OCULAR DRUG DELIVERY SYSTEMS: AN OVERVIEW

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ABSTRACT

The treatment for the ophthalmic diseases are topical route because of the various ocular barrier. Ocular drug delivery systems are considered as major challenges by today's pharmacologist and formulation scientist. Topical eye drop is the most convenient and patientcompliant route of drug administration, especially for the treatment of anterior segment diseases. tissues. In the past two decades, ocular drug delivery research acceleratedly advancedtowards developing a novel, safe and patient compliant formulation and drug delivery techniques, which may surpass these barriers and maintain drug levels in tissues. There are many eye ailments which affected to eye and one can loss the eye sight also. Therefore, many ophthalmic drug delivery systems are available. These are classified as conventional and non-conventional (newer) drug delivery systems. Most commonly available ophthalmic preparations are eye drops and ointments about 70% of the eye dosage formulations in market.So overcome to these problems newer pharmaceutical ophthalmic formulation such as in-situ gel, nanoparticle, liposome, nanosuspension, microemulsion, intophoresis and ocular inserts have been developed in last three decades increase the bioavailability of the drug as a sustained and controlled manner.

KEY WORDS: *Occular, Drug delivery, Liposomes, Development.*

1. INRTODUCTION

Human eye is a complex structure, both anatomically and physiologically, that makes it a unique organ consisting of its physiologically independent functions. Its wide range of varied structures also challenges to develop drug delivery systems for it [1]. The major problem in the conventional ocular drug delivery system with eye drops is their fast and extensive elimination from the eye, causing extensive loss of the drug. In eye drops, only a small portion of a drug penetrates through the corneal layer and arrives in the internal tissues present in the eye. Broad classification of ocular drug delivery results in two types, those concerned with the anterior and posterior segments. For vision-threatening ocular diseases, conventional drug delivery systems, such as eye drops, suspensions and ointments, cannot be used for optimal treatment. About 90% of the ophthalmic formulations in the market are available in the form of eye dropsand the sites of action are diseases occurring in the anterior segment of the eye [5-7]. Topical delivery of drugs through conventional approaches is unable to make it reach the posterior segment of the eye. Formulations like eye drops and ointments, when instilled into the cul-de-sac, are wiped away from eye region quickly because of the flow of tear and lachrymal nasal drainage. Most of the drug is drained away and only a small portion reaches the site of action; so, it needs frequent dosing to achieve a therapeutic effect. The eye's posterior segment includes the retina, vitreous humour and choroid; the diseases occurring in these regions can be cured by using intravenous and intravitreal drug delivery systems, implants or by administering drug through periocular route and needs high concentration of the drug as well. For ophthalmic drug delivery, the posterior segment of eye is frequently a choice of interest to locate drugs using novel approaches. The rationale behind this review and novelty of this study
are to highlight the newer developments in the pharmaceutical ophthalmic formulations, such as formulation of in situ gels, nanoparticles, liposomes, nanosuspension, microemulsion, ocularinserts and so on, and their progress to overcome the problems associated with the existing conventional dosage forms and also to improve the bioavailability as well as the sustained release of the drug at the target location.

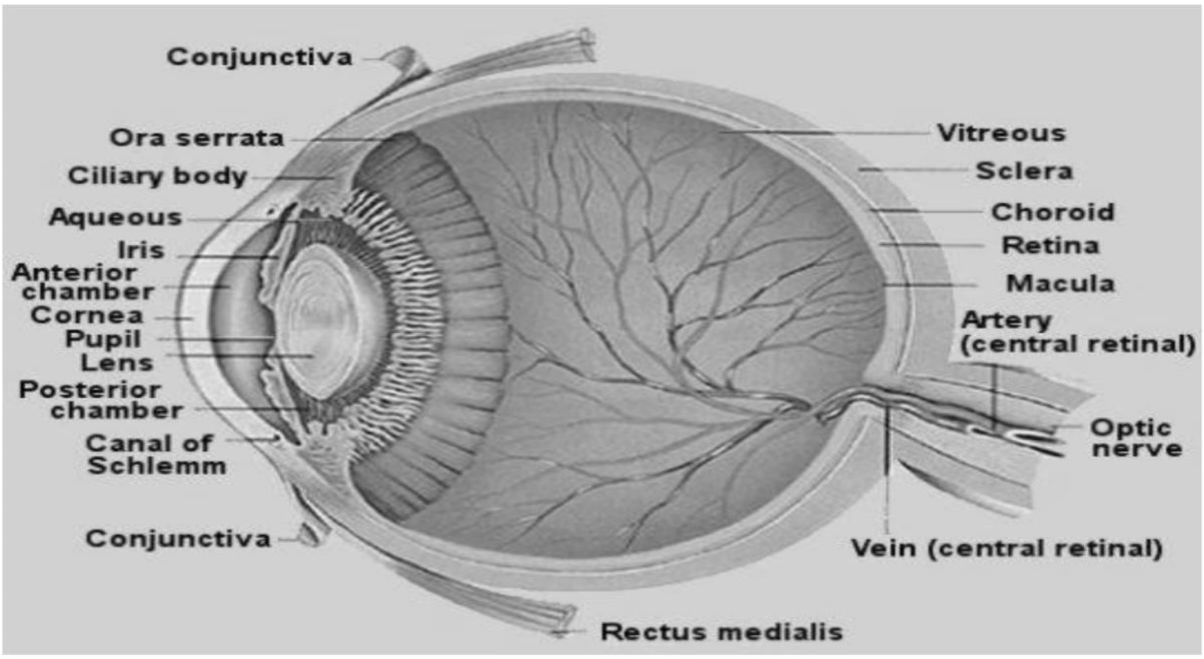

Fig.1: Cross section view of an eye

2. Barriers for ocular drug delivery

The various barriers for ocular drug delivery are as follows:

I. Drug loss from the ocular surface

After using the dosage form of the drug in the ocular system, flow of lacrimal fluid wipes out a portion of the drug from its surface and its turnout rate is only about 1 µl/min, whereas a major portion of the drug is wiped out through the nasolacrimal duct quickly within minutes. Other sources of drug removal include the systemic absorption of the drug, instead of being absorbed through the ocular route. Systemic absorption is mostly directed through the conjunctival sac to the local blood capillaries or takes place after the solution flows to the nasalcavity [9].

II. Lacrimal fluid-eye barriers

Absorption of the drug from the lacrimal fluid can be limited by the corneal epithelium present in the eye. Tight junctions formed from corneal epithelial cells limit the permeation of the drug paracellularly. Lipophilic drugs show

higher permeability in the cornea as compared to hydrophilic drugs. In other terms, we can say that conjunctiva has leaky epithelium compared to that of the cornea and also has twenty times greater surface area than the cornea that supports rapid systemic absorption.

III. Blood-Ocular barriers

The blood–ocular barrier system is formed by two main barriers: the blood–aqueous barrier and the blood–retinal barrier (BRB). One of these barriers, the BRB, is particularly tight and restrictive and is a physiologic barrier that regulates ion, protein, and water flux into and out of the retina. The BRB consists of inner and outer components, the inner BRB being formed by tight junctions between retinal capillary endothelial cells and the outer BRB by tight junctions between retinal pigment epithelial cells.

The BRB is essential to maintain the eye as a privileged site and is essential for normal visual function. Treatment of retinal diseases must deal with the BRB either by using its specific transport mechanisms or by circumventing it through intravitreal injections.

3. Routes of ocular drug delivery

The selection of the route of administration depends primarily on the target tissue. Design of the dosage form can have big influence on the resulting drug concentrations and on the duration of drug action.

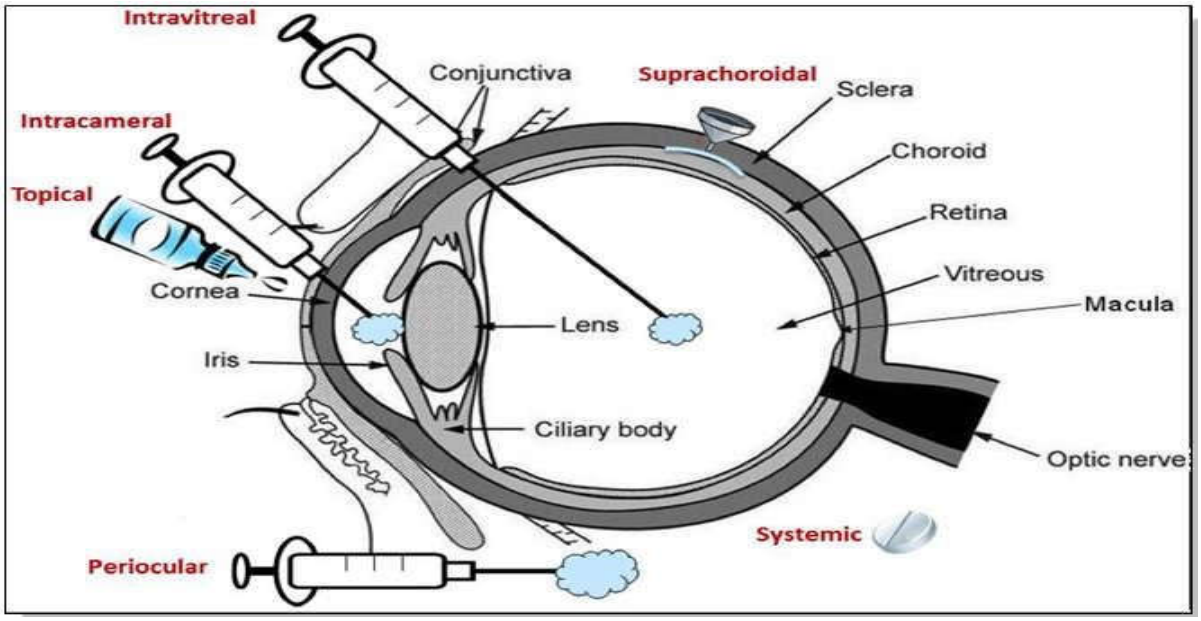

Fig.2: Routes of ocular drug delivery [2]

Topical ocular

Typically, topical ocular drug administration is accomplished by eye drops, but they have only a short contact time on the eye surface. The contact, and thereby duration of drug action, can be prolonged by formulation design (e.g., gels, gelifying formulations, ointments, and inserts)[3].

Intra-vitreal administration

In recent advancement in the surgical procedures, intra- vitreal administration of therapeutic agents by direct injection into the mid-vitreous region and sustain and controlled released intra-vitreal implants have become a mainstay treatment option of posterior segment diseases. Longer retention time and higher vitreous concentration of drugs was obtained following this route of administration.

In order to overcome the risks related to direct intra- vitreal injection such as cataract, retinal detachment and vitreous hemorrhage. Vitrasert® is a non- biodegradable GCV intraocular implant. Sustain therapeutic concentration of ganciclovir in to the vitreous humor for a period of 5-6 months can be achieved by this intra- vitreal implant. Removal of implant requires a skillful surgical procedure and possesses risks of retinal detachment and hemorrhage [4].

Scleral administration

Due to its large surface area, easy accessibility and relatively high permeability to macromolecules, the sclera recently has become a potential vector for posterior segment drug delivery. Scleral drug delivery has been attempted by different ways, such as scleral plugs and implants, sun conjunctival injection, subtenon injection. Trans-scleral administration of drugs offers a promising therapeutic approach for the treatment of various posterior segment diseases.

Systemic administration
Due to the presence of blood retinal barrier, systemic administration has achieved a limited success to deliver drugs to the vitreo-retinal tissues. Only 1-2% of plasma drug concentration is achieved in the vitreous humor and therefore requires frequent administration to maintain therapeutic drug level. This route of administration may also result in non-specific binding of drug to other tissues and cause systemic cytotoxicity.

4. Approaches in ophthalmic drug delivery systems

A number of approaches have been used in the early stages for better results. These approaches, categorized into two types, are:

Bioavailability improvement Controlled release drug delivery

The first type aims to maximize corneal drug absorption and minimize precorneal drug loss using viscosity and penetration enhancers, prodrugs, gels and liposomes. The second one is forthe delivery of active ophthalmic moiety in the form of a sustained delivery system by providing controlled and continuous delivery like implants, inserts, nanoparticles, micro particulates, and colloids. There are a number of traditional approaches, such as viscosity enhancers, gel, penetration enhancer, prodrug and liposomes which enhance the bioavailability, while the newer developments, i.e., ocuserts, nanosuspension, nanoparticles, liposomes, niosomes and implants improve both bioavailability and release of drugs in a controlled mannerin the anterior segment of the eye. In the posterior segment of the eye, drug reaches through intravitreal injections, iontophoresis, subconjunctival injection and periocular routes [6, 7].

5. Approaches to improve ocular bioavailability

Use of viscosity enhancers
Viscosity-increasing polymers are highly preferred additive in the ophthalmic formulations due to their properties of enhancing viscosity and thereby imparting benefit to the penetration of the drug into the anterior chamber of the eye by lowering the elimination rate from the preocular area, resulting in increase in precorneal residence time and trans corneal penetration, but having very fewer effects for enhancing bioavailability in human beings. Examples of polymers are polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), methylcellulose, hydroxyl ethyl cellulose, hydroxyl propyl methylcellulose (HPMC) and hydroxypropyl cellulose [18]. As perSaettone et al. (1984), in their study of tropicamide solution, by using PVA, HPMC, and PVP solution, at concentrations yielding the same viscosity of 20 cst, PVA has been reported to be the most effective among all, probably due to the adhesive property of PVA and its capability to enhance the thickness of the precorneal tear film [18]. Saettone et al. (1982) have stated in their study that the retention of drug in the precorneal tear film does not strictly belong to vehicle viscosity, but also with surface spreading properties of the vehicle and to the capabilityof a polymer to use water as the vehicle spreads over the ocular surface with each eye blinking [13]. Gel formulation Gels are known to be significantly dilute cross-linked systems, which show rigidity in the steady-state. Gels are generally liquid, but behave like solids due to their three-dimensional cross-linked structure within the liquid [14]. On the other side, if the gels have extremely high viscosity, they cannot improve bioavailability; instead, they will control the release, which leads to reduced frequency of dosing to once a day. The highly viscous solution even leads to blurred vision and matted eyelids, which substantially decrease patient's compliance. In aqueous gel, viscosity building agents, such as PVA, polyacrylamide, poloxamer, HPMC, Carbomer, polymethyl vinyl ether, Maleic anhydride, and hydroxyl propyl ethyl cellulose are incorporated, whereas hydrogel or swellable water-insoluble polymers give rise to controlled drug delivery systems [15]. Prodrug formulation by the development of prodrugs, many properties of the formulation can be improved, which make it suitable for increasing drug permeability through the cornea. It includes modification of the chemical structure that imparts new characteristics to the active moiety i.e., site-specificity and selectivity [15].

Liposomes: Liposomes are microscopic lipid vesicles designed to entrap drugs. Liposomes composed of natural lipids are biodegradable, biologically inert, weakly immunogenic, produce no antigenic reactions and possess limited intrinsic toxicity. Therefore, drugs encapsulated in liposomes are expected to be transported without rapid poly (lactide-co- glycolide) degradation and minimum side effects to the recipients. Moreover, efforts have been made to assess the specificity of drug carriers to the target organs, cells or compartments within the cells. They have been used locally as well as systemically for targeting of drugs to specificorgans or for prolonging drug effect. The encapsulation of drugs in liposomes has been shownto reduce the toxicity, provide solubility in plasma, and enhance permeability through tissue barriers. The main drawbacks associated with liposomes are their short shelf life and difficulty in storage, limited drug loading capacity and instability on sterilization and finally, transient blurring of vision after an intra- vitreal injection.
A method has been developed to target drugs locally in the eye via a light-based mechanism. The method, called laser-targeted delivery23-24 consists of encapsulating a drug in heat- sensitive liposomes, injecting them intravenously, and releasing their content at the site of choice by non-invasively warming up the targeted tissue with a laser pulse directed through thepupil of the eye. The specific temperature needed for the phase transition is 41oC (105.8 F), which causes the liposomes to release their contents in the blood in less than 0.1 second. Ciprofloxacin containing therapeutic systems were developed using gel and liposome-based formulations to minimize tear-driven dilution in the conjunctival

sac, a long-pursued objective in ophthalmology. For gel preparation, the bio-adhesive poly (vinyl alcohol) and polymethacrylic acid derivatives were applied in various concentrations. The polymer hydrogels used in our preparations ensured a steady and prolonged active ingredient release25.Development and optimization of reverse phase evaporation ciprofloxacin hydrochloride liposomes for ocular drug delivery was carried out using a 25 full factorial design based on fiveindependent variables. The effects of the studied parameters on drug entrapment efficiency, particle size, and percentage of drug released after 1 and 10 h were investigated.

In addition to gene and drug delivery applications, liposomes can be used as carriers for the delivery of dyes to textiles,[16] pesticides to plants, enzymes and nutritional supplements to foods, and cosmetics to the skin.[17]

6. CONCLUSION

Increasing the residence time of an ophthalmic formulation on the corneal surface increases thedrug bioavailability and therefore reduces frequency of administration. Although recent advances have been made in ocular drug delivery systems, eye drops are still the most commonly used formulations as they are the least expensive preparations, easy to use and do not interfere with vision. However, frequent administration is necessary. Efficient and safe delivery of therapeutic agents to the ocular tissues, mainly posterior segment tissues, is a major challenge for the formulation scientists due to the presence of various physiological barriers. Various approaches have been studied to achieve therapeutically effective concentrations of drugs into the ocular tissues. Recent technological advancement has changed the field of ocular drug delivery from conventional drops to sustained release and targeted ocular delivery systems. In the recent era of technology, combinatorial approach seems to be a focus of research in the development of safe and efficient ophthalmic drug delivery systems.

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