Ocular Drug Delivery- A Review

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Abstract- *The reason of this review is giving a current update of the information in this field of ocular drug delivery. The ocular drug delivery has been a most important task to drug delivery scientists usually due to its special anatomy and physiology. An update of current research development in ocular drug delivery necessitates and helps drug delivery scientists to modulate their suppose procedure and boost novel and secure drug delivery strategies. Current review intends to summarize the current conventional formulations for ocular delivery and their developments observed via current nanotechnology primarily based method developments. Also, current trends with different ocular drug delivery techniques using insitu gels, implants, dendrimers, microemulsion have been mentioned.*

Keywords- Introduction, structure of eye, conventional ocular drug delivery system, novel drug delivery system.

I. INTRODUCTION

The eye is a complicated organ with an special anatomy and physiology. The structure of eye can be divided into two major parts: anterior section and posterior section. Anterior section of the eye occupies about one-third while the remaining portion is occupied through the posterior segment. Tissues such as cornea, conjunctiva, aqueous humor, iris, ciliary body and lens make up the anterior portion. Back of the eye or posterior phase of the eye consist of sclera, choroid, retinal pigment epithelium, neural retina, optic nerve and vitreous humor. The anterior and posterior section of eye is affected by way of a number of vision threatening diseases. Diseases affecting anterior phase include, however now not restricted to glaucoma, allergic conjunctivitis, anterior uveitis and cataract. While, age-related macular degeneration (AMD) and diabetic retinopathy are the most common diseases affecting posterior section of the eye[1].

Ophthalmic drug delivery is most interesting and challenging delivery system dealing with the pharmaceutical scientist. The anatomy, physiology, and biochemistry of the eye render this organ fantastically secure to overseas substances. A significant task to the formulator is to keep away from the protecting barriers of the eye except causing permanent tissue damage. To optimize ocular drug delivery systems the following characteristics are required:

- A appropriate corneal penetration.
- A persevered contact time of drug with corneal tissue.
- Easiness in installation and removal.
- A non-irritative form.
- Good rheological properties[2].

In eye drops, only a small portion of a drug penetrates via the corneal layer and arrives in the interior tissues existing in the eye [3, 4]. Broad classification of ocular drug delivery effects in two types, these involved with the anterior and posterior segments[5].Ocular drug targets are placed in anatomically distinct regions in the anterior or posterior tissues of the eye. The efficacy of the treatment depends on the ailment state, drug properties, and delivery to the target sites[8].

Topical instillation is the most extensively preferred non-invasive route of drug administration to treat ailments affecting the anterior segment. Conventional dosage types such as eye drops account for 90% of the marketed ophthalmic formulations. The purpose may also be attributed to ease of administration and patient compliance. Nonetheless, the ocular bioavailability is very low with topical drop administration. Numerous anatomical and physiological constraints such as tear turnover, nasolachrymal drainage, reflex blinking, and ocular static and dynamic limitations posea challenge and obstruct deeper ocular drug permeation. Hence, less than 5% of topically utilized dose reaches to deeper ocular tissues[9].To overcome the ocular drug delivery barriers and enhance ocular bioavailability, a number of conventional and novel drug delivery systems have been developed such as emulsion, ointments, suspensions, aqueous gels, Nano micelles, nanoparticles, liposomes, dendrimers, implants, contact lenses, nanosuspensions, microneedles, and in situ thermo sensitive gels for the before point out ocular diseases[1].

Structure of the Eye:

The eye is made up of 3 main parts:

i. Eyeball
ii. Orbit (eye socket)
iii. Accessory (adnexal) structures

The Eyeball:

The primary part of the eye is the eyeball(also referred to as the globe). Each eye is sphere-shaped and is about 2.5 cm (1 inch) in diameter 6. The eyeball is rich in blood vessels. The interior of the eyeball is stuffed mostly with a clear, jelly like fluid known as vitreous humor. Vitreous humor fills the again (posterior) phase of the eye. It helps assist the interior structures and maintain the structure of the eye. The outer part of the eyeball is referred to as the wall of the eye, structure of eye as shown in determine 01. It can be divided into three layers;

1. **Outer layer:** The outermost layer or protecting of the wall of the eye is made up of the sclera and cornea and is called the fibrous tunic

Sclera: The sclera is the tough, white connective tissue that covers most of the outside of the eyeball. The sclera is considered as the white portion of the eye and serves as the protective covering. The optic nerve and blood vessels pass thru the sclera in the back of the eye. Muscles that manage the motion of the eye connect to the sclera[3,4].
Cornea: The cornea is the clear, dome-shaped protecting at the the front of the eye that lets in light. The cornea covers the pupil and the iris. It does no longer include any blood vessels.

2. **Middle Layer:** The middle layer of the wall of the eye is known as the vascular tunic. The uvea has three major parts:

Iris: The iris is the thin, muscular, colored section of the eye. It is placed at the the front (anterior) of the eye, between the cornea and the lens. The iris opens and closes the pupil (the small central opening) to alternate the amount of light getting into the eye.

Choroid: The choroid is a skinny layer of tissue that contains many tiny blood vessels that provide oxygen and nutrients to the retina. The choroid contains many pigment producing cells known as melanocytes. These cells help absorb any extra light and decrease reflections inside the eye.

Ciliary body: The ciliary body lies simply at the back of the iris and extends ahead from the choroid. It is the muscular ring of tissue that helps the eye focus. It adjustments the shape of the lens so it can center of attention on close to or a ways objects. The ciliary body consists of cells that make aqueous humor, which is the clear fluid in the the front of the eye between the cornea and lens.

3. **Inner Layer:** The innermost layer of the wall of the eye is made up of the retina or neural tunic. The retina is the thin layer of cells at the again of the eyeball and works like the film of a camera. It is made up of nerve cells that are sensitive to mild. These cells are linked to the brain via the optic nerve, which sends data from the eye to the talent and approves us to see.

Lens: The lens is a obvious structure in the internal section of the eye, which lies without delay at the back of the cornea and iris. The lens modifications structure to enable the eye to focus on objects. The lens focuses mild rays on the retina

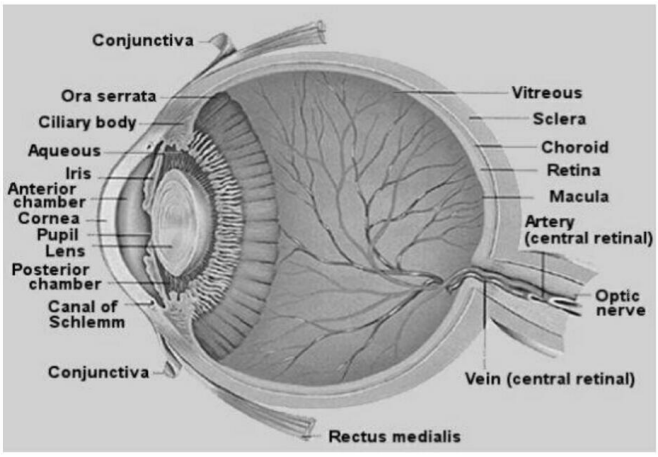

Figure 1. Cross section of human eye[6]

Orbit: The orbit (eye socket) is a bowl-shaped cavity made up of bone formed from the skull that includes the eyeball and the connective tissues surrounding the eyeball. The bone and connective tissues cushion and protect the eye. Muscles connected to the eyeball make it move in specific directions. These small muscle tissues attach to the sclera close to the the front of the eye and to the bones of the orbit at the back. The orbit additionally consists of nerves, fat, blood vessels and a range of connective tissues[3,4]

Advantages of ocular drug delivery system[2,4,5]

The merits of ODDS are followings:

- Increased correct dosing, to overcome the side effects of pulsed dosing produced via traditional systems.
- To supply sustained and managed drug delivery.
- To enlarge the ocular bioavailability of drug via growing the corneal contact time. This can be completed via effective adherence to corneal surface.
- To supply focused on inside the ocular globe so as to prevent the loss to different ocular tissues.
- To circumvent the defensive limitations like drainage, lacrimation and conjunctive absorption.

- To supply comfort, higher compliance to the patient and to enhance therapeutic overall performance of drug.
- To supply higher housing of delivery system.

Disadvantages[3,4.7]:

Various disadvantages of ocular drug delivery system are given below.

- The drug solution stays very short time in the eye surface.
- It shows poor bioavailability.
- Shows instability of the dissolved drug.
- There is a need to use preservatives.
- The physiological restriction is the limited permeability of cornea ensuing into low absorption of ophthalmic drugs.
- Required frequent dosing.

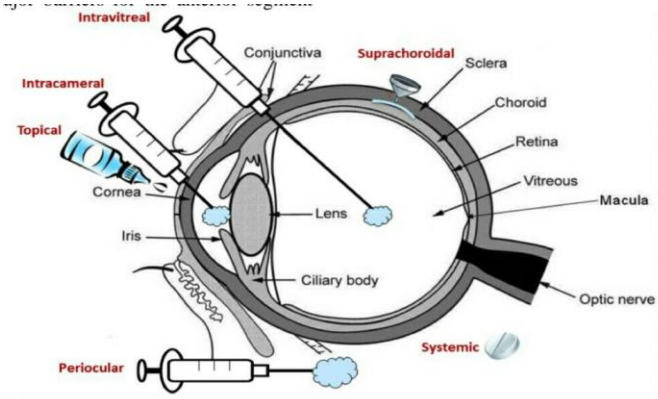

Figure 2. Routes of administration Ocular drug delivery[3]

CONVENTIONAL OCULAR DRUG DELIVERY SYSTEMS:

Topical drop instillation into the decrease precorneal pocket is a patient compliant and broadly recommended route of drug administration. However, most of the topically administered dose is lost due to reflux blinking and only 20% of instilled dose is retained in the precorneal pocket. Concentration of drug accessible in the precorneal region acts as a using force for its passive diffusion throughout cornea[1].However, for environment friendly ocular drug delivery with eye drops, excessive corneal permeation with longer drug cornea contact time is required. Several efforts have been made towards enhancing precorneal residence time and corneal penetration. To enhance corneal permeation iontophoresis, prodrugs, ion-pair forming agents and cyclodextrins are employed[3].

1. Topical liquid/solution eye drops:

Topical drops are the most convenient, safe, immediately active, patient compliant and noninvasive mode of ocular drug administration. An eye drop solution gives a pulse drug permeation post topical drop instillation, after which its awareness unexpectedly declines. The kinetics of drug awareness decline may also observe an approximate first order[1].The kinetics of drug concentration decline can also follow an approximate first order. Therefore to enhance drug contact time, permeation and ocular bioavailability; various components may additionally be delivered to topical eye drops such as viscosity enhancers, permeation enhancers and cyclodextrins[3].

2. Emulsions:

An emulsion based totally formulation method provides an advantage to enhance each solubility and bioavailability of drugs. There are two kinds of emulsions which are commercially exploited as vehicles for active pharmaceuticals: oil in water (o/w) and water in oil(w/o) emulsion systems. For ophthalmic drug delivery, o/w emulsion is frequent and broadly preferred over w/o system. The reasons consist of much less irritation and higher ocular tolerance of o/w emulsion[3].

3. Liposome:

Liposome is biocompatible and biodegradable lipid vesicles made up of natural lipids and about 25-10,000nm in diameter. They are having an intimate contact with the corneal and conjunctiva surfaces which is desirable for drugs that are poorly absorbed, the pills with low partition coefficient, poor solubility or these with medium to excessive molecular weights and for this reason increases the chance of ocular drug absorption. The corneal epithelium is thinly lined with negatively charged mucin to which the positive charged surface of the liposome might also bind. Formulated and evaluated smooth contact lenses covered with ciprofloxacin entrapped in liposome[3].

4. Suspensions:

Suspensions are another class of non-invasive ocular topical drop drug carrier systems. Suspension may be described as dispersion of finely divided insoluble API in an aqueous solvent consisting of a suitable suspending and dispersing agent. In different words, the carrier solvent system is a saturated solution of API. Suspension particles preserve in precorneal pocket and thereby improve drug contact time and period of action relative to drug solution

5. Prodrug:

Prodrugs enhance corneal drug permeability through modification of the hydrophilic or lipophilicity of the drug. The method includes modification of chemical structure of the drug molecule, thus making it selective, site specific and a safe ocular drug delivery system. Drugs with increased penetrability through prodrug formulations are epinehrine, phenylephrine, timolol, p ilocarpine[12].

NOVEL OCULAR DRUG DELIVERY SYSTEM:

1. Nanotechnology based ocular drug delivery:

In a last few decades, many procedures have been utilized for the therapy of ocular diseases. Nanotechnology based totally ophthalmic formulations are one of the techniques which is currently being pursued for each anterior, as properly as posterior section drug delivery. Nanotechnology based systems with an appropriate particle measurement can be designed to make sure low irritation, adequate bioavailability, and ocular tissue compatibility. Several Nano carriers, such as nanoparticles, Nano suspensions, liposome's, Nano micelles and dendrites have been developed for ocular drug delivery. Some of them have proven promising effects for improving ocular bioavailability[1,3].

2. Micro emulsions:

Micro emulsions are novel ocular delivery systems that are basically dispersions of water and oil alongside with a surfactant. Micro emulsions confer advantages such as greater thermodynamic stability, increased solubility, and improved corneal permeation. The essential parameters that have an effect on the balance of the micro emulsion system are selection of aqueous phase, organic phase, and surfactant/cosurfactant systems. Cyclosporine A used to be formulated with micro emulsions made of Brij 97 and loaded into 2-hydroxyethyl methacrylate (p-HEMA) hydrogels. Release of cyclosporine from these formulations was determined for a duration of 20 days in an in-vitro launch study[2].

3. Implants:

For chronic ocular diseases like cytomegalovirus retinitis, implants are superb drug delivery system. Earlier non biodegradable polymers had been used however they needed surgical techniques for insertion and removal. Presently biodegradable polymers such as Poly Lactic Acid are secure and effective to deliver drugs in the vitreous cavity and exhibit no poisonous signs and symptoms[3].

4. Dendrimers:

Dendrimers are characterised as nanosized, highly branched, star shaped polymeric systems. These branched polymeric systems are available in exclusive molecular weights with terminal end amine, hydroxyl or carboxyl useful group. The terminal useful group may be utilized to conjugate focused on moieties. Dendrimers are being employed as carrier systems in drug delivery. So, the advantages of the use of dendimers as carrier of drugs for topical applications are enhancement of the drug residence time in the pre-corneal area, increase in bioavailability of drugs and extended therapeutic impact[3,5].

5. In situ forming gels:

In-situ hydrogels refer to the polymeric solutions which bear sol-gel section transition to form viscoelastic gel in response to environmental stimuli. The important disadvantages of the in situ gels are that they get affected through temperature, pH or ions. Bazzaz et al.(2018) mentioned that in situ gelling system offers higher and prolonged impact of a drug rather than conventional eye drops.The progress has been made in gel technology for the de velopment of droppable gel. They are liquid upon instillation and under go phase transition in the ocular cul-de-sac to form visco-elastic gel andthis provides a respons e to environmental changes. Three methods have been employed to cause phase transition in the eye surface. These are change in pH, change in temperature and ion activat ion[1,5,12].

6. Liposomes:

They may be multilamellar vesicles or unilamellar depending upon the number of concentric interspersing layers of phospholipids and waterless phases. They can be prepared by sonication of dissipation of phospholipids, rear phase evaporation, solvent injection, Soap junking or calcium convinced fusion. Liposomes were also estimated in an attempt to ameliorate bioavailability of ophthalmic medicines after topical instillation, because they are stable, biocompatible and biodegradable liquid medications. The implicit of liposomes in optical medicine delivery is limited by their rapid-fire concurrence from the precorneal area[12].

II. CONCLUSION

Finally I concluded that a novel approaches on ocular drug delivery system was growing the ophthalmic solutions are easy because we can easily target the eye to treat ocular diseases with huge variety of novel approaches. Progress in the subject of ocular drug delivery has been installed recently with managed loading and sustained release. Hence, effective drug delivery and targeting is faced by using challenges to overcome these barriers as a conventional drug delivery system.

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