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A REVIEW ON OCULAR DRUG DELIVERY SYSTEM

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ABSTRACT

Ocular drug delivery systems are one of the dosage forms that have the potential for development in the near future. Conventional topical eye drops show acceptable patient compliance but have several drawbacks. The dynamic, static and precorneal ocular barriers interfere with drug penetration to the target site. In addition, bioavailability and therapeutic levels are not sustained for prolonged durations. The current research aims to develop a safe ocular drug delivery system that penetrates the barriers with ease and maintains the desired drug levels by incorporating viscosity and penetration enhancers. The experimentations lead to the development of in situ gels,ocular implants, intravitreal and periocular injections, nanosuspensions, nanoparticles, liposomes etc.

INTRODUCTION

Human eye is a complex structure with 2 parts, anterior segment and posterior segment. Both these regions are affected by various diseases. Anterior segment mainly consists of cornea, conjunctiva, aqueous humour, iris, ciliary body and lens which makeup one third of eyes. These regions are affected by diseases like glaucoma, allergic conjunctivitis, cataract etc.Posterior segments include sclera,choroid retinal pigment epithelium, neural retina, optic nerve and vitreous humour which are affected by age related macular degeneration,diabetic retinopathy etc.Conventionally topical eye drops, ointments and suspensions were used. Although eye drops account 90% of commercial dosage forms, they are incapable of efficiently penetrating through the barriers and also are wiped away by nasolachrimal drainage, blinking and tear flow. Hence less than 5% of the drug is able to reach the innermost regions resulting in inability to maintain required therapeutic level in these areas. To overcome these difficulties various novel drug delivery approaches have recently been developed. Intravenous or intravitreal drug delivery approaches are generally used to deliver the medicaments to posterior areas of eyes. But inravitreal administration require repeated eye invasion through puncturing which may consequently cause haemorrhage or retinal detachment. Although transcleral mode is less invasive drug penetration is limited by static barriers like sclera, choroid etc and dynamic barriers like lymphatic and blood flow in conjuctiva.

Anatomy of Eye: The human eye is a sphere of diameter 23mm which works through highly complex and intrinsic mechanism to transmit light and obtain visual information from the brain. Light enters the eye through the pupil, and the amount of light entering is controlled by iris,pupil etc.It is then directed towards the lens.The eyeball consist of 3 layers,the outer coat of cornea and sclera, the middle coat of iris, choroid and ciliary body and the innermost layer of retina.

- **Iris**: It is the coloured visible portion anterior to the lens and controls the amount of light entering through the central opening called pupil.
- **Pupil**: It undergoes constriction(narrowing) and dilation (widening) to regulate light entry depending upon the brightness of the surrounding.
- **Cornea**: It is the anterior most circular portion of the eye that refracts the light and directs it onto the retina. It is devoid of any blood vessels but extremely sensitive to pain. It is composed of epithelium, bowmen's membrane,stroma,descement's membrane and endothelium, with a thickness of 0.5-0.7mm.
- **Lens**: The shape of this transparent structure,which is located anterior to pupil, is adjusted by ciliary body. It refracts the incoming light and focuses it onto the retina.
- **Choroid**: Located in between retina and sclera, it consisst of pigment, which absorb excess light and pevents blurring of vision.
- **Ciliary body**: Connect the choroid to the iris.
- **Retina**: It is composed of rods and cones that are sensitive to light and linethe interior of eye. Approximately 125million rods are present, which assist vision in dim light. About 6-7million cones assist vision in bright light and coloured vision.
- **Macula and fovea**: Macula is a yellow spot on the retina surruonding the fovea. Fovea has the greatest concentration of cone cells.
- **Optic nerve**: Transmit visual information to brain. The optic disc is the beginning of optic nerve, also called a blind spot.
- **Sclera**: It is the white portion that, alongwith cornea, forms the protective covering of the eye.
- **Fluid system of the eye**: Aqueous and vitreous humour

Mechanism of drug absorption: It includes

- Non-corneal absorption

Drug permeates through sclera and conjunctiva into ocular tissue. Generally large hydrophilic drugs undergo absorption through this route. A large fraction of absorbed drug is passed onto the systemic circulation. Hence this route is inefficient.

- Corneal absorption

It is the transport of majorly lipophilic molecules through cornea into the ocular tissue via aqueous humour. The tight junctions of epithelial barrier limits the entry of hydrophilic drugs through this route.

ADVANTAGES

- ✓ Maintained and controlled release of drugs is possible.
- ✓ In order to stop the loss of ocular tissues, the ocular globe must be targeted.
- ✓ They avoid protective optical barriers like conjunctival absorption, drainage and lacrimation.
- ✓ Result in fewer systemic and visual side effects.
- ✓ Rapid absorption.
- ✓ They improve dosing rate precision and uniformity.
- ✓ By prolonging the time that a drug is in contact with the cornea, they improve the drug's ocular bioavailability, which is made possible by the drug's successful adhesion to corneal surface.

- ✓ They enhance therapeutic efficacy of drug, provide comfort and increase patient compliance.
- ✓ They allow for the self-administration of medications.

DISADVANTAGES

- Minimal time between the drug & the eye surface.
- Inadequate bioavailability.
- In an emergency, discontinuing a dosage form is not possible.
- Obstruction to vision.
- Trouble in placing and removing the dosage form.
- There may occasionally be drug loss while sleeping or rubbing eyes.
- Preservatives are used.

CHALLENGES: The design of a therapeutic system that can deliver a drug at target site at an ideal concentration and with high therapeutic efficiency presents challenges for ocular drug delivery systems. Because of the structure, physiology and barrier functions of cornea, medications are absorbed quickly. Therefore, fast instillations of eye drops are necessary to maintain the therapeutic level in tear film. Consequences of utilizing medications often include the potential for toxicity at ocular surface and cell damage. The majority of ocular dosage forms have a poor bioavailability owing to precorneal loss, which involves solution drainage, lacrimation and tear dynamics.

Anterior Segment Delivery Challenges: In ocular delivery system, topical formulations take precedence over systemic formulations. The majority of drugs poor bioavailability is caused by precorneal loss. Additionally, repeated administration of eye drops isrequired to keep a desired therapeutic level in target site, but doing so with highly concentrated drug solutions runs the risk of damaging the eye's surface cells and causing toxic side effect.

Posterior Segment Delivery Challenges

Blood retinal barrier (BRB) prevents medications used topically for eyes from entering the posterior segment of eye. Some variables at the posterior region of ocular tissue limit medication delivery, which leads to poor ocular bioavailability. BRB helps in minimising the effects of intravenous drug delivery at the posterior location as well as restricting the entry of systemically delivered medications into the retina.

BARRIERS OF OCULAR DELIVERY OF DRUGS

- **Drug Loss from the Surface:**
  - ➢ Drug spillage by overflow

Tear volume in a healthy individual is approximately about 7ml.In the absence of blinking, a normal human eye can hold upto 30ml without spilling from a palpebral fissure. If a drop volume of about 50mL is administered, almost 70% of the drug is lost by overflow. Drug dilution by turnover of tears

Numerous factors, like the type of drug particle, pH, tonicity, adjuvants, etc may stimulate the tear turnover rate, which otherwise is 16% in a normal individual. As a result, these factors may affect drug administration in the cul-de-sac.Nasolacrimal drainage and systemic absorption. Subsequent to the drug administration, lachrymal flow on the surface wipes out a considerable fraction of drug, resulting in a turnout rate of approximately 1 microlitre per minute. This nasolacrimal drainage leads to the systemic absorption of drugs through the nasal mucosa and gastrointestinal tract, resulting in multiple systemic effects. Another factor in drug loss is system absorption instead of ocular absorption. It mainly occurs through conjunctival sac and then through blood capillaries after the solution flows to the nasal cavity. Conjunctival absorption. It mainly occurs through the conjunctival sac and then through blood capillaries after the solution flows to the nasal cavity. **Enzymatic metabolism:** Additional drug loss occurs through enzymatic metabolism in the precorneal space or cornea.

Ocular Surface Barriers: Ocular surface mainly includes corneal and conjunctival superficial layers. These act as a barrier against permeation of unwanted substances.

Corneal surface makes up 5 % and conjunctiva 95%. In this case, intracellular drug penetration is mainly hindered by the outermost layers of the corneal squamous epithelium.

Ocular Wall Barrier: The eyeball is covered by scleral covering, which has an internal lining of uveal tract.Posteriorly, 80% of the eyeball is enveloped by the sclera, excluding a small area occupied by the optic nerve head. Scleral thickness in humans is in the range of 0.3 to 10 mm.

Retinal Barriers: The posterior barrier between blood stream and the eye consists of tight wall of retinal capillaries and retinal pigment epithelium.

The only way to overcome all these barriers and deliver the drug to various parts of the eye is administering the ophthalmic medications more frequently at higher dose, but this manner of multiple dosing may accentuate the occurrence of adverse effects along with fluctuation in drug levels.

Drug Solubility and Ionisation: Various factors, like pH and pKa, affect the drug's solubility. Normally, ionized molecules permeate at a slower rate than ionized molecule. One such example of drug is pilocarpine. Unionized pilocarpine shows two-fold greater permeability than its ionised form. The corneal epithelium has a negative charge at pH of lachrymal fluid. Hence the charge of ionized species greatly affects its permeation. This is evident as the cationic species permeate at a faster rate.

Lipophilicity of Drug: Various layers of cornea exhibit the differential permeability rates in accordance with different drugs. Lipophilic drugs permeate relatively more easily than hydrophilic ones. In contrary to this hydrophilic stroma supports the permeability of hydrophilic drugs.

Molecular Weight and Size: Corneal epithelium supports the permeation of drugs having molecular weight less than 500 Daltons.

ROUTE OF ADMINISTRATION

1. Topical administration

Although ease of administration and low cost make this the most convenient route, it can only be used for treatment of abnormalities in the anterior segment.

Attempting to deliver medications to posterior segment through this route may cause drug loss through anterior and precorneal barriers which also includes absorption in iris ciliary body and anterior chamber metabolism.

2. Systemic Administration

The blood aqueous barrier for anterior segment of eye and blood retinal barrier for posterior region of eye are the common obstacle to administration of ophthalmic medicines by this route. Systemic administration has insufficient effectiveness in getting the medication into vitreoretinal tissues due to the presence of blood retinal barriers. This limitation makes the repeated dosing of the drug necessary to attain therapeutic drug level as otherwise only one to two percent of the drug is able to reach the vitreous humour. This mode of delivery may also lead to systemic cytotoxicity and non-specific drug binding to various other body tissues.

3. Intravitreal Administration

Due to the recent improvements in surgical techniques, sustained and controlled release intravitreal implants or intravitreal administration of therapeutic drugs which is achieved by direct injection into mi vitreous region is being used as the primary curative treatment option for posterior segment disorders. This injection method led to longer retention period for the medication as well as higher drug concentration in vitreous humour. However, the main barrier to the clinical application of this route was occurrence of pain, discomfort and noncompliance to a higher degree.

4. Scleral Administration

Sclera is currently gaining attention as a possible route of posterior segment drug delivery because of its large surface area, ease of accessibility and relatively high permeability to macromolecules. Several methods including subtendon injection, sub conjunctival injection and scleral implants and

plugs have been tried for scleral drug delivery. Transscleral drug delivery presents a therapeutic strategy that is seen as a promising option to treat a range of posterior segment disorders.

5. Intra Cameral Route

The drugs administered by this route act either on the anterior or posterior chambers of the eyes. Anaesthetic injection into anterior chamber of eye, typically during operations may be attended by this route.

6. Periocular Route

This method of drug administration involves putting the medicines around the eyes. Example involves periocular injections of steroids around the eyes as a mode of treatment for intraocular inflammation.

7. Sub Conjunctival Route

This method involves application of medication on the mucous membranes including the inner surface of eyelid and open space inside the eyeball.

8. Suprachoroidal Route

Suprachoroidal space is the area existing between choroid and sclera. The target area for this route is the area of eye above the choroid.

METHODS TO OVERCOME INTRAOCULAR BARRIER

- **Microneedle**

Drug coated microneedles with length of about 500 to 750micrometers have been developed as a non- invasive means of drug delivery to treat diseases in the posterior portions of the eye. Here the desired medicament coated on a solid metal needle which after administration are rapidly dissolved, followed by the removal of the needle. Consequently, we are able to attain higher drug concentration in comparison conventional eye drops. E.g. Sodium fluorescein when administered by identical method penetration was found to be 60 times higher and in case pilocarpine spontaneous pupil constriction was produced.

Likewise, intrascleral microneedles are efficient in delivering microparticles, nanoparticles and drug solutions. In case of microparticles, spreading enzymes like collagenase are administered simultaneously to hydrolyse the collagenous extracellular barrier of sclera. Various types of microneedles used include dissolving microneedles with polymers like PVA and PVP, coated microneedle, hollow microneedle and bio-inspired microneedles.

- **Ultrasound-Mediated Drug Delivery**

Ultra sound technique has gained increased popularity in recent years. This technique is used for the delivery of beta blockers such as atenolol, timolol etc for the treatment of glaucoma. As aresult, the corneal permeability is considerably enhanced. E.g. Ultrasound frequency of 880kHz is applied to deliver sodium fluorescein which ultimately result in tenfold increase in corneal permeation.

- **Iontophoresis**

This technique is used to facilitate the transport of ionised drugs through membranes with low intensity electric current. For completion of the circuit an electrode must be positioned on a separate location on the body. The two major mechanisms involved are migration and electro-osmosis.

Ocular iontophoresis is further categorized into transcorneal, corneoscleral and transscleral. Transscleral delivery is a non-invasive and simple means of delivering the drug into posterior segment. The merits of this route include

i. Easy dose modulation which eliminates the risk of toxicity.
ii. Ability to deliver a wide range of medication to treat various disease of the posterior segment of eye.
iii. Higher patient compliance.
iv. Can be used in combination with several other drug delivery systems.
v. Lower incidence of infections and ulceration.
vi. Applicable for the treatment of fungal keratitis, uveitis, retinitis etc.

Limitations faced by this technique are

i. Variability in half life.
ii. Need for frequent administration.
iii. Adverse effects showing mild pain in few cases.

iv. Limited to drugs in ionic form and it should be in adequate concentration

E.g. OcuPhor system is developed to deliver drugs into various parts of eye including retina and choroid. It is intricately designed to contain an applicator, dispersive electrode and dose controller for transscleral iontophoresis. Various antibiotics like gentamycin and tobramycin, antifungals and steroids are successfully delivered.

- **Intravitreal Injection:**

A 30G needle is used for safe delivery of drugs into the vitreous via pars plana. This technique is highly advantageous in achieving large drug concentrations in vitreous and retina. On the contrary,it may lead to various complications such as retinal detachment, endophthalmitis,and intravitreal haemorrhage. In addition to these adverse effects, it has several disadvantages, like the involvement of first order kinetics, diminishing drug efficacy below the limiting drug concentration level, and short half-life, which leads to the need for repeated drug administration.

APPROACHES TO IMPROVE OCULAR BIOAVAILABILITY

STRATEGIES TO ENHANCE BIOAVAILABILITY

- **Viscosity Enhancers**

Viscosity enhancing polymers are particularly favoured due to the effect of increasing viscosity. As a result, they decrease the rate of elimination of drug from the preocular area and in doing so enhances the penetration of drug into anterior chamber. Furthermore, they also increase precorneal residence time along with trans corneal penetration while having fewer effects on enhancing bioavailability. Some ideal polymers being extensively used are poly vinyl alcohol (PVA), Poly vinyl pyrrolidine (PVP), Methyl cellulose, Hydroxy ethyl cellulose, Hydroxy propyl methyl cellulose (HPMC).

On the basis of numerous research studies, PVA has been found to be the most effective among PVA, HPMC and PVP solutions at individual concentrations used for producing identical viscosity of 20cst. It is mainly due to the adhesive property of PVA and its ability to increase the depth of precorneal tear film along with its surface spreading properties.

- **Gel Formulation**

The gels have been defined as the considerably diluted crosslinked system that exhibit firmness under steady state condition. Gels are often liquids but because of their three-dimensional crosslinked structure they act like solids. Conversely if the gels are extremely viscous, they will not be able to increase the bioavailability instead they will regulate the release which will cause the frequency of dosing to be reduced to once daily. Furthermore, matted eyelids and impaired vision may also occur from highly viscous solution which significantly reduce patient compliance. Controlled drug delivery may be attained by hydrogel or swellable hydrophobic polymers whereas in aqueous gel, viscosity building agents like PVA, HPMC, carbomer, maleic anhydride etc may be used.

- **Prodrug Formulation**

Researches have indicated that prodrugs are suitable for raising the drug permeability through cornea as numerous formulation characteristics can be made better through creation of prodrugs. Examples of ophthalmic medications have been formulated as prodrugs include epinephrine, phenylephrine timolol and pilocarpine. Prodrug formulations include changing the chemical structure of the moiety to give the active component new traits like selectivity and site of specificity. Other prodrug of epinephrine like dipiverine exhibits seventeen-fold increase in corneal penetration over epinephrine due to its six-hundred-fold greater lipophilicity at pH 7.2. Therefore, small amount of prodrug solution covers the whole of the eyeball and acts therapeutically in manner identical to the pharmacological effect of epinephrine. Additionally, there is also noticeable decrease in adverse effect.

- **Penetration Enhancers**

With regard to permeability, the corneal epithelial membrane plays a significant role surrounding the cornea can therefore be improved by raising the degree of permeability

of the active agent. Such agents include chelating agents, bile salts and preservatives such as benzalkonium chloride. However, the use of this agents in the manufacture of ophthalmic formulation is restricted due to the occurrence of local toxicity upon their use.

***In Situ* Forming Gels:** The early 1980s brought about the discovery of novel idea of *in situ* gels. The primary purpose of *in situ* gel system is to minimize the drug outflow from the cornea by increasing the viscosity of the formulation. The environmental sensitivity of the ophthalmic polymers used in ophthalmic *in situ* gelling cause minor alteration in its structure in response to variation in temperature, ionic strength and pH. When injected into the eye *in situ* forming gels are generally in liquid state. But they quickly undergo the process of gelling cul-de-sac to produce viscoelastic gels in response to the variations in the surrounding environment. This dosage form releases the medication gradually in a biological setting as a result, the gels formed has a longer residence time and greater bioavailability leading to the decrease in the frequency of administration. One of the primary drawbacks of his technique is that they are greatly susceptible to fluctuation in temperature pH etc. The temperature triggered in situ gel is generally formulated at precorneal temperature of 35℃. The liquid form exists below low critical solution temperature and gelation above this temperature. In case of pH induced *in situ* gels, changes in temperature promote sol-gel phase shift due to the polymer which contains acidic or basic functional groups.

Dendrimers: Dendrimers are symmetric structures composed of repeatedly branched particles encircling the central core. Polypropylene imines, poly-amidoamine and phosphorous dendrimers are commonly utilized for drug administration in ophthalmic tissue. Mainly low molecular weight hydrophilic or lipophilic drugs or nucleic acid-based drugs are delivered by dendrimer carriers. Pharmaceuticals can be supplied by dendrimers in two distinct techniques. One involves linking medicinal products to dendrimer surface and other involves encapsulating lipophilic medication inside hydrophobic dendrimer cavity to render them water soluble.

Micro emulsion: Microemulsions are isotropic stable liquid mixtures of water in oil containing a combination of surfactant and cosurfactant in order to reduce the surface tension. This dosage form exhibits several benefits including a clear appearance, reduce droplet size of approximately 100nm, and an excellent temperature stability.

Nanosuspension and Nanodispersion

Medications that are not particularly soluble in water can be suspended at nano scale range in appropriate solvent for dispersion to create nanosuspension. This method can be effectively applied to compounds that form high energy crystals which are unable to dissolve in hydrophilic or lipophilic solvent. Polymeric resins are generally being used to formulate nano particle suspension. The major advantages include absence of any irritation to cornea, iris or conjunctiva. Example Brimonidine tartarate nanosuspension incorporated *in situ* gel showed about 30% drug release in 3 hours and sustained release for 24 hours.

Nanoparticles or Nanospheres

In this dosage form, the drug is generally dissolved, entrapped, encapsulated or absorbed in polymeric colloidal particle in size range of 1 to 10nm. The medications are formulated in a variety of ways to yield nanoparticles such as by incorporating the drug into the matrix or adhering the drug to the surface of biodegradable polymers used in this preparation. It is generally made up of several biodegradable materials including metals, lipids, phospholipids and natural artificial polymers. Nanoparticles generally used include polylactides, polycyanoacrylates, poly D and L -lactides and natural polymers include albumin, gelatin, chitosan etc. Nano capsules and nanospheres are tiny capsules with solid matrix spheres and polymeric membrane encircling the central cavity.

Microparticle: Oil, surfactant, and water droplets with sizes ranging 20 to 200 nm form an isotropic, transparent, translucent, and thermodynamically stable system known as microparticles. Microparticles are micron sized polymeric particles in which pharmaceuticals are suspended in polymeric matrix in a liquid media. Drugs are either evenly disseminated in the polymeric matrix or covalently bonded to the polymer. When these particles are applied to the eye, they enter the ocular cul-de-sac and the drug is released by a variety of mechanisms such as diffusion, chemical reaction, or polymer breakdown. Microparticles extend the precorneal residence duration, and thereby facilitating the prolonged drug release. Ultimately this leads to increased ocular bioavailability of the drug and minimises frequency of dosing, however microparticulate preparations are normally not delivered to the eye due to discomfort caused by their high particle size. Microparticles exhibit various features such as bioadhesion, biodegradability and biocompatibility.

Inserts: Solid patches called ocular inserts that reduces the pace of medication release when inserted into the eye 's conjunctival sac. Ocular inserts assist in resolving the issue of frequent dosing by effectively preserving drug concentration and enabling for regulated, prolonged, and continuous drug administration. They offer a number of benefits, such as improved drug absorption from longer contact times and lower doses and frequency of usage. The main drawbacks of these insets include patient resistance with repeated sensations of foreign body entering the eye, trouble faced during self-administration, and sense of inert loss from the eye. Ocular inserts are produced using a variety of methods that render them soluble, erodible, and hydrogel-like. Mechanism of drug release from the ocular inserts includes diffusion from pores of non-erodible carrier, osmosis from reservoir, bioerosion of bio erodible matrix.

Implants: The goal of developing an intraocular implant is to use a polymer to extend the drug's action and provide controlled release. Drug delivery systems that are injectables, such as liposomes and nanoparticles, are simple to use, but they have the drawback of being difficult to remove once inserted in the event of a complication, such as adverse reactions. Therefore, employing implants to regulate the rate and period of release of drugs is advantageous. Ocular implants are simple to remove and may be done so with surgery. Two implants can be distinguished according to the properties of the polymers that are used:

i. Nonbiodegradable implants

They are not damaged in vivo, nor do they disintegrate to any appreciable degree.

ii. Biodegradable implants

Through mechanisms like enzymatic or non-enzymatic degradations, they primarily dissolve in vivo with soluble components.

CONCLUSION

In absence of a suitable drug delivery system even the greatest novel medicinal entity in the world has negligible value. The main objective of the novel approaches is to increase the drugs bioavailability and simultaneously enhance the drugs residence time at the site of desired action which ultimately decreases the administration frequency. In spite of numerous advanced formulations, topical eyedrops are still the most preferred dosage forms due to the ease of administration and safety in terms that they do not obstruct vision but, they require more frequent administration. An important issue faced by the scientist in formulation of ophthalmic drugs are the aspects of safety and efficiency. Researchers are contributing immense amount of time and effort to enhance *in vivo* characteristics of conventional formulations. With advent of nano technology, sustained or controlled release formulations, liposomes etc there is a great probability that these formulations may replace the invasive mode of delivery to posterior eye segments with sufficient research.

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