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REVIEW ARTICLE

A Review on Occular Drug Delivery System (ODDS)

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ABSTRACT

Ocular drug delivery to the eye has one of the most challenging researches for formulation scientists to series of specified characteristics according to the physiological structure of the eye. Eye is a unique and challenging organ for therapeutic drug delivery on to the surface as well as in the interior part of the ocular structure. However, one of the major drawbacks associated with topical ocular drug delivery is the rapid and extensive precorneal loss caused by drainage in the extra ocular area and high tear fluid turnover. Ophthalmic drug delivery, probably more than any other route of administration, may benefit from the uniqueness of Nano-approaches -based drug delivery. The use of Nano carriers provides attractive replacements for topical ocular drug delivery, mainly because of their capacity to protect the encapsulated molecule, along with its facilitated transport to the different compartments of the eye. Additionally, nanostructures may offer the possibility of controlling drug delivery, thus being attractive vehicles for the treatment of some chronic ocular diseases like glaucoma, CMV retinitis, retinal neovascular-ization and dry eye disease.

Keywords: Ocular drug delivery, Eye, Precorneal, Nano carriers, Ocular diseases, controlling drug delivery

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1. Introduction

Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientists. The anatomy, physiology and biochemistry of the eye render this organ exquisitely impervious to foreign substances. The challenging Jo the formulator is to circumvent the protective barriers of the eye without causing permanent tissue damage. The development of newer, more sensitive diagnostic techniques and therapeutic agents renders urgency to the development of successful and advanced ocular drug delivery systems.[1] The goal of pharmacotherapeutics is the attainment of an effective drug concentration at the intended site of action for a desired

length of time. Eye, as a portal for drug delivery is generally used for the local therapy as against systemic therapy in order to avoid the risk of eye damage from high blood concentrations of drug, which are not intended for eye.

Table 1: Difference between Ophthalmic and Ocular drug delivery system

Ophthalmic drug delivery system	Ocular drug delivery system
Conventional System	Novel System
Old Concept	New Concept
Addition of Preservatives	Do Not Addition of Preservatives
High Dosing Frequency	Low Dosing Frequency
Minimum release rate of drug	Maximum release rate of drug
Limited Flexibility	Extreme Flexibility
Minimum Absorption rate	Maximum Absorption rate
Minimum Bioavailability	Maximum Bioavailability

Physiology of the Eye:

The eye consists of transparent cornea, lens, and vitreous body without blood vessels. The oxygen and nutrients are transported to this non-vascular tissue by aqueous humor which is having high oxygen and same osmotic pressure as blood. The aqueous humor in human is having volume of 300 µl that fills the anterior chamber of the eye which is in front of lens. The cornea is covered by a thin epithelial layer continuous with the conjunctiva at the cornea sclerotic junction. The main bulk of cornea is formed of criss-crossing layers of collagen and is bounded by elastic lamina on both front and back. Its posterior surface is covered by a layer of endothelium. The cornea is richly supplied with free nerve endings. The transparent cornea is continued posteriorly into the opaque white sclera which consists of tough fibrous tissue. Both cornea and sclera withstand the intra ocular tension constantly maintained in the eye. The eye is constantly cleansed and lubricated by the lacrimal apparartus which consists of four structures[2,3].

- lacrimal glands
- lacrimal canals
- lacrimal sac
- nasolacrimal duct

The lacrimal fluid secreted by lacrimal glands is emptied on the surface of the conjunctiva of the upper eye lid at a turnover rate of 16% per min. It washes over the eye ball and is swept up by the blinking action of eye lids. Muscles associated with the blinking reflux compress the lacrimal sac, when these muscles relax; the sac expands, pulling the lacrimal fluid from the edges of the eye lids along the lacrimal canals, into the lacrimal sacs. The lacrimal fluid volume in humans is 7 µl and is an isotonic aqueous solution of bicarbonate and sodium chloride of pH 7.4. It serves to dilute irritants or to wash the foreign bodies out of the conjuctival sac. It contains lysozyme, whose bactericidal activity reduces the bacterial count in the conjunctiva sac. The physiological barriers to diffusion and productive absorption of topically applied drug exist in the precorneal and corneal spaces. The precorneal constraints that are responsible for poor bioavailability of conventional ophthalmic dosage forms are solution drainage, lacrimation, tear dilution, tear turn over and conjuctival absorption[4].

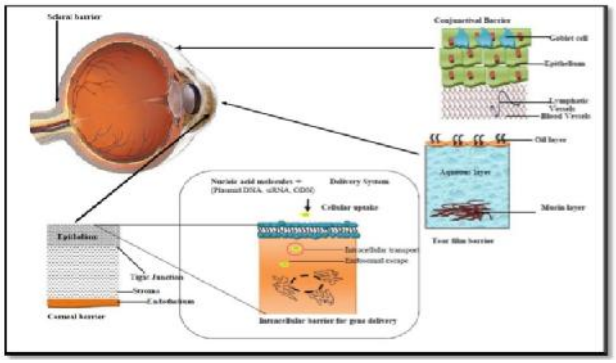

Fig 1: Physiology of eye and drug delivery in various sites of eye

2. Common Eye Infections

Bacteria are the causative pathogens for a large number of eye infections. In addition virus, fungus and protozoans also cause eye infections. As such eyes are prone to number of diseases but more commonly found are mentioned here.

Lid and ocular infections

Blepharitis: Inflammation of the eye lid margin**.**

Conjunctivitis: An inflammation of the conjunctiva that may be caused by bacterial and viral infection, pollen and other allergens, smoke and pollutants.

Keratitis: An inflammation of the cornea caused by bacterial, viral or fungal infection.

Glaucoma:

The buildup of pressure in the anterior and posterior chamber of the choroids layer that occurs when the aqueous humor fails to drain properly.

Iritic: Commonly has an acute onset with the patient suffering pain and inflammation of the Eye.

Conventional approaches in topical ocular delivery

Conventional dosage forms such as solutions, suspensions and ointments account for almost 90% of the currently accessible ophthalmic formulations on the market. They offer some advantages such as their ease of administration by the patient, ease of preparation and low production costs. However, there are also significant disadvantages, especially with the use of conventional solutions, including the very short contact time with the ocular surface and the fast nasolacrimal drainage, both leading to poor bioavailability of the drug. Nevertheless, conventional eye drops remain the most commonly used dosage forms in ocular delivery[5,6].

Solutions:

The reasons for choosing solutions over other dosage forms include their favorable cost, simplicity of formulation development and production, and high acceptance by the patients. However, they also exhibit major drawbacks, such as rapid and extensive pre-corneal loss, the high absorption via the conjunctiva and nasolacrimal duct leading to systemic side effects, as well as increased instillation frequency resulting in low patient compliance. Some of

these problems have been reduced by the addition of viscosity enhancing agents such as cellulose derivates, which are believed to increase the viscosity of the preparation and consequently reduce the drainage rate.

Suspensions:

Suspensions of the micronized drug (<5μm) in a suitable aqueous vehicle are formulated, where the active compound is water insoluble. It is assumed that the drug particles remain in the conjunctival sac, thus promoting a sustained release effect. According to Davies topical ophthalmic suspensions have a number of limitations. They need to be adequately shaken before use to ensure correct dosing, and the amount of drug required to achieve therapeutic benefit, only a moderate increase in bioavailability, rendering suspensions expensive in terms of their production costs. Moreover, the drug particle size plays a major role in the formulation process, with particles greater than 10 μm causing patient discomfort, and therefore reflex tearing.

Ointments:

Ointments generally consist of a dissolved or dispersed drug in an appropriate vehicle base. They are the most commonly used semisolid preparations as they are well tolerated, fairly safe and increase the ocular bioavailability of the drug. On application, ointment breaks up into small oily droplets that remain in the cul-de-sac as a drug depot. The drug eventually gets to the ointment-tear interface due to the shearing action of the eyelids. In a broader sense, ophthalmic ointments offer the following advantages: reduced dilution of the medication via the tear film, resistance to nasolacrimal drainage, and an increased pre-corneal contact time. However, oily viscous preparations for ophthalmic use (such as ointments) can cause blurred vision, matting of the eyelids thus, causing discomfort by the patient as well as occasional ocular mucosal irritation. Ointments are therefore generally co-administered with eye drops, during the day, while the ointment is applied at night, when clear vision is not required.

Viscosity enhancing systems:

In order to reduce the lachrymal clearance of ophthalmic solutions, various polymers have been added to increase the viscosity of the conventional eye drops. Among the range of hydrophilic polymers investigated in the area of ocular drug delivery are polyvinyl alcohol (PVA) and polyvinyl pyrrolidone (PVP), cellulose derivatives such as methylcellulose and polyacrylic acids (Carbopols®) evaluated the use of a methylcellulose solution of pilocarpine in albino rabbits and found a decrease in the drainage rate with increasing viscosity. The same group later, investigated the relationship between viscosity and contact time, and demonstrated an optimum viscosity of 12-15 cps for a methylcellulose solution in rabbits. The ocular shear rate, ranging from 0.03 s-1 during the inter-blinking periods to 4,250- 28,500 s-1 during blinkinghas a great influence on the rheological properties of viscous ocular dosage forms and consequently the bioavailability of the incorporated drug. Newtonian systems do not show any real improvement in bioavailability below a certain viscosity and blinking becomes painful, followed by reflex tearing, if the viscosity is too high. While the viscosity of Newtonian systems is independent of the shear rate, non-Newtonian pseudo plastic or so called shear-thinning systems exhibit a decrease in viscosity with increasing shear rates. This pseudo plastic behavior is favorable for ocular delivery systems as it offers less resistance to blinking and therefore, shows greater acceptance by patients than Newtonian systems of the same viscosity.

3. In situ gelling systems

In situ gelling systems are viscous polymer-based liquids that exhibit sol-to-gel phase transition on the ocular surface due to change in a specific physico-chemical parameter (ionic strength, temperature or pH). They are highly advantageous over preformed gels as they can be easily instilled in liquid form, but are capable of prolonging the residence time of the formulation on the surface of the eye due to gelling. The principal advantage of in situ gelling systems is the easy, accurate and reproducible administration of a dose compared to the application of preformed gels. The concept of forming gels in situ (e.g. in the cul-de-sac of the eye) was first suggested in the early 1980s, and ever since then various triggers of in situ gelling have been further investigated. Gellan gum is an anionic polysaccharide, which undergoes phase transition under the influence of an increased ionic strength. The gel strength increases proportionally with the amount of mono- or divalent cations present in the tear fluid. As a consequence, the usual reflex tearing, which leads to a dilution of common viscous solutions, further enhances the viscosity of gellan gum formulations due to the increased amount of tear fluid and thus higher cation concentration[7].

Ocular Inserts As Controlled Drug Delivery Systems

Ocular inserts are defined as preparations with a solid or semisolid consistency, whose size and shape are especially designed for ophthalmic application (i.e., rods or shields). These inserts are placed in the lower fornix and, less frequently, in the upper fornix or on the cornea. They are usually composed of a polymeric vehicle containing the drug and are mainly used for topical therapy[8,9].

Advantages of ocular inserts:

Ocular inserts offer several advantages which can be summarized as follows:

- Increased ocular residence, hence a prolonged drug activity and a higher bioavailability with respect to standard vehicles.
- Possibility of releasing drugs at a slow and constant rate.
- Accurate dosing contrary to eye drops that can be improperly instilled by the patient and are partially lost after administration, each insert can be made to contain a precise dose which is fully retained at the administration site.
- Reduction of systemic absorption (which occurs freely with eye drops via the naso lacrimal duct and nasal mucosa).
- Better patient compliance due to reduction in frequency of administration.
- Increased shelf life with respect to aqueous solutions.
- Exclusion of preservatives, thus reducing the risk of sensitivity reactions.

- Possibility of incorporating various novel chemical/ technological approaches.

Disadvantages of ocular inserts:

The disadvantages1,14 of ocular inserts are as follows:

- A capital disadvantage of ocular inserts resides in their solid consistency, which means that they are perceived by patient as a foreign body in the eye.
- This may constitute a formidable physical and psychological barrier to user acceptance and compliance.
- Their movement around the eye, in rare instances, the simple removal is made more difficult by unwanted migration of the insert to the upper fornix.
- The occasional inadvertent loss during sleep or while rubbing the eyes.
- Their interference with vision.
- Difficult placement of the ocular inserts and removal for insoluble types.

Mechanism of Drug Release

The mechanism of controlled drug release into the eye is as follows:

- Diffusion
- Osmosis
- Bioerosion.

Diffusion:

In the diffusion mechanism, the drug is released continuously at a controlled rate through the membrane into the tear fluid, if the insert is formed of a solid non- erodible body with pores and dispersed drug. The release of drug can take place via diffusion through the pores. Controlled release can be further regulated by gradual dissolution of solid dispersed drug within this matrix as a result of inward diffusion of aqueous solutions.

Osmosis:

In the osmosis mechanism, the insert comprises a transverse impermeable elastic membrane dividing the interior of the insert into a first compartment and a second compartment; the first compartment is bounded by a semipermeable membrane and the impermeable elastic membrane and the second compartment is bounded by an impermeable material and the elastic membrane. There is a drug release aperture in the impermeable wall of the insert.

Bioerosion:

In the Bioerosion mechanism, the configuration of the body of the 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 the drug by bioerosion of the matrix. The drug may be dispersed uniformly throughout the matrix but it is believed a more controlled release is obtained if the drug is superficially concentrated in the matrix. In truly erodible devices, the rate of drug release is controlled by a chemical or enzymatic hydrolytic reaction that leads to polymer solubilization, or degradation to smaller, water-soluble molecules.

Nanomedicine approaches in Ocular drug delivery system: The use of nano-approaches like nano-suspensions, nanoparticles, nanoemulsion, niosomes and liposomes has led to the solution of various solubility and permeability related problems of poorly soluble drugs like dexamethasone, cyclosporin, dorzolamide, gancyclovir and many more. Drugs can also be targeted to ocular tissue to allow region specific delivery and minimize side effects to other organs. Besides this, depending on their particle charge, surface properties and relative hydrophobicity, nanoparticles can be designed for successfully overcoming corneal barriers. In addition tothese points, encapsulation of drug in nanoparticles, nanospheres, liposomes etc, can also provide stability to the drug along with prolonged exposure of the drug by controlled release behavior[10.11].

Nanoparticles [NPS]/ Nanospheres/ Nanocapsules :

Nanoparticles are sub-microscopic, colloidal system consisting of macromolecular substances that vary in size from 10 nm to 1000 nm. The drug may be dissolved, entrapped, adsorbed, attached or encapsulated into the nanoparticle matrix. Depending on the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained with different properties and release profile for the encapsulated drugs.Nanoparticles may be made up of biodegradable and non-biodegradable polymers. Non-biodegradable polymers based nanoparticles are neither digested by enzymes nor degraded in vivo through a biochemical pathway. Upon the administration of these particles suspension in the eyes, particles reside at the delivery site and the drug is released from the polymer matrix through diffusion, erosion, ion exchange, or combinations thereof[12].

Chitosan Nanoparticles

Natural cationic polymer chitosan (CH) Nano carriers have attracted a great deal of attention because of its unique properties, such as acceptable biocompatibility and biodegradability. Chitosan (CH) is a cationic polysaccharide able to gel when it comes in contact with specific multivalent polyanions, such as sodium tripolyphosphate (TPP). Nanoparticles are spontaneously formed upon mixing of CH and TPP solutions, through the formation of inter- and intermolecular linkages between the phosphate groups of TPP and the amino groups of CH. Using this technique, it has been possible to efficiently associate hydrophilic compounds such as small molecules, peptides, proteins and genes.

Microemulsion/Nanosuspension (MS/NS)

Nanoemulsions are defined as the dispersions of water and oil in the presence of combination of surfactant and co-surfactant (Smix) in a manner to reduce interfacial tension. On the basisof nature of dispersion and disperse phase, NEs were classified as: o/w, w/o & bicontinuous type. These systems are usually characterized by clear appearance, higher thermodynamic stability, small droplet size (<200 nm), high drug solubility, drug reservoir for lipophilic and hydrophilic drugs. Moreover, microemulsions achieve sustained release of a drug applied to the cornea and higher penetration into the deeper layers of the ocular structure and the aqueous humor than the native drug. These systems offer additional advantages including: low viscosity, a greater ability as drug delivery vehicles and increased properties as absorption promoters[13].

Liposomes: Liposomes are the microscopic vesicles composed of one or more concentric lipid bilayers,

separated by water or aqueous buffer compartments with a diameter ranging from 100 nm to 10µm. Liposomes offer advantages over most ophthalmic delivery systems in being completely biodegradable and relatively non-toxic. Another potential advantage of liposomes is their ability to come in an intimate contact with the corneal and conjunctival surfaces, thereby, increasing the probability of ocular drug absorption.

Niosomes

Niosomes in topical ocular delivery may prefer over liposomal vesicular system as they are chemically stable than liposomes, incur lower production cost and they are composed of biodegradable and no immunogenic materials. Unlike phospholipids, niosomes do not require expensive handling (storage at freezers and preparation under nitrogen gas). Moreover, they handle surfactants with no special precautions or conditions; they can improve the performance of the drug via better availability and controlled delivery at a particular site; they are biodegradable, biocompatible and non-immunogenic.

Dendrimers

As per the definition given by Sahoo et al., "Dendrimers are macromolecular compounds made up of a series of branches around a central core". Their nanosize, ease of preparation, functionalization and possibility to attach multiple surface groups render them suitable alternative vehicle for ophthalmic drug delivery. Dendrimers are liquid or semi-solid polymers and contain amine, carboxylic and hydroxyl surface groups, which keep on increasing as the generation number increases (G0, G1, G2, and so on). Dendrimers based on poly (amidoamine) (PAMAM) have been widely employed in drug delivery. This system of branched polymers represents unique architecture, and can entrap both hydrophilic and lipophilic drugs into their structure[14].

Solid lipid nanoparticles (SLN)

Solid lipid nanoparticles (SLN) are characteristically spherical particles with an average diameter between 50 to 100nm (Muller et al, 2004). SLNs are particularly advantageous in ocular drug delivery as they have the ability to enhance the ocular bioavailability of both hydrophilic and lipophilic drugs. Furthermore, they can be easily autoclaved for sterilization which is an important aspect of ocular administration for drug formulation of SLN in the management of glaucoma and concluded that higher therapeutic efficacy, retarded occurrence of maximum action, and more prolonged effect of methazolamide was found in comparison of drug solution and commercial product.

4. Conclusion

Ocular drug delivery system is a one of the challenging controlled drug delivery system. It is mainly used to treatment of eye infections like glaucoma and conjunctivitis. The most commonly used conventional dosage of ocular drug delivery such as solutions, ointments and suspensions However, the major drawback of conventional dosge forms to delivery of rapid and extensive precorneal loss caused by drainage in the extra ocular area and high tear fluid turnover. To overcome this problem several nanotechnology based carrier systems are being developed and studied at large such as nanoparticles, liposomes, nanomicelles, nanosuspensions and dendrimers. Few of these are commercially manufactured at large scale and are applied clinically. Nanotechnology is benefiting the patient body by minimizing the drug induced toxicities and vision loss.

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