be more acceptable and excellent drug delivery system by using various biodegradable and water soluble polymers. It has been found from the literature survey that novel ophthalmic formulations have great applications for local treatment of eye disease with relatively lesser side effects reducing dose as compared to other drug delivery system.

ACKNOWLEDGMENT
Authors would like to thanks Department of pharmacy, Teerthanker Mahaveer University, Moradabad and Bacfo Pharmaceuticals Pvt. Ltd., Noida for providing necessary guidance and facilities during manuscript preparations.

REFERENCES
23. P.D. Amin, Srividya, Rita M. Cardoza, “Sustained ophthalmic delivery of ofloxacin from a pH