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AN OVERVIEW ON EUDRAGIT BASED NANOPARTICULATE DRUG DELIVERY CARRIERS FOR OCULAR DELIVERY

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ABSTRACT

Eye is sense organ of vision. It is one of the sensitive organs of the body. There are number of diseases which are into the focus of scientists. But the major problem faced in treatment of eye diseases is the low ocular bioavailability for most of the drugs. A number of approaches are introduced time to time for increasing the ocular bioavailability. In this series of approaches, Nanoparticulate drug delivery system is best one. Numerous types of polymers are being used for ocular drug delivery systems. Eudragit is one of those polymers. Eudragit is a cationic polymer having potential of controlled delivery of drug. In present review the potential of eudragit polymer as a drug delivery vehicle for the eye is covered.

INTRODUCTION

Eye disorders have been challenge for health scientists since long back. Time to time the drug delivery systems have been utilized for ocular drug delivery. Drugs may be delivered to the eye through the application of four primary modes of administration: systemic, topical, intravitreal, and periocular. Topical administration is generally considered the preferred route for the administration of ocular drugs due to its convenience and affordability. Among various delivery systems tried till date, the eudragit based nanoparticulate drug delivery systems are proved safe and effective for ocular delivery of various drugs[1].

Structure of the Eye:

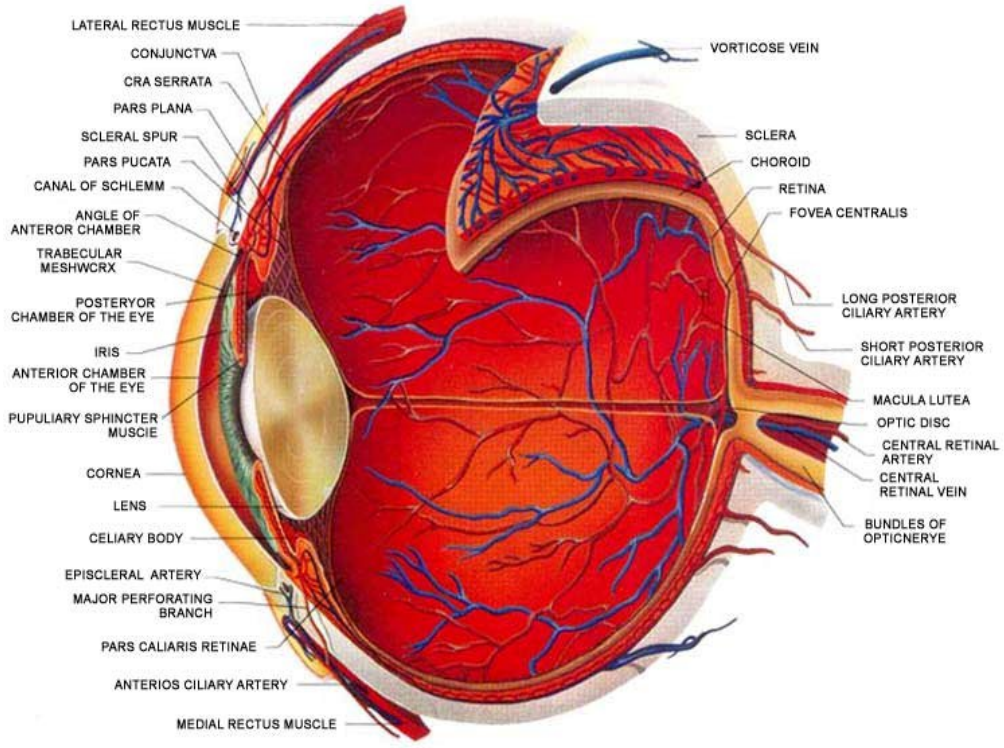

Figure 1: Structure of the Eye

Eye is one of the sense organs of the human body and employed for vision of objects. Light enters the eye through a small hole called the pupil and is focused on the retina, which is like a camera film. Eye also has a focusing lens, which focuses images from different distances on the retina. The colored ring of the eye, the iris, controls the amount of light entering the eye. It closes when light is bright and opens when light is

dim. A tough white sheet called sclera covers the outside of the eye. Front of this sheet (sclera) is transparent in order to allow the light to enter the eye, the cornea. Ciliary muscles in ciliary body control the focusing of lens automatically. Choroid forms the vascular layer of the eye supplying nutrition to the eye structures. Image formed on the retina is transmitted to brain by optic nerve. The image is finally perceived by brain. A jelly like substance called vitreous humor fill the space between lens and retina. The lens, iris and cornea are nourished by clear fluid, aqueous humor, formed by the ciliary body and fill the space between lens and cornea. This space is known as anterior chamber. Fluid flows from ciliary body to the pupil & is absorbed through the channels in the angle of anterior chamber.The delicate balance of aqueous production& absorption controls pressure within the eye[2].

Eye Disorders:

The leading causes of blindness and low vision in the world are age-related eye diseases such as age-related macular degeneration, cataract, diabetic retinopathy, and glaucoma. Other common eye disorders include amblyopia and Strabismus[3].

Low Ocular Bioavailability: Reasons

It is well known fact that the drug applied topically into the eye shows low bioavailability. Since the eye is protected by a mechanism known as tear production, any foreign particle if entered into the eye is drained out by tear formed in the eye. Same case is occurred with the drug. As the drug (in any form) is entered into the eye it is washed out by tear. The dose which is instilled into eye is not the dose which crosses the cornea. Because major amount of drug instilled is drained out with tear fluid. This is the major cause of low ocular bioavailability. Lacrimation and tear turnover, Drug metabolism are some other factors which are responsible for low ocular bioavailability. Some drugs are metabolized in the ocular site, and give another reason of low ocular bioavailability. Another major cause of it is inability of drugs to cross the cornea. Major group of drugs show compromised lipophilicity so that these drugs are incapable to cross the cornea. For ocular delivery the drug comes in contact with cornea. The low surface area of cornea is also a drawback for ocular delivery. Low corneal surface area provides low area for absorption of drugs. Some drugs also bind with lachrymal proteins and results in low ocular bioavailability[4].

Conventional Ophthalmic Vehicles:

Solutions, suspensions and ointments are used as conventional ophthalmic vehicles.). Solutions are undoubtedly the most commonly used and accepted forms. They are relatively simple to make, filter and sterilize. Suspensions, while not as common as solutions, are widely used for formulations involving anti-inflammatory steroids (for example, prednisolone alcohol and acetate). Much published data suggests that a proper particle size and a narrow size range, ensuring low irritation and adequate bioavailability, should be sought for every suspended drug. Other formulation factors, i.e. the use of correct wetting, suspending and buffering agents, protective colloids, preservatives, etc., should also be considered attentively. Semisolid, petrolatum-based ointments presented problems for years because they could not be filtered to eliminate particulate matter, could not be made truly sterile and no adequate tests had been devised to indicate the suitability of added preservatives. In time, most of these problems have been solved, and sterile, filtered ophthalmic ointments are currently available on the market. These preparations, however, occupy a position of minor importance since they are ill-accepted on account of their greasiness, vision-blurring effects, etc., and are generally used as night-time medications.

Novel Approaches for ocular drug delivery:

Conventional drug delivery vehicles are not able to deliver the drug in ocular site efficiently. From time to time there are number of approaches are emerged for efficient ocular drug delivery.

In situ- Hydrogel systems:

The basic principle of this approach is to convert the liquid dosage form to semisolid dosage form as it comes in contact of ocular environment. Number of gelling agents e.g. Carbomer and Cellulose delivatives like hydroxy propyl methyl cellulose has been tried for delivery of drugs time to time. In these types of systems the dose is prepared as a solution dosage form. And it is instilled into the eye. Since it is in solution form so that it can be easily installed into the eye. As it is installed, it converts to semisolid consistency. Now the semisolid consistent dose provides higher contact time for active molecule with cornea and higher corneal penetration results.

Techniques to enhance the permeation through corneal barrier

Low penetration through the cornea is a major cause for low ocular bioavailability. It is intrinsic property of the active molecule, some molecule crosses the cornea in sufficient amount but some struggles. The more the lipophilicity of the molecule more will be the permeation through the cornea. Enhancing permeation through the cornea can be achieved through effective pro-drug design, or use of solubilization vehicles. In prodrug concept, the active molecule having low permeation efficiency is converted into a prodrug having higher permeation efficiency. This prodrug irreversibly is converted into the active molecule at the site of action. Example includes prodrug of Prostaglandin free acid forms to their corresponding alkyl esters or amides. Some ocular penetration enhancers are also in use these days, which increases the fluidity of corneal tight junction and allows the drug to cross the corneal barrier easily.

Iontophoresis

Iontophoresis is a minimally invasive method that propels charged compounds (e.g., lowMWdrugs, highMWbiological proteins [<15 kDa]) into ocular tissues. Iontophoresis uses a small electrical current that has the same charge as the drug to create repulsive electromotive forces and thus allow drugs with poor ocular penetration to be driven into ocular tissue. To date, there are no studies that have been reported on the use of ocular iontophoresis on veterinary patients; however, use iontophoresis to increase the penetration of methyl prednisolone and DNA to the ocular posterior segment may allow treatment of uveitis and retinal degeneration.

Microneedles

Solid and hollow microneedles have been described to enhance drug delivery to the eye. Solid microneedles (500–750 lm in length) coated with fluorescein or pilocarpine and inserted into the cornea resulted in fluorescein concentrations in the anterior chamber that were 60 times greater than those achieved by topical application and pilocarpine concentrations that resulted in profound miosis; both without measurable inflammatory responses caused by microneedle insertion. Hollow microneedles (200–300 lm) were used to deliver 10–35 lL of fluid into the sclera. Recently, slightly larger microneedles have been demonstrated to allow delivery of drugs to the anterior suprachoroidal space.

Drug-Eluting Contact Lenses

Conventional contact lenses have been used for years as a type of sustained release drug delivery system, usually used by soaking the lens in a drug solution and allowing retention of the drug in the 70% water component of the lenses. The drug was then allowed to release to the ocular surface once the contact had been placed on the eye. Although delivery of a drug via a contact lens does improve the contact time of the drug compared with topical eye drops, drugs released by a contact lens results in a burst of drug at therapeutic levels only for a few hours. Drug-eluting contact lenses composed of a polymer-drug film encapsulated within a poly-2-hydroxyethyl methacrylate (pHEMA) hydrogel have been described. This contact lens has been shown to deliver ciprofloxacin with zero-order kinetics up to 4 weeks. Also, poly-2-hydroxyethyl methacrylate hydrogels containing beta-cyclodextrin (pHEMA/beta-CD) have been investigated as a platform for sustained release of ophthalmic drugs. In rabbit eyes, use of this contact lens allowed higher mean residence time and aqueous humor concentration of a drug compared to topical application. These specialized drug-eluting contact lenses may prove to be very beneficial in the treatment of ocular surface and anterior segment disease in veterinary patients.

Eye Misters and Micro droplets

Eye misters and microdroplet application of drugs have been described as methods to improve compliance and possibly ocular drug penetration. An eye mister, if tolerated by veterinary patients, could have a profound effect on improving compliance, especially in large animals or possibly zoo animal patients with ocular disease. In one study, an ultrasonic nebulizer was used to create a mist of vitamin B12 that was delivered to the ocular surface in humans and compared with a control group that received a topical eye drop of vitamin B12. Twelve hours later, aqueous humor was collected and analyzed for B12 concentrations. None of those receiving eye drops had detectable vitamin B12 in the aqueous humor; however, 29% in the nebulizer group had detectable vitamin B12 concentrations. This suggests that the small particle size, increased surface area of the eye treated, and possibly increased contact time obtained from an eye mist may provide better ocular drug delivery than eye drops. Further development is underway.

Implant Strategies for Drug Delivery

Eroding implants Ocular implants have many advantages including the ability to deliver constant therapeutic levels of drug directly to the site of ocular disease while minimizing systemic side effects. These devices for controlled, sustained drug release are classified as biodegradable (i.e., eroding) and nonbiodegradable (i.e., noneroding). Biodegradable implants have the advantage of being able to be fashioned into various shapes and they do not require removal. Nonbiodegradable implants have the advantage of steady, controlled release of a drug for potentially long periods of time (i.e., years) and the disadvantage of removal and/or replacement when the drug is depleted. The targeted disease process dictates the site and placement of the implant. In general, episcleral implantation is used for the treatment of anterior segment disease, whereas intrascleral, suprachoroidal, and intravitreal placement of implants target posterior segment disease. Eroding implants typically follow first-order kinetics and have a burst of drug release followed by a slow decline. Therefore, these implants are best used to treat acute-onset diseases that require a loading dose followed by tapering doses of the drug from 1-day to 6-month release time. Eroding implants are commonly composed of copolymers polylactic-acid and/or poly-lactic-glycolic acid (PLGA), which degrade to water and carbon dioxide in vivo. The rate and extent of drug release from the implant can be modified by altering the relative concentrations of lactide (slow) and glycolide (fast), altering the polymer weight ratios, adding additional coats of polymer, or using hydrophobic, insoluble drugs. Biodegradable ocular inserts can be placed in the lower conjunctival sac for sustained release of drugs.

Nanoparticle technologies:

Nanotechnology is the most potential approach till date for ocular delivery of drugs. Nanoparticles and solid lipid nanoparticles are attracting the attention of researchers. Nanoparticles are delivery devices made up of polymers which release the drug in a controlled manner. Solid lipid nanoparticles are lipid based nanocarriers for delivery of drugs and again it releases the drug in a controlled manner[5].

Eudragit based drug delivery systems:

For the ocular delivery of drugs nanoparticulate delivery systems are showing good results. Various polymers are used for the preparation of nanoparticles. Poly lactic

glycolic acid, Poly lactic acid, Chitosan and Eudragit. Among these polymers, eudragit is attracting the attention of many researchers since long back. EUDRAGIT® RL 100 and EUDRAGIT® RS 100 chemically are copolymers of ethyl acrylate, methyl methacrylate and a low content of a methacrylic acid ester with quaternary ammonium groups (trimethylammonioethyl methacrylate chloride). The ammonium groups are present as salts and make the polymers permeable. Eudragit polymers are having an added advantage of mucoadhesiveness. It is a cationic polymer and capacity of mucoadhesion with ocular site since, former is having negative surface. Due to this mucoadhesion property, eudragit is capable of higher retention time in ocular surface. The long time residence permits the drug to cross the corneal barrier in sufficient amount[6].

Eudragit Based Delivery Carriers for Ocular Delivery:

Eudragit polymer is tried with variety of active molecules for the treatment of long range of diseases. Not only for ocular delivery but for other delivery routes also it is utilized as an efficient carrier of drug molecules. Although there are number of examples to cover of this polymer as an ocular carrier system, some of them are covered in following table.

CONCLUSION

From the above discussion it is clear that the eudragit polymer is a potential option for ocular drug delivery. It is getting immense popularity day by day because of its cationic and efficient drug release profiles. It is capable of drug release in a controlled manner. So that it is good option for sustained and long time treatment of drug in an efficient approach.

Table: 1- Eudragit based drug delivery vehicles:

SN	Delivery system	Molecule	Description	Researcher(s)	Ref.
1	Nanoparticles	Amphotericin B	In this study, the potential of Eudragit RL nanoparticle for the specific delivery of antifungal drug to the ocular mucosa was Investigated. The advantages of these systems in ocular drug delivery include their ability to contact intimately with the corneal and conjunctival surfaces, thereby increasing delivery to external ocular tissues without compromising inner ocular structures and systemic drug exposure, and to provide these target tissues with long-term drug levels.	Das et. al.	07
2	Nanoparticles	Cyclosporin A	NPs which combine the PLGA with the positively charged properties of Eudragit®RL or coated with the mucoadhesive Carbopol®. The results indicate that both the mean diameter and the surface charge on NPs were markedly affected by the polymer type. The P:E-CsA (75:25) NPs showed small particle size and positive surface charge, which makes them suitable for ocular use. The cytotoxic effects of NPs formulations were found to be time and concentration dependent. The P:E-CsA (75:25) NPs formulation also showed significantly higher degree of cellular uptake, tear film concentration of the CsA and AUC0→24 value in comparison with the other NPs formulations. In conclusion, we have demonstrated that NPs with different properties could modulate the drug release.	Aksungar et al.	08

3	Nanosuspension	Ibuprofen	A series of polymeric nanoparticle systems have been, described, obtained by co-dispersion of IBU sodium salt and Eudragit RS100 polymer in water. The resulting nanosuspensions showed interesting mean sizes for oph-thalmic applications, a positive surface charge, which can help corneal adhesion and good stability upon storage, particularly at low temperatures. The formulations could also been successfully freeze-dried to allow a long term conservation. In the in vivo test on rabbit eye, one of the nanosuspen- sions (containing an IBU concentration of 0.1%, so that no further dilution of the formulation was required), showed a very good ocular tolerability. The comparison with an aqueous solution of IBU lysine salt showed that the nanoparticle system is able to give a gradual and prolonged release of the drug which, associated with an increased retention to the corneal surface, resulted in higher drug levels in the aqueous humour. Ultimately, this led to a higher, even though it was not significant, capacity to inhibit the miosis induced by a surgical trauma than the reference eye-drops. The described systems are good candidates for a valid therapeutic approach for the topical treatment of inflamma-tory conditions of the eye, as well as in maintaining mydriasis during surgery.	Pignatello et al	**09**

4	Nanosuspension	Ibuprofen	A comparative study between the release of Ibuprofen (IBU) from Eudragit RS100® (RS) and RL100® (RL) nanosuspensions as well as the free drug to a biological model membrane, consisting of dimyristoylphosphatidylcholine (DMPC) multilamellar vesicles (MLV), was carried out by DSC technique. The aim was to assess the suitability of such calorimetric technique to determine the kinetics of drug release from a polymer system, compared with a classical release test by dialysis method. The system showed good results.	Castelli et al.	**10**
5	Nanosuspension	Cloricomene	--	Pignatello et al	**11**
6	Nanoparticles	Ciprofloxacin	--	Dillen et al	**12**
7	Nanosuspension	Flurbiprofen	The present work investigated the release of Flurbiprofen (FLU) from Eudragit RS100® (RS) and Eudragit RL100® (RL) nanosus-pensions to a biological model membrane consisting of Dimyristoylphosphatidylcholine (DMPC) multi-lamellar vesicles (MLV). This release was com-pared with those observed from solid drug particles as well as with dialysis experiments. This drug release-uptake model evidences that a) Eudragit RL100 nanosuspensions is a better deliv-ery system than RS100 to sustain the drug release; b) DSC technique applied to the drug interaction with biomembrane represents a good tool to follow the drug release; and c) this model, representing an alternative in	Castelli et al.	**13**

			vitro tool, could be employed to de-termine the different kinetics involved in the drug transfer from a drug delivery system to a membrane selected as an uptake site.		
8	Nanosuspension	Flurbiprofen	Nanoparticle suspensions were made by Eudragits Retard polymer resins and containing different amounts of FLU.The drug was incorporated with very high yields in the polymer matrices. One formulation was tested in the rabbit compared to a commercial eye-drop product containing an equivalent amount of FLU sodium salt. The incorporation of the drug in the polymer system enhanced FLU antagonising activity against the miosis induced by a surgical trauma to the eye anterior chamber and increased its active concentration in the aqueous humour. For the possibility of modulating the preparation conditions and the stability shown upon storage, as the original suspensions or after freeze-drying, for the very good tolerability, the described formulations may be useful in clinical practice to maintain mydriasis during cataract or other eye surgical treatments.	Pignatello et al	**14**
9	Nanoparticels	Indomethacin	Indomethacin-loaded nanocapsules were prepared by deposition of poly-(D,L-lactide) polymer at the o/w interface following acetone displacement from the oily nanodroplets. An attempt was made to elucidate the mechanism of formation in terms of interracial turbulence diffusion and surface tension decrease (Marangoni effect).	Fessi et al	**15**

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