Review Article

Recent Trends in Ocular Drug Delivery System

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ABSTRACT

There is a various route of drug delivery, but today amongst them, the ocular drug delivery system becomes the most interesting and challenging attempt in front of pharmaceutical scientists. Eye is a unique, isolated, very delicate and valuable organ of our body. There are a bulk of eye disorders which can affect the eye and even some of them can cause the loss of eye sight also. The clear cut aim of designing ocular drug delivery system is to attained optimal concentration of a drug at the target site of the body for the most appropriate duration. A successful design of drug delivery system must have an integrated knowledge of drug molecule and the restriction offered by the route of administration. This review focused on controlled and sustained drug delivery has become the backbone in the present pharmaceutical design and also on the recent developments in the other ocular drug delivery strategies such as in situ gel, implants, contact lens, micro needles etc. To overcome the ocular drug delivery barriers, variety of drug delivery systems have been developed such as suspensions, emulsions , ointment, nanoparticles, liposome and in situ thermo sensitive gel for the earlier describe ocular diseases.

Keywords: ocular drug delivery system, drug delivery, eye diseases.

INTRODUCTION

Ocular drug delivery is one of the most attractive and interesting but ardous struggle facing by the pharmaceutical scientists. The ancient ophthalmic solutions, suspensions and ointment dosage forms are no longer satisfactory to give the therapeutic action as much as necessary to some current virulent diseases[1]. On the basis of anatomy and physiology eye is a unique, complex and incomparable structure[2]. It can be divided into two segments.

- Anterior segment
- Posterior segment

1/3 portion of the eye occupied by the anterior segment while rest portion comes under posterior segment. Cornea, conjunctiva, iris, ciliary body and lens make the anterior portion of the eye.

Posterior segment of the eye include sclera, choroid, retinal pigment epithelium, neural retina, optic nerve and vitrous humor[3,4].

To overcome the ocular drug delivery barriers and to improve bioavailability for ocular system, variety of conventional and novel drug delivery system have been established such as suspensions, emulsions, ointments, aqueous gel, nanomicelles , nanoparticles, liposome, implants, nano suspensions , micro needles and in situ thermosenstive gel for the earlier describe ocular diseases[5].

Accessory Organs of the Eye

Eye brows

Eyelids

Lacrimal apparatus[6].

Road Map or Routes of Ocular Drug Delivery System

Depending upon the terget tissue, mainly there are 3 route:

- TOPICAL ROUTE: Eye drops are main tool for topical route administration of drugs, but have a short contact time on the eye surface.

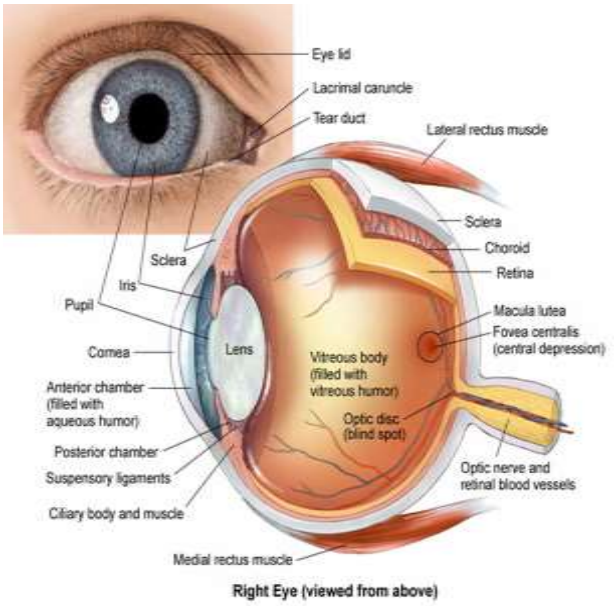

Figure 1: Structure of Human Eye

- **Subconjuctival Administration**: Mainly sub conjunctival injection have been designed to make their supply at increased level to the uvea/posterior chamber.

- **Intravittreal Administration:** This type of administration is used to deliver the drug into the vitreous chamber[7].

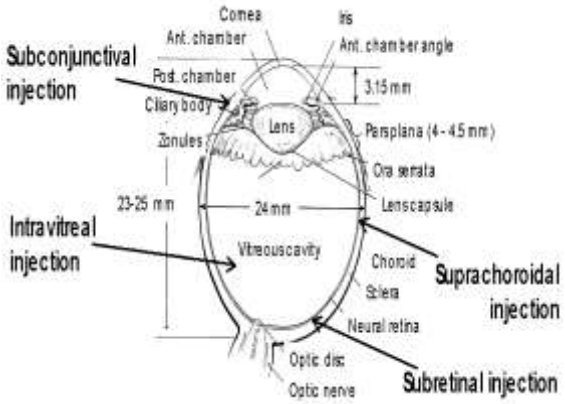

Figure 2: Routes of Ocular Drug Delivery System

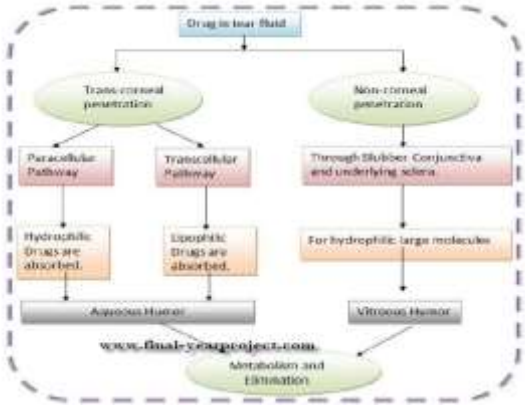

Figure 3: Pathway for the Drug Absorption

Barriers for Ocular Drug Delivery System

Drug Loss from the Ocular Surface

After the infusion of drug into the eye, the lacrimal fluid flow, remove the instilled or infused drug compound from the surface of eye. Even the lacrimal turnover rate is only about 1 micro litter per minute. Another method of non productive drug removal is its systemic absorption in the body instead of ocular absorption.

Lacrimal Fluid Eye Barriers

Corneal epithelium act as a barrier and limit the drug absorption from the lacrimal fluid into the eyes, there for, typically the lipophilic drugs have the higher permeability in the cornea as that of hydrophilic drugs. Generally the conjunctiva has the 20 times greater surface area then that of cornea.

Blood Ocular Barriers

Eye prevent from xenobiotics in the blood stream by blood ocular barriers. Mainly these barriers are divided into two parts:

Blood aqueous barrier – anterior blood eye barrier

Blood retina barrier – posterior blood eye barrier[8].

Mechanism of Ocular Drug Absorption

Drug administration by instillation must penetrate the eye and do so primarily through the cornea followed by the non corneal routes. The non corneal route involves conjunctiva and sclera and diffusion occurs mainly across these areas and appears to be particularly important for the drugs that are poorly absorbed across the cornea[9].

Mechanism of Drug Release

The mechanism of controlled drug release into the eye is shown below:

- **Diffusion**: In this mechanism the drug is released continuously at a controlled rate through the membrane into tear fluid. The release of drug can take place via diffusion through the pores. The drug diffuse from a region of higher to lower concentration across the concentration gradient[10].
- **Osmosis**: In this mechanism the inserts comprise a transverse impermeable elastic membrane dividing the interior of inserts into the first compartment and a second compartment; first compartment is bounded by the semi permeable membrane and impermeable elastic membrane, and the second compartment is bounded by an impermeable material and the elastic membrane. The drug release aperture in the impermeable wall of insert[11].
- **Bioerosion**: In this mechanism, the symmetry of the body of insert is constituted from a matrix of bioerodible material in which the drug is dispersed. Contact of the insert with tear fluid results in controlled sustained release of drug[12, 13].

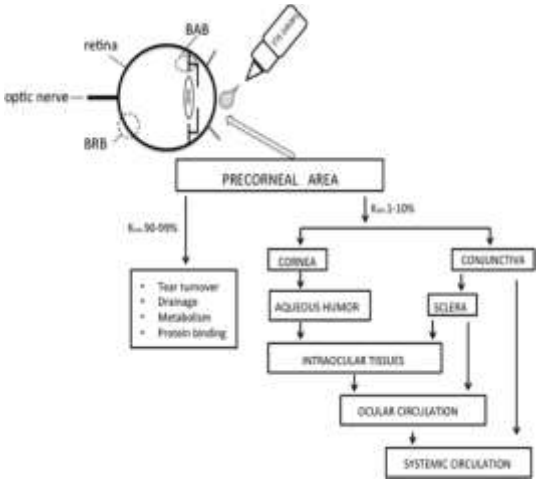

Figure 4: Mechanism of Action

Snags Associated with Opthalmic Drug – Delivery Systems

Insubstantial Space of the Lower Conjuctival SAC

Lower conjuctival sac is the important or key point location for the instilment of eye formulations. For the eye drop instillation, firstly dragging downwards the lower eyelid skin of the lower conjunctival sac molds a funnel shape reservoir providing capacity to take in

highest volume of 25 ml. On kept free eye lid to gone back to its original position, the volume of conjuctival sac shorten by 70%-80% i.e. less than 10 ml[14].

Tear Discharge

The degree of discharge of the tear has been found 1.2 ml/min. In an normal human eye, tear reversal count in a minute is closely 16% of the whole tear volume[15]. Whenever any annoying stimulus excites cornea and conjunctiva, due to that reflexive lacrimation takes place so as to increase the tear volume about 16 ml, with a range of 5 to 66 ml[16].

Involuntary Nictitating Phenomenon

Involuntary nictitation of the human eye is protection machinery, which is rapid, adequate to come before any harmful object accessing the eye. Winking of the eye also use a pumping tool for the drainage of tear through the lacrimal drainage apparatus. The wink speed in human is 15 to 20 per min[17].

Pre-Ocular Retention

The volume of the liquid that the conjuctival sac can take inside is ~20-30 UL and the volume of the tear film is 7 u L[18]. Owing to physical restriction of eye drop volume when produced from a standard dropper, most bottles transfer 30-50 u L instead of the ideal drop size of 10-20 u L the delivery of this larger volume reflex blinking, which boosts the drainage rate to the nasolacrimal canal[19].

Corneal Absorption

Cornea is the heart for the intraocular absorption. Due to the small surface area and corresponding impermeableness show this region as an effective barrier to drug absorption[20]. In comparison to conjunctiva, the area of conjunctiva in human is 17 times bigger than the cornea[21]. When the drug is topically administered to the pre-ocular area, conjuctival drug absorption phenomenon results in a substantial loss of drug, and alters the amount of drug absorbed via corneal absorption[22].

Drug Binding to Tear Proteins

Human beings tears accommodate approximately 0.7% of the total –body protein. Due to this reason, whenever a drug come in contact with tear fluid, it could bind to the tear protein also just like albumin, globulin and lysozyme[23]. Biological action of many ophthalmic drugs is manipulated by drug –protein interaction in tissues and fluids of the eye[24].

Melanin Binding

Melanin is found in retina and can affect the ocular bioavailability of topically administered drug. Melanin binds to drug by electrostatic and van der Waals forces[25]. From the literature point of view all basic and lipophilic drugs bind to melanin. Thereby, melanins binding significantly lower pharmacological activity[26,27].

Drug Metabolism

Miscellaneous enzymes in the eye can metabolize the active drug, resulting in declined ocular bioavailability. Drugs that are bio-transformed via oxidation or reduction are not so much acceptable to metabolism than those altered by hydrolysis[28].

Formulations Emergence for Better Ocular Bioavailability

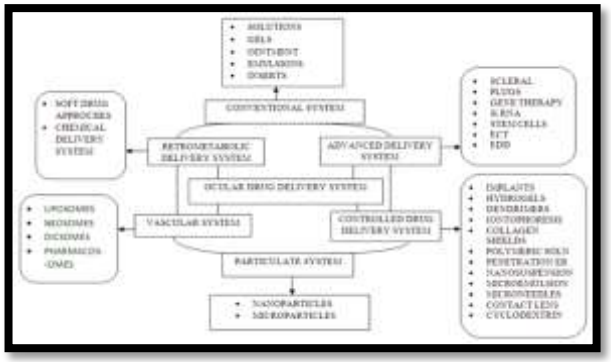

Figure 5: Classification of Ocular Drug Delivery System

Sol to Gel System

Means gel in situ was suggested first time in 1980s. So it is widely accepted that if there is increasing the viscosity of a drug formulation in the precorneal region then there is increase in bioavailability, due to slower drainage from the cornea. The system can be triggered by p H, temperature or by ion activation. These preparation gave the better release property of a drug over a long period of time in the rabbit's eye as compared to conventional eye drops[29].

Solution and Suspensions

Solutions are the pharmaceutical forms mostly used to administer drug that must be active on the eye surface or in the eye after passage through the cornea and conjunctiva. But there are some advantages of solutions that for very short time the solution stays at the eye surface, its poor bioavailability, the instability if dissolved drug and the necessity of using preservatives. The retention of a solution in the eye is influenced by viscosity, hydrogen ion concentration, the osmolality and the instilled volume[30,31].

Sprays

Sprays are used in the eye for dilating the pupil or for cycloplegics examination. Even sprays are not commonly used, but some practitioners use mydriatics or cycloplegics alone or in combination in the form of eye spray[32].

Contact Lenses

These lenses absorb the water–soluble drugs when soaked in drug solutions. Now these saturated lenses are settled down in the eyes for releasing the drug for long period of time. In humans, the Bionite lens which is made

from hydrophilic polymers has been used to produce a greater penetration of fluorescein[33].

Artificial Tear Inserts

LACRISERT, A rod shaped pellet of hydroxyl propyl cellulose without preservative is commercially available. This device is designed as sustained release artificial tear for the treatment of eye problems[34].

Filter Paper Strips

Sodium fluorescein and rose Bengal dyes are commonly used in this strip. These dyes are used for the diagnostic purpose in corneal injuries and infections[35].

Microemulsions

Micro emulsions are a promising dosage form for the natural defense of the eye, due to their intrinsic properties and specific structure[36]. Microemulaions are prepared by inexpensive processes through auto emulsification or supply of energy and can be easily sterilized, so they are stable and have high capacity of dissolving the drugs. The *in vivo* results and preliminary studies on healthy volunteers have shown a delayed effect and an increase in the bioavailability of drug[37,38].

Ocular Inserts

These are the solid dosage forms and can overcome the disadvantages and problems reported with traditional ophthalmic preparations like aqueous solutions, suspensions and ointments.

These inserts maintain an effective drug concentration in the target tissues[39]. A number of ocular inserts were prepared by using different techniques to make soluble, erodible, nonerodible and hydro gel inserts[40].

Collagen Shield

This one is regarded as one of the most useful biomaterial. Due to the outstanding biocompatibility and safety due to its biological characteristics such as biodegradability and weak antigenecity made collagen the primary recourse in medical applications[41,42].

The collagens shields are hydrated before they are placed on the eyes, having been stored in a dehydrated state. Typically the drug is loaded into the drug solution for a period of time prior to its application[43].

Ocular Iontophoresis

In this process the direct current drives the ion into cells or tissues. When we use the iontophoresis for drug delivery, the ions of importance are charged molecule of drugs. If the drug molecules carry a positive charge, they are driven into the anode part of the tissue, if negatively charged, driven at the cathode.

The advantages of this process is that the drug delivery system is fast, painless and safe, and in most cases, it results in the delivery of high concentrations of drug to a specific site[44].

Liposomes

Liposomes are the phospholipids – lipid vesicles, which are used to targeting drugs for specific site in the body. They provide the controlled and sustained drug delivery and also improve the bioavailability[45]. Liposomes are completely biodegradable and relatively non toxic but they are less stable then polymeric drug delivery system.

Niosomes

Niosomes are chemically more stable as compared to liposomes. They can entrap both the hydrophilic and hydrophobic drug. Generally they are nontoxic and do not require special handling techniques[46].

Mucoadhesive Dosage Forms

Mucoadhesive polymers are usually macromolecular hydrocolloids with numerous hydrophilic functional groups such as carboxyl-hydroxyl, amide and sulphate, capable of creating electrostatic interactions[47]. These dosage forms showed more bioavailability of the drug as compared to conventional dosage forms.

Nanoparticles and Microparticles

Polymeric drug delivery includes micro and nanoparticles. Maximum size range limit for micro particle for ophthalmic administrations is about 5-10mm. Above this size, some kind of irritational feeling in the eye can result after ocular application[48]. The binding of the drug depend on the physiochemical properties of drugs, as well as the nano or micro particle polymers .After the optimal binding of the drug particles, the drug absorption in the eye is enhanced significantly in comparison to eye drops[49].

CONCLUSION

A few new products have been commercialized as a result of the research into the ophthalmic drug delivery.

An ideal system should be able to achieve an effective drug concentration at the target tissue, while minimizing systemic exposure. In addition, the system should be comfortable and easy to use.

Major improvements are required in each of the technologies discussed in this review. Some approaches are relatively easy to manufacture, but limited in their ability to provide sustained drug release.

But within that, other approaches are promising with regard to sustained release, but are difficult to manufacture.

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