Current Trends on Ocular Drug Delivery System

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ABSTRACT

Topical administration for ocular therapeutics is ideal because of smaller doses required compared to the systemic use, its rapid onset of action and freedom from systemic toxicity. Topically applied ocular drugs have to reach the inner parts of the eye and trans-corneal penetration is believed to be the major route for drug absorption. Corneal absorption is much slower process than elimination. The specific aim of designing a therapeutic system is to achieve an optimal concentration of a drug at the active site for the appropriate duration. Ideal ophthalmic drug delivery must be able to sustain the drug release and to remain in the vicinity of front of the eye for prolong period of time. The purpose of this review is to provide an update on the current knowledge within this field of ocular drug delivery. Ocular drug delivery has been a major challenge for scientists due to its unique anatomy and physiology which contains various types of barriers such as different layers of cornea, sclera and retina including blood aqueous and blood–retinal barriers, choroid and conjunctival blood flow etc. These barriers cause a significant challenge for delivery of a drug alone or in a dosage form, especially to the posterior segment of the eye. To overcome these problems, the newly developed particulate and vesicular systems like liposomes, pharmacosomes and discoes are useful in delivering the drug for a longer extent and helpful in reaching the systemic circulation.

KEYWORDS: ocular drug delivery, ophthalmic chemotherapy, Subconjunctival, Intravitreal, Nasolacrimal drainage system.
INTRODUCTION
Eye is most interesting organ due to its drug disposition characteristics. Generally, topical application of drugs is the method of choice under most circumstances because of its convenience and safety for ophthalmic chemotherapy.\[^1\] A significant challenge to the formulator is to circumvent (bypass) the protective barriers of the eye without causing permanent tissue damage. Development of newer, more sensitive diagnostic techniques and novel therapeutic agents continue to provide ocular delivery systems with high therapeutic efficacy. Conventional ophthalmic formulations like solution, suspension, and ointment have many disadvantages which result into poor bioavailability of drug in the ocular cavity. The specific aim of designing a therapeutic system is to achieve an optimal concentration of a drug at the active site for the appropriate duration.\[^2\] Ocular disposition and elimination of a therapeutic agent is dependent upon its physicochemical properties as well as the relevant ocular anatomy and physiology. A successful design of a drug delivery system, therefore, requires an integrated knowledge of the drug molecule and the constraints offered by the ocular route of administration.\[^3\] The various approaches that have been attempted to increase the bioavailability and the duration of the therapeutic action of ocular drugs can be divided into two categories. The first one is based on the use of sustained drug delivery systems, which provide the controlled and continuous delivery of ophthalmic drugs. The second involves maximizing corneal drug absorption and minimizing precorneal drug loss.\[^3\]

IN SITU FORMING GELS FOR OPHTHALMIC DRUG DELIVERY
Recently, controlled and sustained drug delivery has become the standard in modern pharmaceutical design and an intensive research has been undertaken in achieving much better drug product effectiveness, reliability and safety. In this regard many polymers are very useful which undergo reversible sol to gel phase transition in response to physiological stimuli.\[^5\] In situ gels are conveniently dropped as a solution into the conjunctival sac, where they undergo a transition into a gel with its favorable residence time. The sol-gel transition occurs as a result of a chemical/physical change induced by physiological environment. This type of gel combines the advantage of a solution being patient convenient with the favorable residence time of a gel for enhancing the ocular bioavailability.\[^6,7\] The sol-gel transition can be induced by a shift in the pH as for cellulose acetate phthalate, a shift in temperature as for the thermo gelling Poloxamer 188 or by presence of cations as for acetylated gellan gum and alginates. Thus, the in situ gelling systems for ophthalmic use can be classified as pH sensitive, temperature sensitive and ion-activated systems. The rate of gel formation in situ, is
important since when dropped in the eye, before a strong gel is formed, a solution or a weak gel is prone to elimination by the fluid mechanics of the eye \[^8\]. The ion activated in situ gelling system can be formulated using sodium alginate, the sodium salt of alginic acid, as a natural hydrophilic polysaccharide containing two types of monomers, β-D-mannuronic acid (M) and α-L-guluronic acid (G) which forms a gel in the cul-de-sac due to the presence of divalent calcium ions in the lacrimal fluid.\[^9\] Thus with the use of these in situ gelling systems, residence time of the drug in the eye is increased. Continuous delivery of drugs in a controlled manner to the anterior chamber of the eye will eliminate the requirement for frequent drug administration, causing better patient compliance and will result in extended duration of action, hence lower amount of total dose required, which in turn will minimize the local and/or systemic side effects.\[^10\]

**ROUTES OF OCULAR DRUG DELIVERY**

There are several possible routes of drug delivery into the ocular tissues. The selection of the route of administration depends primarily on the target tissue.

**Topical route**

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).

**Subconjunctival administration**

Traditionally subconjunctival injections have been used to deliver drugs at increased levels to the uvea. Currently this mode of drug delivery has gained new momentum for various reasons. The progress in materials sciences and pharmaceutical formulation have provided new exciting possibilities to develop controlled release formulations to deliver drugs to the posterior segment and to guide the healing process after surgery.

**Intravitreal administration**

Direct drug administration into the vitreous offers distinct advantage of more straightforward access to the vitreous and retina. It should be noted; however that delivery from the vitreous to the choroid is more complicated due to the hindrance by the RPE (Retinal Pigment Epithelium) barrier. Small molecules are able to diffuse rapidly in the vitreous but the mobility of large molecules, particularly positively charged, is restricted.
Advantages of Ocular Drug Delivery Systems.\[11-14\]
- Easy convenience and needle free drug application without the need of trained personnel
- Assistance for the application, self-medication, thus improving patient compliances compared to parenteral routes.
- Good penetration of hydrophilic, low molecular weight drugs can be obtained through the eye.
- Rapid absorption and fast onset of action because of large absorption surface area and
- High vascularization. Ocular administration of suitable drug would therefore be effective in emergency therapy as an alternative to other administration routes.
- Avoidance of hepatic first pass metabolism and thus potential for dose reduction compared to oral delivery.

Disadvantages of Ocular Drug Delivery Systems.\[11-14\]
- The physiological restriction is the limited permeability of cornea resulting into low absorption of ophthalmic drugs.
- A major portion of the administered dose drains into the lacrimal duct and thus can cause unwanted systemic side effects.
- The rapid elimination of the drug through the eye blinking and tear flow results in a short duration of the therapeutic effect resulting in a frequent dosing regimen.

Ophthalmic Disorders \[15, 12, 16\]
- **Conjunctivitis**: an inflammation of the conjunctiva that may be caused by bacterial and viral infection, pollen and other allergens, smoke and pollution.
- **Dry eye syndrome**: the inadequate wetting of the ocular surface.
- **Glaucoma**: the buildup of pressure in the anterior and posterior chambers of the choroid layer that occurs when the aqueous humour fails to drain properly.
- **Iritis**: commonly has an acute onset with the patient suffering pain and inflammation of the eye.
- **Keratitis**: an inflammation of the cornea, caused by bacterial, viral or fungal infection.
- **Other conditions**: the ophthalmic complications of rosacea, blepharitis (inflammation of the lid margins) and chalazia (meibomian cysts of the eyelids).
ANATOMY AND PHYSIOLOGY OF EYE

Figure no1: Structure of the eye

The eye is a spherical structure with a wall made up of three layers; the outer part sclera, the middle parts choroid layer, Ciliary body and iris and the inner section nervous tissue layer retina. The sclera is tough fibrous coating that protecting the inner tissues of eye which is white except for the transparent area at the front, and the cornea allows light to enter to the eye. The choroid layer, situated situated in the sclera, contains many blood vessels that modified at front of the eye as pigmented iris the coloured part of the eye (blue, green, brown, hazel, or grey).

The structure of the cornea

The clear transparent bulge cornea situated at the front of the eye that conveys images to the back of the nervous system. The adult cornea has a radius of approximately 7-8mm that covers about one-sixth of the total surface area of the eye ball that is a vascular tissue to which provides nutrient and oxygen are supplied via lachrymal fluid and aqueous humour as well as from blood vessels of the junction between the cornea and sclera in fig.1 The cornea is made of five layers as epithelium, bowman’s layer, stroma, descemet’s membrane and endothelium that is main pathway of the drug permeation to eye . The epithelium made up of 5 to 6 layers of cells. The corneal thickness is 0.5–0.7 mm in the central region. The main barrier of drug absorption into the eye is the corneal epithelium, in comparison to many other epithelial tissues (intestinal, nasal, bronchial, and tracheal) that is relatively impermeable. The epithelium is squamous stratified, (5-6 layer of cells) with thickness of around 50-100 μm and turnover of about one cell layer every day. The basal cells are packed with a tight junction, to forming not only an effective barrier to dust particle and most microorganisms, and also for drug absorption. The transcellular or paracellular pathway is the main pathway to penetrate drug across the corneal epithelium. the lipophilic drugs choose the transcellular
route whereas the hydrophilic one chooses paracellular pathway for penetration (passive or altered diffusion through intercellular spaces of the cells). The Bowman’s membrane is an a cellular homogeneous sheet with 8-14μm thick situated between the basement membrane of the epithelium and the stroma. The stroma, or substantia propria, composed of around 90% of the corneal thickness that contains about 85% water and about 200-250 collagenous lamellae. The lamellae provide physical strength while permitting optical transparency of the membrane. The hydrophilic solutes diffuse through the stroma’s open structure. The descemét’s membrane is secreted by the endothelium and lies between the stroma and the endothelium.

Figure no 2 structure of cornea

Figure No3: Structure of Corneal Endothelium

Conjunctiva:- (2)
The conjunctiva protects the eye and also involved in the formation and maintenance of the precorneal tear film. The conjunctiva is a thin transparent membrane lies in the inner surface of the eyelids and that is reflected onto the globe. The conjunctiva is made of an epithelium, a highly vascularized substantia propria, and a sub mucosa. The bulbar epithelium contains 5 to 7 cell layers. The structure resembles a pallisade and not a pavement corneal epithelium cells are connected by tight junctions, which render the conjunctiva relatively impermeable. The molecules up to 20,000 Da can cross the conjunctiva, while the cornea is restrict to molecules larger than 5000 Da. The human conjunctiva is about 2 and 30 times more absorption of drugs than the cornea and also proposed that loss of drug by this route is a major path for drug clearance. The highest density of conjunctiva is due the presence of 1.5 million goblet cell varying with age depended among the intersujects variability and age. The vernal conjunctivitis and atopic kerato conjunctivitis occurs due to the great variation in goblet cell density results only in a small difference in tear mucin concentration.

Figure no 4: Conjunctiva structures.

Nasolachrymal drainage system

Figure no 5: Schematic diagram of nasolachrymation drainage system
Nasolacrimal drainage system consists of three parts; the secretory system, the distributive system and the excretory system. The secretory portion is composed of the lacrimal gland that secreted tears are spread over the ocular surface by the eyelids during blinking. The secretory system is stimulated by blinking and temperature change due to the tear evaporation and reflux secretors that have an efferent parasympathetic nerve supply and secrete in response to physical and emotional state e.g. crying. The distributive system consists of the eyelids and the tear meniscus around the lid edges of the open eye, which spread tears over the ocular surface by blinking, thus preventing dry areas from developing. The excretory part of the Nasolachrymal drainage system consists of the lachrymal puncta, the superior, inferior and common canaliculi; the lachrymal sac, and the nasolachrymal duct. In humans, the two puncta are the openings of the lachrymal canaliculi and are situated on an elevated area known as the lachrymal papilla. It is thought that tears are largely absorbed by the mucous membrane that lines the ducts and the lachrymal sac; only a small amount reaches the nasal passage.\(^1\)

**The nasolacrimal drainage system consists of three parts.**

I. **The secretory system:** - It consists of basic secretors that are stimulated by blinking and temperature change due to tear evaporation and reflex secretors that have an efferent parasympathetic nerve supply and secrete in response to physical or emotional stimulation.

II. **The distributive system:** - It consists of the eyelids and the tear meniscus around the lid edges of the open eye, which spread tears over the ocular surface by blinking, thus preventing dry areas from developing.

III. **The excretory system:** - The excretory part of the nasolachrymal drainage system consists of - lachrymal puncta, the superior, inferior and common canaliculi; the lachrymal sac; and the nasolachrymal duct. In humans, the two puncta are the openings of the lachrymal canaliculi and are situated on an elevated area known as the lachrymal papilla. It is thought that the tears are largely absorbed by the mucous membrane that lines the ducts and the lachrymal sac; only small amount reaches the nasal passages. The cul-de-sac of the eye normally holds around 7-9 μl. If care is taken not to blink, the normal tear flow rate is 1μl /min and pH is maintained at 6.5-7.6\(^{17}\).
Table 1: Barriers for the Ocular delivery

<table>
<thead>
<tr>
<th></th>
<th>Conjunctiva</th>
<th>Cornea</th>
<th>Sclera</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface area</td>
<td>17.65 ± 2.12 cm²</td>
<td>1.04 ± 0.12</td>
<td>16 – 17</td>
</tr>
<tr>
<td>Thickness</td>
<td>-</td>
<td>0.57 mm</td>
<td>0.4 - 0.5 mm</td>
</tr>
<tr>
<td>Structural composition</td>
<td>Mucus membrane Epithelium Vasculature</td>
<td>5 layers Epithelium Bowman’s membrane Stomata Descemet’s membrane Endothelium</td>
<td>Collagen fibers Water Proteoglycans Monopoly saccharides Elastic fibers Fibroblast</td>
</tr>
</tbody>
</table>

Table 2: Marketed ophthalmic products

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Drug</th>
<th>Dosage Form</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acivir eye</td>
<td>Acyclovir</td>
<td>Ointment</td>
<td>For eye infection</td>
</tr>
<tr>
<td>Acuvail</td>
<td>Ketorolac tromethamine</td>
<td>Eye solution</td>
<td>Cataract surgery</td>
</tr>
<tr>
<td>Alocril</td>
<td>Nedocromil</td>
<td>Eye solution</td>
<td>Allergic conjunctivitis</td>
</tr>
<tr>
<td>Betnisol</td>
<td>N Betamethasone</td>
<td>Eye drops</td>
<td>In eye infection</td>
</tr>
<tr>
<td>Chloromycetin</td>
<td>Chloramphenicol palmitate</td>
<td>Ointment</td>
<td>In conjunctivitis and eye inflammation</td>
</tr>
<tr>
<td>Dichol</td>
<td>Carbachol</td>
<td>Sterile solution and prefilled syringes</td>
<td>In ophthalmic surgery</td>
</tr>
<tr>
<td>Elestat</td>
<td>Epinastine solution</td>
<td>Eye solution</td>
<td>Allergic conjunctivitis</td>
</tr>
<tr>
<td>Geltear</td>
<td>Carboxer</td>
<td>Bio adhesive gel</td>
<td>As a lubricant, in burning, irritated an dried</td>
</tr>
</tbody>
</table>

**CONCLUSION**

New ophthalmic delivery system includes ocular inserts, collagen shields, ocular films, disposable contact lens and other Novel drug delivery systems like hiosomes 20 and
nanoparticles. The extensive work in ocular drug delivery during the earlier period. It has been intend, to extend the residence time of topically applied drugs in the corneal and conjunctiva section. Some new approaches such as nanoparticles, liposome, contact lenses, ocular inserts, collagen shield, in situ activated gel formation, non-corneal route of ocular drug diffusion, and nanoparticles-based polymeric solutions and gels are being developed by the pharmaceutical sciences.

REFERENCE

