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PROGRESSIVE STUDIES IN OCULAR DRUG DELIVERY

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ABSTRACT

The ocular drug delivery passes through a number of anatomical physiological and ocular barriers, which have been a bottleneck for the ophthalmologists. The ocular barriers decrease the absorption of the therapeutic agents. Transportation of drugs followed by traditional dosage forms is restricted to the eye, and therapeutic drug concentrations in the target tissues are not maintained for a long duration since the eyes are protected by a unique anatomy and physiology. For the treatment of the anterior segment of the eye, various droppable products to prolong the retention time on the ocular surface have been introduced in the market. On the other hand, direct intravitreal implants, using biodegradable or non-biodegradable polymer technology, have been widely investigated for the treatment of chronic vitreoretinal diseases. There is urgent need to develop ocular drug delivery systems which provide controlled release for the treatment of chronic diseases, and increase patient's and doctor's convenience to reduce the dosing frequency and invasive treatment. In this article, review of the study is to highlight the newer developments in the pharmaceutical ophthalmic formulations, such as formulation of in situ gels, nanoparticles, liposomes, nano-suspension, micro-emulsion, ocular inserts 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

Keywords: eye; drug delivery systems; ocular barriers; intravitreal implant

1. Introduction:

The eye-ball is an organ protected from exogenous substances and external stress by various barriers (Figure 1), therefore, therapeutic drugs must be transported across several protective barriers regardless of which administration route is utilized, such as eye-drops, and subconjunctival, intravitreal injection and/or implants.

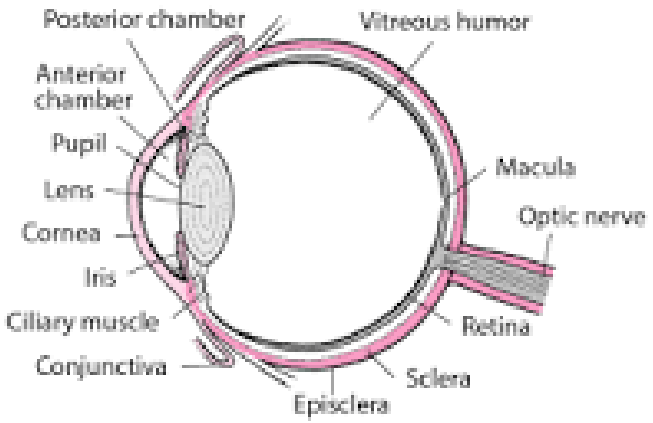

Fig.1: structure of eye-ball

Ophthalmic preparations (eye preparations) are sterile, liquid, semi- solid, or solid preparations that may contain one or more active pharmaceutical ingredient(s) intended for application to the conjunctiva, the conjunctival sac or the eyelids. The choice of base and any excipients used for the preparation of ophthalmic preparations must be proven through product development studies not to affect adversely either the stability of the final product or the availability of the active ingredients at the site of action. [1] For the treatment of the anterior segment of the eye (cornea, conjunctiva, sclera, anterior uvea), usually topical ocular eye-drops are used. An eye-drop of certain instilled volume, often eliminates rapidly within five to six minutes after administration, and only a small amount (1–3%) of an eye-drop actually reaches the intraocular tissue [2]. Thus, it is difficult to provide and maintain an adequate concentration of drug in the precorneal area. More than 75% of applied ophthalmic solution is lost via nasolachrymal drainage and absorbed systemically via conjunctiva, hence ocular drug availability is very low [3]. To increase the ocular bioavailability and prolong the retention time on the eye surface, ophthalmic vehicles such as viscous solutions,suspensions emulsions, ointments, aqueous gels, and polymeric inserts, have been investigated for topical application to the eye. In general, topical applied drugs do not reach the posterior segment of the eye (retina, vitreous, choroid), therefore, systemic administration, periocular or intraocular injections of drugs are normally applied in clinical therapeutics [4, 5]. However, the unique anatomy and physiology of the eye and its protective barriers prevent the administrated drugs from penetrating into the target tissues. Currently there is also rapidly growing interest in drug delivery systems (DDSs) to the posterior segment of the eye. The rationale behind this review study is to highlight the newer developments in the pharmaceutical ophthalmic formulations, such as formulation of in situ gels, nanoparticles, liposomes, nanosuspension, microemulsion, ocular inserts and so on, and their progress to overcome the problems associated with the current conventional dosage forms and also to improve the bioavailability as well as the sustained release of the drug at the target location [6].

2. Advantages of ocular drug delivery systems

They impart accuracy and uniformity in dosing rate.

Pulsed dosing of conventional systems can be avoided.

Sustained and controlled release of drugs can be achieved.

By increasing corneal contact time, they cause enhancement in the ocular bioavailability.

For the prevention of loss of ocular tissues, targeting within the ocular globe is to be done.

They bypass the protective ophthalmic barriers, such as drainage, lacrimation and conjunctival absorption.

They also improve patient's compliance, offer comfort and enhance therapeutic drug performance

Systemic and visual side effects are lower and absorption is faster [7].

3. Disadvantages of ophthalmic drug delivery systems

Short contact time of drug solution and eye surface

. Poor bioavailability.

Instability for dissolved drugs.

Use of preservatives [8].

4. Limitations of ocular drug delivery

Termination of the dosage form is not possible during an emergency.

Interference with vision.

Faces difficulty in placement and removal of the dosage form.

5. Barriers for ocular drug delivery

Ocular drug delivery suffers from the following barrier effects:

5.1 Drug loss from the ocular surface

After using the dosage form of the drug in the ocular system, flow of lacrimal fluid completely removes 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 removed 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 [9].

5.2 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 when 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 which supports rapid systemic absorption.

5.3 Blood-ocular barriers

Blood-ocular barriers are present in the bloodstream. It comprises of two parts, namely blood aqueous barrier and blood-retina barrier. The anterior blood-eye barrier is composed of endothelial cells in the uvea, i.e., the middle layer of the eye below sclera, iris, ciliary body and choroid. This barrier works to prevent the entry of hydrophilic drugs present in plasma to the aqueous humor and also limits the entrance of plasma albumin in aqueous humor. The posterior barrier which resides in between the eye and stream of plasma consists of retinal pigment epithelium (RPE) and retinal capillaries, resulting in tight wall junction. Choroid vasculature comprises of extensive blood flow and leaky walls, due to which easy access of drugs occurs in the choroidal extravascular space, but their distribution in the retina is limited due to the presence of RPE and retinal endothelium [10].

6. Drug Delivery Systems to the Anterior Segment of the Eye

6.1. Eye-Drops

A broad-spectrum antibiotic, azithromycin ophthalmic solution, formulated with Durasite® (AzaSite® , Inspire Pharmaceuticals Inc., Durham, NC, U.S.) for the treatment of bacterial conjunctivitis was launched in the United States in 2007 [11. This utilizes Durasite® , which is a combination of azithromycin and dexamethasone (DEX) (ISV-502; AzaSite Plus™, InSite Vision Inc.), for the treatment of blepharoconjunctivitis and is currently in Phase III [12]. Bromfenac in DuraSite® (ISV-303, InSite Vision Inc.) is in Phase I/II to reduce inflammation and pain after ocular surgery [13]

Novasorb® (Novagali Pharma S.A., Evry, France) is a cationic emulsion, based on electrostatic attraction that occurs between the oily droplets of a positively-charged emulsion loaded with active ingredient, and negatively charged ocular surface [14]. Therefore, Novasorb® improves solubility and absorption of lipophilic drugs, reduces the number of instillation times and side effects, leading to better efficacy and compliance. Cationorm® , which is composed of only cationic emulsion without any active ingredients, has been launched for mild dry eye [15]. NOVA22007, a cationic emulsion incorporated cyclosporine, has completed Phase III studies for dry eye [16] and Phase II/III studies for vernal kerato conjunctivitis [17].

6.2. Contact Lens

Soft contact lens-based DDSs have been investigated by several approaches: (1) Soak and absorption of drug solution [18]; (2) piggyback contact lens combined with a drug plate or drug solution [19]; (3) surface-modification to immobilize drugs on the surface of contact lenses [20] (4) incorporation of drugs in a colloidal structure dispersed in the lens [21]; (5) ion ligand-containing polymeric hydrogel [22]; and (6) molecularly imprinting of drugs [23,24]. The soft contact lens based drug delivery devices are being developed by the following two companies, but details have not been disclosed. Vistakon Pharmaceuticals, LLC (Philadelphia, PA U.S.) has completed a multicenter Phase III clinical trial for a contact lens presoaked to release an antihistamine drug, ketotifen, to prevent allergic conjunctivitis in contact lens wearers [25,26]. SEED Co., Ltd. (Tokyo, Japan) and

Senju Pharmaceutical Co., Ltd. (Osaka, Japan) have co-developed a disposable soft contact lens to release incorporated sodium cromoglicate for one day.

6.3. Cul-de sac Inserts

Ocusert® provides uniform controlled release (20 or 40 μg/hour for 7 days) of pilocarpine as an ocular hypotensive drug, and has been commercialized in 1974 [27]. Ocusert® consists of two outer layers of ethylene-vinyl acetate copolymer (EVA), and an inner layer of pilocarpine in alginate gel within di-(ethylhexyl)phthalate for a release enhancer, sandwiched between EVA layers [28]. However, Ocusert® has not become widely used because of unsatisfactory IOP control due to various causes, including difficulty of inserting the device, ejection of the device from eye, and irritation during insertion [29]. Lacrisert® (Aton Pharma, Inc., Lawrenceville, NJ, U.S.) is a rod-shaped, water-soluble cul-de-sac insert composed of hydroxypropyl cellulose without preservatives and other ingredients (1.27 mm diameter, 3.5 mm long), and is indicated in moderate to severe dry eye syndrome [30]. Lacrisert® has not been applied as a drug delivery carrier as yet. Although previously many inserts including collagen shield, Ocufit SR® , New Ophthalmic Delivery System, and Minidisc ocular therapeutic system have been developed [28,31], there are no further activities at present.

6.4. Punctal Plugs

To prolong the retention time and increase absorption and efficacy after instillation of eye-drops, inhibition of drainage through nasolacrimal system using punctal plug into the pancta is a long-standing approach [32]. Efficacy of an ocular hypotensitive agent in eye-drops in conjunction with punctual occlusion by punctual plug has been evaluated. QLT Inc. (Vancouver, Canada) and Vistakon Pharmaceuticals, LLC have individually developed punctal plugs as DDSs for latanoprost and bimatoprost, respectively. QLT Inc. has reported Phase II data for a punctual plug containing a latanoprost dose of 44 μg, 81 μg, and two different release rates of 95 μg. A retention rate based on available data from 185 eyes with 12 weeks of follow-up in conjunction with previous studies was 81%, but a dose-response for IOP reduction was not observed [33].

6.5. Subconjunctival/Episcleral Implants

LX201 (Lux Biosciences Inc., Jersey City, NJ, U.S.) is a silicone matrix episcleral implant designed to deliver cyclosporine A to the ocular surface for one year. The implant is flat on the bottom in contact with the episclera, and the top is rounded, in contact with anterior surface. LX201 is available in two different lengths of 0.5 and 0.75 inches. Each implant is 0.08 inches wide and 0.04 inches high [34]. In preclinical studies using rabbits and dogs, the episcleral cyclosporine implant delivered continuously potentially therapeutic cyclosporine levels to the lacrimal gland, and showed efficacy in a model of keratoconjunctivitis [34,35]. Phase III study of LX201 to prevent corneal transplant rejection is now ongoing [36]. An episcleral implant developed by 3T Ophthalmics (Irvine, CA, U.S.) is also composed of silicone and looks like a tiny bathtub, less than 1.0 cm long. It can be re-filled with drugs in any form, such as a solution, gel or matrix [37]. In animal studies using model compound (sodium fluorescein), the episcleral implant facilitates diffusion of fluorescein through the sclera, leading to high levels in the retina and posterior vitreous, and tissue levels are markedly increased compared with periocular injection of the same amount of fluorescein [38]. At present, 3T Ophthalmics plans to enter clinical trials for retinoblastoma in the near future [37]. A subconjunctival insert containing latanoprost (Latanoprost SR insert) in Phase I clinical study developed by Pfizer, Inc. (New York, NY, U.S.) is composed of a poly (DL-lactide-co-glycolide) (PLGA) tube containing a latanoprost-core. One end of the tube is capped with an impermeable polymer, silicone, and the other end is capped with a permeable polymer, polyvinyl alcohol (PVA). Latanoprost is released across the PVA-end and its release rate is regulated by an internal diameter of PLGA tube. Duration of latanoprost release is designed for 3–6 months [39].

7. Drug Delivery Systems to Posterior Segment of the Eye

7.1. Intravitreal Implant

Durasert™ Technology System Durasert™ technology system (pSivida Corp., Watertown MA, U.S.) uses a drug core with one or more surrounding polymer layers, and delivers drugs for predetermined periods of time ranging from days to years. The drug release is controlled by permeability of the polymer layers [40]. Using the Durasert™ system, an antiviral drug, ganciclovir (GCV)-loaded intravitreal implant (Vitrasert®, Bausch & Lomb Inc., Rochester, NY, U.S.) for the treatment of cytomegalovirus retinitis, has been developed as the first intravitreal DDSs that avoids systemic side effects and does not involve frequent intravitreal injections. This implant is made of EVA and PVA, and releases GCV by passive diffusion through a small opening in EVA at the base of the device for 6–8 months [41, 42]

Retisert® (Bausch & Lomb Inc.), an intravitreal implant containing fluocinoloneacetonide (FA) [43, 44 45], is approved by FDA for the treatment of non-infectious posterior uveitis. The constitution of the implant and drug release duration are different from the above-mentioned Vitrasert®. The implant contains 0.59 mg of FA and was designed to deliver the drug for up to 1,000 days. The Retisert® implant is composed of a central core consisting of FA compressed into a 1.5 mm diameter tablet [46]. Each FA tablet is encased in a silicone elastomer cup containing a release orifice. A semi-permeable layer of PVA coats the tablet inside the cup reservoir near the release orifice, creating a membrane between the tablet and the orifice that serves as an additional barrier for drug release from the cup. A suture tab, made from a sheet of heat cured PVA film, is attached to the silicone cup using silicone adhesive. The suture tab is used to anchor the implant in the eye through a suture hole. Both the silicone adhesive and the silicone elastomer material are impermeable to FA, while PVA is permeable to diffusion of the drug. By varying the size of the silicone elastomer cup's release orifice and the permeability of the PVA layer between the tablet and the orifice, the rate of drug release from the implant can be controlled. Release of FA from the cup reservoir occurs as water from the exterior of the implant penetrates into it and dissolves some of the drug. The dissolved drug substance then diffuses across the release orifice through the semi-permeable layer of PVA into the medium.

7.2 Cortiject®

Cortiject® (NOVA63035, Novagali Pharma S.A.) is a preservative-free emulsion composed of oily carrier and phospholipid as surfactant, encapsulating a target tissue-activated corticosteroid prodrug [47]. A single intravitreal injection provides sustained release over 6–9 months.

7.3 Visudyne®

Liposomes can also be designed to intervene in intercellular biological responses between receptors and ligands in physiological or pathological conditions and also to receive external signals by laser beam or an electric or magnetic field [48,49,50]. Therefore, liposomes may become available for a drug targeting system. Visudyne® (QLT Ophthalmics, Inc., Menlo Park, CA, U.S.) is an intravenous liposomal formulation containing photosensitizer, verteporfin, in photodynamic therapy for predominantly classic subfoveal choroidal

neovascularization due to AMD, pathologic myopia or presumed ocular histoplasmosis [51]. Plasma lipoproteins, such as low-density lipoprotein (LDL), have been proposed to enhance the delivery of hydrophobic verteporfin to malignant tissue since tumor cells have been shown to increase numbers of LDL receptors [52].

7.4 Iontophoresis

Ocular iontophoresis is one of the growing fields in research due to its noninvasive nature of delivering drugs to both the anterior and posterior segments of eye. Iontophoresis is defined as a noninvasive procedure for the transfer of ionized drugs via membranes with low electrical current [24, 25]. The drugs can move across the membranes by two ways, migration and electro-osmosis. Ocular iontophoresis, categorized as transcorneal, corneoscleral, or transscleral [24], is considered as one of the most attractive options. OcuPhor™ system has been designed with the help of an applicator, dispersive electrode and a dose controller for transscleral iontophoresis [26]. The device works, as it releases the active drug moiety into retina-choroid. Another similar device being made known by name called Visulex™, which allows specific transport of ionized molecules through the sclera.

8. Conclusion

The eye is one of the most complex organs in the human body. Many successes in anterior drug delivery systems for prolonging retention time and reducing administration frequency have been achieved. Additional needs in this field is to improve patient's and doctor's compliance. On the other hand, many implantable sustained drug delivery systems for chronic vitreoretinal diseases, using biodegradable or non-biodegradable polymers, are being developed. In order to reduce side-effects during long-term drug exposure, intelligent posterior drug delivery strategies, which respond to external environment changes and/or disease-oriented pathophysiological signals, are needed. Due to transparent ocular mediums, intraocular tissues (vitreous and retina) are relatively easy to be observed without invasion, and various administration approaches including intravitreal or subretinal injection/implantation could be developed.

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