Review Article

AN INSIGHT TO OPHTHALMIC DRUG DELIVERY SYSTEM

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ABSTRACT
Treating various ailments of eye utilizes mostly two strategies i.e. delivery of the therapeutic agent by development of a novel delivery system or by enhancing the permeation of therapeutically active agent by the use of penetration enhancers or by the alteration of its physicochemical properties. Conventional ophthalmic drugs delivery system including eye drops, ointments and gels, are no longer sufficient to treat vision threatening disorders as they delivery drugs only to anterior segment of eye. A major problem in ocular therapeutics is attainment of an optimal drug concentration at the site of action. Poor bioavailability of drugs from ocular dosage forms is mainly due to the pre-corneal loss factors which include tear dynamics, non-productive absorption, transient residence time in the cul-de-sac, and the relative impermeability of the corneal epithelial membrane. This article reviews various novel approaches like in – situ gel, ocular films or ocuserts, nanoparticles, liposomes, niosomes, collagen shields, ionotophorosis, eye implants. These novel approaches have significant technological challenge with a corresponding problem of patient compliance with dosage forms. In near future, a great deal of attention will be paid to develop noninvasive sustained drug release for both anterior and posterior segment eye disorders. Current momentum in the invention of new drug delivery system holds a promise toward much improved therapies for the treatment of vision-threatening disorders.

1. INTRODUCTION:

Eye is most interesting organ due to its drug disposition characteristics. For ailments of the eye, topical administration is usually preferred over systemic administration, before reaching the anatomical barrier of the cornea, any drug molecule administered by the ocular route has to cross the pre-corneal barriers. These are the first barriers that slow the penetration of an active ingredient into the eye and consist of the tear film and the conjunctiva. The medication, upon instillation, stimulates the protective physiological mechanisms, i.e., tear production, which exert a formidable defense against ophthalmic drug delivery. Another serious concomitant of the elimination of topically applied drugs from the pre-corneal area is the nasal cavity, with its greater surface area and higher permeability of the nasal mucosal membrane compared to that of the cornea. Normal dropper used with conventional ophthalmic solution delivers about 50-75µl per drop and portion of these drops quickly drain until the eye is back to normal resident volume of 7µl. Because of this drug loss in front of the eye, very little drug is available to enter the cornea and inner tissue of the eye. 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. Consequently it is imperative to optimize ophthalmic drug delivery, one of the way to do so is by addition of polymers of various grades, development of viscous gel, development of colloidal suspension or using erodible or non erodible insert to prolong the pre-corneal drug retention.

2. Modes of drug administration to eye and challenges for absorption through these routes:

i) Systemic route**:**

Systemically administered drugs have to cross blood – retinal – barrier (BRB) to reach posterior ocular tissue and blood – aqueous barrier to reach anterior ocular tissue. Due to these barriers the intra-vitreal drugs levels of poorly lipid soluble drug was found to be 10% less than serum levels [1]. To maintain therapeutic conc. of drug in eye frequent administration is required which lead to systemic side effects or toxicity especially with drugs having low therapeutic index [2]. So systemic route can be utilized only when following conditions are there:-

- For drugs with large therapeutic indices.
- Drugs having limited systemic side effect.
- When other localized delivery route are not available [3]

ii) Topical route**:**

Drugs are packaged in multiple forms of solution, suspensions and ointments.6 Drugs absorptions occur through corneal and non corneal pathways. Non – corneal absorption occurs via the nasolacrimal dust while most of drug transported to cornea [4].

Corneal absorption limited by:-

- Drainage of the instilled solutions
- Lacrimation
- Tear turnover
- Metabolism
- Tear evaporation
- Limited corneal area
- Poor corneal permeability
- Binding with lachrymal proteins
- Enzymatic degradation
- Cornel epithelium (lipophilic)

These factors reduce corneal absorption to <5%. To overcome these challenges novel topical approaches are used these days which increase bioavailability like use of penetration enhancers, use of mucoadhesives polymer and result in controlled delivery such as Inserts, implants, Nanoparticles, niosomes etc [5].

iii) Intra-vitreal route:

It refers to the direct injection of drug into the vitreous cavity through parsplana. Pharmacokinetic properties of drug administered via this route are not clearly understood. But patient compliance is major issue especially in elderly patients. Other challenges to this route are significant adverse side effects including retinal detachment retinal hemorrhage, endophthalmitis, and uveitis.

iv) Periocular route**:**

This route includes four unique injections:

- Retro bulbar injection

- Per bulbar injection
- Sub-tenon injection
- Subconjuctival injection

Drug delivered through this method reach to sclera as it is more permeable than cornea. But the drug intended for ocular tissue other than choroid must permeate BRB so challenges to bioavailability of posterior segment. The periocular administration of controlled release formulation presents potential path.

3. Approaches to increase Ocular Bioavailability:

3.1 Viscosity enhancer: First attempt made to prolong the contact time of applied drug with cornea was to increase the viscosity of the preparation. Viscosity-increasing polymers are usually added to ophthalmic drug solutions on the premise that an increased vehicle viscosity should correspond to a slower elimination from the pre-ocular area, which lead to improved pre-corneal residence time and hence a greater trans-corneal penetration of the drug into the anterior chamber [6]. It has minimal effects in humans in terms of improvement in bioavailability. The polymers used include polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), methylcellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose (HPMC), and hydroxyl propylcellulose. But maximum viscosity increased can be up to 15 to 150 cp because more increase may cause blurring of vision and resistance to eyelid movements.11 Viscosity vehicles may increase contact time but not produce a sustained effect. Ointments and gels are ophthalmic preparations having high viscosity.

3.2 Mucoadhesive polymers: This approach relies on vehicles containing polymers which will attach, via non- covalent bonds, to conjunctival mucin (a glycoprotein) thus remaining in contact with the pre-corneal tissues until mucin turnover cause elimination of the polymer. Mucoadhesive polymers are usually macromolecular hydrocolloids with numerous hydrophilic functional groups, such as carboxyl -, hydroxyl-, amide and sulphate capable of establishing electrostatic interactions [7].

a) Polyarylic acid

i) Carbopol: Cross linked polyacrylic acid to have excellent mucoadhesive properties causing significant enhancement in ocular bioavailability. Carbopol 934 P is high cross link water swellable acrylic polymer with molecular weight approximately 3000000 Da. which is appropriate to use in pharmaceutical industry

ii) Polycarbophil: It is cross linked poly acrylic acid polymer which is insoluble in water but swells and can incorporate large quantity of water. Carbophil cross linked with divinyl glycol found to give good bioadhesion as compare to conventional non bioadhesive suspention.

b) Carboxymethyl cellulose: Sodium CMC found to be excellent mucoadhesive polymer. Ophthalmic gel formulated using NaCMC, PVP and corbopol on the in vivo studies on the gel showed diffusion coefficient in corbopol 940 1%> NaCMC 3%> PVP 23% [8].

3.3 Penetration enhancers: One of the principal problems in ocular delivery of drugs is relatively low permeability of these drugs across ocular tissues. The proposed mechanism by which penetration enhancers improve corneal drug transport is by two methods. The first method is an expanded para-cellular pathway; i.e. compounds that change the cell cytoskeleton, alter tight junctions by promoting the transport of glucose or amino acids with sodium transport and choosing cationic molecules. The second approach is to enhance trans-cellular transport through interaction with lipid membrane and interaction with the protein component of the cell membrane [9].

Inclusion of these agents such as cetylpyridinium chloride [10], ionophore such as lasalocid [11], benzalkonium chloride [12], Parabens, Tween 20, saponins [13], Brij 35, Brij 78, Brij 98, ethylenediaminetetraacetic acid, bile salts [14], and bile acids (such as sodium cholate, sodium taurocholate, sodium glycodeoxycholate, sodium taurodeoxycholate, taurocholic acid, chenodeoxycholic acid, and ursodeoxycholic acid), capric acid, azone, fusidic acid, hexamethylene lauramide, saponins, hexamethylene octanamide, and decylmethyl sulfoxide [15] in different formulations have shown a significant enhancement in corneal drug absorption.

4. Approaches to provide Controlled and Continuous Drug Delivery

4.1 Ocular inserts:

Films, erodible and non-erodible inserts, rods and shields are the most logical delivery systems aimed at remaining for a long period of time in the front of the eye. These polymeric delivery systems sustain and control drug release and thus avoid pulsed entry characterized by a transient overdose, followed by a relative short period of acceptable dosing, which is in turn followed by a prolonged period of under dosing [16,17]. From a therapeutic point of view, inserts have been a success in the improvement of accurate dosing, and drug bioavailability and by the reduction of systemic absorption, and consequently side effects. However, the inserts are not well tolerated or accepted by patients, due to difficulties encountered in the application, psychological factors, and possible interference with vision**.** Inserts dissolve and/or erode on contact with the ocular surface and therefore need to be used in addition with other artificial tears to initiate the dissolving process [18,19]. Although the sustained release effect is very pronounced, various disadvantages are high cost, as well as the difficulty in handling inserts in elderly people, and intense foreign body sensation.

Types of inserts are as follows:

4.1.1 Erodible inserts: They have to be removed from body tissue after release of drug.

a) Occuserts (figure 1): It is a flat, flexible, elliptical devices consisting of three layers. Two outer layers of ethylene vinyl acetate (EVA) enclose the inner core of pilocarpine gelled with alginate. A retaining ring of EVA impregnated with titanium dioxide for visibility enclose the drug reservoir circumferentially. It is preprogrammed to release pilocarpine at constant rate of 20 or 40ugm/hr for seven days.

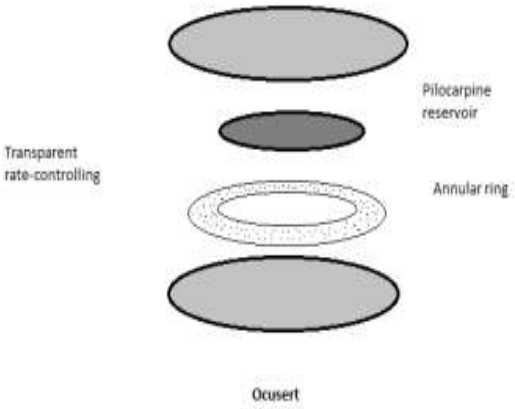

Figure 1: Occuserts

b)Contact lenses:

They are presoaked hydrophilic contact lenses used to aid corneal wound healing in patients with infections, corneal ulcers & thining of cornea. Disadvantages are residence time of drug is not long as most of the drug is release within the first 30 min. Use of the preservative may be toxic to cornea & supply of oxygen to eye is interrupted. An alternative approach other then soaking in drug solution the drug is incorporated in it as a solution or suspension of solid particles in monomer mix & then polymerization is done to fabricate it which results in increase in drug residence time.

c) Diffusional inserts:

They have a central reservoir of drug enclosed in semipermeable or microporous membrane for diffusion of drug. Diffusion is controlled by lachrymal fluid penetrating through it.

4.1.2 Non Erodible inserts: They do not have to be removed from body tissues.

a) Lacriserts**:** Sterile rod shaped device made up of hydroxypropylcellulose without any preservative. It is used for treatment of dry eye syndrome & keratitis. Inserted in inferior phoenix where it imbibes water from conjuctiva and cornea & forms a hydrophilic film which stabilizes tear film, hydrates/ lubricates the cornea.

b) SODIs**:** Soluble ocular drug inserts are small oval shaped wafer. It is made from acrylamide, N-vinyl pyrrolidone and ethylacrylate.

c) Minidisc**:** A contoured disc with a convex front & a concave back in contact with eyeball. Its like a minute contact lens of symmetric circular design. Major component of minidisc is a silicone based prepolymer which is α-ω-bis(4-methacryloxy)- butyl poly dimethyl siloxane (M2Dx) where M- methacryloxy butyl functionality & D- dimethyl siloxane funtionality Example is sulfisoxazole which is a poorly water soluble drug when incorporated in hydrophilic matrix then drug release may increase up to 170 hrs.

Various types of ophthalmic inserts given in table 1.

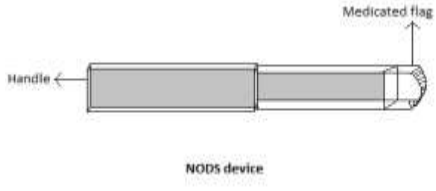

Figure 2: Implants

Table 1:List of Opthalmic Insert

Name	Description
Bioadhesive ophthalmic drug inserts(BODO)	Adhesive rods based on mixtures of hydroxyl propyl cellulose, ethyl cellulose, poly acrylic acid cellulose acetate phthalate
Collagen shields	Erodable discs composed of cross-linked (porcine sclera) collagen
Dry drops	A preservative-free drop of hydrophilic polymer solution (hydroxyl propyl methyl cellulose) that is freeze-dried on the tip of a soft hydrophobic carrier strip, immediately hydrates in the tear film
Gelfoam	Slabs of Gelfoam impregnating with a mixture ofcetyl ester wax in chloroform
Lacrisert	Rod-shaped device made from hydroxylpropylcellulose used in the treatment of dry eye syndrome as an alternative to artificial tears
Minidisc or ocular therapeutic system	4-5 mm diameter contored either hydrophilic or hydrophobic disc
NODS (New or Novel ophthalmic drug delivery)	Medicated solid polyvinyl alcohol flag that is attached to a paper-covered handle. On application, the flag detaches and gradually dissolves, releasing the drug
Ocuserts	Flat, flexible elliptical insoluble device consisting of two layers enclosing a reservoir, used commercially to deliver pilocarpine for 7 days
Opthalmic inserts	A cylindrical device containing mixtures of silicone elastomers and sodium chloride as a release modifier with a stable polyacrylic acid (PAA) or polymethyl acrylic acid (PMA) interpenetrating polymer network grafted onto the surface

4.2 Implants:

The goal of the intraocular implant design (figure 2) is to provide prolonged activity with controlled drug release from the polymeric implant material. Intraocular administration of the implants always requires minor surgery. In general, they are placed intravitreally, at the pars plana of the eye (posterior to the lens and anterior to the retina) [20,21]. Although this is an invasive technique, the implants have the benefit of: (a) by-passing the blood-ocular barriers to deliver constant therapeutic levels of drug directly to the site of action, (b) avoidance of the side effects associated with frequent systemic and intra-vitreal injections, and (c) smaller quantity of drug needed during the treatment. The ocular implants are classified as non-biodegradable and biodegradable devices. Non-biodegradable implants can provide more accurate control of drug release and longer release periods than the biodegradable polymers do, but the non-biodegradable systems require surgical implant removal with the associated risks. The ocular implants are summarized in table 2.

Table 2: Description of current and potential ophthalmic implants

Registered name	Active substance	Mode of administration
Vitrasert	Ganciclovir	Surgical implantation at pars plana
Retisert	Fluocinolone acetonide	Surgical implantation at pars plana
Medidur	Fluocinolone acetonide	Injected in the vitreous cavity
Posurdex	Dexamethasone	Injected or through small incision at pars plana
Surodex	Dexamethasone	Placed underneath the scleral flap

4.3 Nanoparticles :

These are polymeric colloidal particles, ranging from 10 nm to 1 mm, in which the drug is dissolved,

entrapped, encapsulated, or adsorbed [22]. Encapsulation of the drug leads to stabilization of the drug. They represent promising drug carriers for ophthalmic application [23]. They are further classified into nanospheres (small capsules with a central cavity surrounded by a polymeric membrane) or nanocapsules (solid spheres). Marchal-Heussler et al [24]. found that the nanocapsules show a better effect than the nanospheres, probably because the drug (betaxolol, carteolol) is in a unionized form in the oily core and can diffuse at a greater rate into the cornea.

4.4 Niosomes:

Niosomes are bilayered structural vesicles made up of nonionic surfactant which are capable of encapsulating both lipophilic and hydrophilic compounds. Niosomes reduce the systemic drainage and improve the residence time, which leads to increase ocular bioavailability. They are non-biodegradable and non-biocompatible in nature. In a recent approach to deliver cyclopentolate, niosomal formulation was developed. It released the drug independent of pH, resulting in significant enhancement of ocular bioavailability.

4.5 In situ gel formation:

The droppable gels are liquid upon instillation, and they undergo a phase transition in the ocular cul-de-sac to form a viscoelastic gel, and this provides a response to environmental changes. It improves the patient acceptance. It prolongs the residence time and improves the ocular bioavailability of the drug. Parameters that can change and trigger the phase transition of droppable gels include pH, temperature, and ionic strength.

I) pH triggered system: Cellulose acetate hydrogen phthalate latex, typically shows very low viscosity up to pH 5, and forms clear gel in few seconds when in contact with tear fluid pH 7.2 to 7.4 and hence, release contents over prolong period of time. Use of such pH sensitive latex described by Gurny et al [25]. The half-life of residence of CAP dispersion on corneal surface was approximately 400 seconds as compare to 40 second for solution [26].

II) Change in temperature: Poloxamer F127 is in the form of solution in room temp and when this solution is instilled in to eye phase transition occurs from solution to gel at temp of eye thereby prolonging its contact with ocular surface.

III) Ion activation: Gelrite is a polysaccharides, a low acetyl gellan gum shows phase transition in presence of mono or divalent cations [27]. Timolol bioavailability found to be superior with geltrite over equiviscous HEC solution [28].

4.6 Liposomes:

Liposomes are the microscopic vesicles composed of one or more concentric lipid bilayers, separated by water or aqueous buffer compartments. Liposomes possess the ability to have an intimate contact with the corneal and conjunctival surfaces, which increases the probability of ocular drug absorption [29]. This ability is especially desirable for drugs that are poorly absorbed, the drugs with low partition coefficient, poor solubility, or those with medium to high molecular weights. They are classified as: small unilamellar vesicles (SUV) (10-100nm), large unilamellar vesicles (LUV) (100-3000) or if, a number of bilayers are present, multilamellar vesicles (MLV). It is droppable, biocompatible, and biodegradable in nature. It reduced the toxicity of the drug. It provides the sustained release and site-specific delivery. Liposomes are difficult to manufacture in sterile preparation. It has limitation like low drug load and inadequate aqueous stability, and oxidative degradation of phospholipid.

4.7 Ionotophoresis:

Ocular ionotophoresis has gained significant interest recently due to its noninvasive nature of delivery to both anterior and posterior segment. Ionotophoresis is a noninvasive method of transferring ionized drugs through membranes with low electrical current [30,31]. The drugs are moved across the membranes by two mechanisms: migration and electro-osmosis Ocular iontophoresis is classified into transcorneal, corneoscleral, or trans-scleral ionotophoresis. The sclera has larger surface area than the cornea (about 17 cm^2 vs 1.3 cm^2), high degree of hydration, low number of cells, and it is permeable to large molecular weight compounds. Trans-scleral delivery allows drug transfer to the posterior segment. It is noninvasive method and easy to use. It has ability of modulate dosage (less risk of toxicity), a broad applicability to deliver a broad range of drugs or genes to treat several ophthalmic diseases in the posterior segment of the eye, and good acceptance by patients. OcuPhor ^{TM} system has been designed with an applicator, dispersive electrode, and a dose controller for transscleral ionotophoresis (DDT).

5. FUTURE CONSIDERATIONS:

Nonetheless, the sustained delivery of therapeutically effective concentration of drug to treat diseases of eye, particularly disease of posterior segment of eye, remains a significant technological challenge.

An ideal system should be able to achieve an effective drug concentration at the target tissue for an extended period of time, while minimizing systemic exposure. In addition, the system should be both comfortable and easy to use. Patient acceptance will continue to be emphasized in the design of future ophthalmic drug delivery systems. A reasonable strategy to circumvent the drawbacks of individual technologies is to combine technologies.

6. CONCLUSION:

Effective treatment of ocular diseases is a formidable challenge for scientists in the field, especially because of the nature of diseases and presence of the ocular barriers especially in posterior ocular segments. Over last several years, attempts have been made to improve ocular bioavailability through manipulation of product formulation such as viscosity and application of mucoadhesive polymers. Thus far, these approaches to prolong corneal contact time have led to modest improvement in ocular bioavailability. Consequently, it seems logical to consider nonconventional approaches such as nanotechnology, microspheres, liposomes, appropriate prodrug *in situ* forming gel, and ionotophoresis for effective delivery and to further enhance ocular absorption and reduce side effects. They improve ocular drug bioavailability by increasing ocular drug residence time, diminishes side effect due to systemic absorption and

diminishing the necessary therapeutic amount of drug for therapeutic response in anterior chamber.

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