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A Brief Study On Opthalmic Drug Delivery: A Review

Navneet Kumar Verma[*1], Ruchi Mishra[2], Satendra Kumar[3], Vikash Chandra[4]

[1]Associate Professsor, Buddha Institute of Pharmacy, GIDA, Gorakhpur, UP, India-273209 Affiliated to Dr. APJ Abdul Kalam Technical University, Lucknow, Uttar Pradesh, India

[2]Assistant Professor, B.P.S. Educational Institution of Pharmacy, Etah, U.P, India, Affiliated to Dr. APJ Abdul Kalam Technical University, Lucknow, Uttar Pradesh, India

[3]Professor & Director, L.N. Pharmacy College, Deoria, UP, India, Affiliated to Dr. APJ Abdul Kalam Technical University, Lucknow, Uttar Pradesh, India

[4]Faculty of Pharmacy, Uttar Pradesh University of Medical Sciences Saifai Etawah UP.206130

ABSTRACT

The distance from cornea to retina appears to be the difficult path for most of the small molecule therapeutics. Ocular drug delivery is extreme difficult task owing to complexity and intricate barriers of the eye. However, there is an urgency and need to overcome these barriers for the treatment of sight threatening ocular complications. Delivery of drugs through topical application is compromised by physiological, static, dynamic and metabolic barriers. Currently, intravitreal therapy is a gold standard for targeting therapeutic entities to the posterior segment of the eye. Promising treatment for eye conditions involves maintaining a long enough medication concentration at the eye. The barriers defending the eye prevent effective medication transport to the eye. The biggest challenge to overcome is frequently the active drug substance's bioavailability. Eye drops and other traditional ocular dose forms are insufficient to treat ocular illnesses nowadays. 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. The development of novel drug delivery technologies is currently gaining steam, and this bodes well for the development of medicines for vision-threatening illnesses. Because topical delivery for ocular therapies requires less medication than systemic administration, acts quickly, and has no systemic toxicity, it is suitable. The interior portions of the eye must be reached by topically applied ocular medications, and transcorneal penetration is thought to be the main method of drug absorption.

Keywords: *Ophthalmic drug delivery, corneal drug delivery, Controlled and sustained drug delivery*

***Corresponding Author**
Navneet Kumar Verma
Associate Professsor, Buddha Institute of Pharmacy, GIDA, Gorakhpur, UP, India

INTRODUCTION

Due to its properties for drug disposition, the eye is the most fascinating organ. Due to its simplicity and safety for ocular chemotherapy, topical administration of medicines is typically the method of choice [1]. It is a huge difficulty for the formulator to get around (bypass) the eye's defences without enduring long-term tissue damage. Ocular delivery systems with high treatment efficacy continue to be made possible by the development of better, more sensitive diagnostic procedures and innovative therapeutic substances. Traditional ophthalmic formulations, such as solution, suspension, and ointment, have a number of drawbacks that contribute to the drug's poor ocular cavity bioavailability. 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. 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]. 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 in situ gel or colloidal suspension or using erodible or non erodible insert to prolong the pre corneal drug retention [4]

IN SITU FORMING GELS FOR OPTHALMIC DRUG DELIVERY

Modern pharmaceutical design has recently adopted regulated and sustained drug distribution as the norm, and extensive study has been done to improve drug product effectiveness, reliability, and safety. Many polymers that undergo reversible sol to gel phase transitions in response to physiological cues are extremely helpful in this area [5]. In situ gels are easily injected as solutions into the conjunctival sac, where they undergo a transformation +into gels with their preferred residence times. The physiological environment causes a chemical/physical alteration that leads to the sol-gel transition. This type of gel combines the advantage of a solution being patient convenient with the favourable 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 deacetylated 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 x-Lguluronic 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].

THE ANATOMY OF THE EYE

The human eye, elegant in its detail and design, represents a gateway to the process we call vision. The eyeball is spherical in shape and about 1 inch across. It houses many structures that work together to facilitate sight. The human eye is comprised of layers and internal structures, each of which performs distinct functions. The detailed description of each eye part is given below.

A. Sclera

The sclera (white portion of the eye) is the tough white sheath that forms the outer-layer of the ball. It is a firm fibrous membrane that maintains the shape of the eye as an approximately globe shape. It is much thicker towards the back/posterior aspect of the eye than towards the front/anterior of the eye [11].

B. Conjunctiva

The conjunctiva is a thin transparent mucous epithelial barrier, lines the inside of the eyelids, and covers the anterior one-third of the eyeball. The respective portion of conjunctiva is referred to as the palpebral and bulbar conjunctiva. The conjunctiva is composed of two layers: an outer epithelium and its underlying stroma (substantia propria). The exposed surface of the eye includes conjunctiva and cornea and is covered with the tear film. The conjunctiva contributes to the formation of the tear film by way of secreting substantial electrolytes, fluid, and mucins.

C. Cornea

The cornea is a strong clear bulge located at the front of the eye. Surface of the adult cornea has a radius of approximately 8mm. It has an important optical function as it refracts light entering the eye which then passes through the pupil and onto the lens (which then focuses the light onto the retina). The cornea, a non-vascular structure (does not contain any blood vessels) gets the necessary nutrients from the capillaries that terminate in loops at its circumference. It is supplied by many nerves derived from the ciliary nerves. These enter the laminated tissue of the cornea. It is therefore extremely sensitive.

D. Aqueous humor

The aqueous humor is a jelly-like substance located in the outer/front chamber of the eye. It is a watery fluid that fills the "anterior chamber of the eye" which is located immediately behind the cornea and in front of the lens. The aqueous humor is very slightly alkaline salt solution that includes tiny quantities of sodium and chloride ions. It is continuously produced, mainly by the ciliary processes, flows from the posterior chamber through the pupil into the anterior chamber, and exits via the trabecular route at the angle and the uveoscleral route. Schlemm's canal (canal of Schlemm or the scleral venous sinus), is a circular channel that collects aqueous humour from the anterior chamber and delivers it into the bloodstream via the anterior ciliary veins. It is located at the junction of the cornea and the sclera. In human, the rate of aqueous humor turnover is approximately 1% - 1.5% of the anterior chamber volume per minute. The rate of aqueous formation is approximately 2.5 µl/min. Aqueous humor consists of pressure dependent and pressure independent pathways. The pressure dependent outflow refers to the trabecular meshwork-schlemm's canal-venous system, while pressure independent outflow refers to any non trabecular outflow and is called as uveoscleral outflow [12].

E. Pupil

Pupil generally appears to be the dark "centre" of the eye, but can be more accurately described as the circular aperture in the centre of the iris through which light passes into the eye. The size of the pupil (and therefore the amount

of light that is admitted into the eye) is regulated by the pupillary reflex (also known as the "light reflex").

F. Iris

The iris is a thin circular contractile curtain located in front of the lens but behind the cornea. The iris is a diaphragm of variable size whose function is to adjust the size of the pupil to regulate the amount of light admitted into the eye. It is the coloured part of the eye (shades may vary individually like blue, green, brown, hazel, or grey).

G. Ciliary Muscle

The ciliary muscle is a ring of striated smooth muscles in the eye's middle layer that controls accommodation for viewing objects at varying distances and regulates the flow of aqueous humour into schlemm's canal. The muscle has parasympathetic and sympathetic innervation. Contraction and relaxation of the ciliary muscle alters the curvature of the lens. This process may be described simply as the balance existing at any time between two states: Ciliary Muscle relaxed (This enables the eye to focus on distant objects) and Ciliary Muscle contracted (This enables the eye to focus on near objects).

H. Lens

The lens is a transparent structure enclosed in a thin transparent capsule. It is located behind the pupil of the eye and encircled by the ciliary muscles. It helps to refract light travelling through the eye (which first refracted by the cornea). The lens focuses light into an image on the retina. It is able to do this because the shape of the lens is changed according to the distance from the eye of the object(s) the person is looking at. This adjustment of shape of the lens is called accommodation and is achieved by the contraction and relaxation of the ciliary muscles.

I. Vitreous Humour

The vitreous humour (also known as the vitreous body) is located in the large area that occupies approximately 80% of each eye in the human body. The vitreous humour is a perfectly transparent thin-jelly-like substance that fills the chamber behind the lens of the eye. It is an albuminous fluid enclosed in a delicate transparent membrane called the hyaloid membrane.

J. Retina

The retina is located at the back of the human eye. The retina may be described as the "screen" on which an image is formed by light that has passed into the eye via the cornea, aqueous humour, pupil, lens, and finally the vitreous humour before reaching the retina. The function of the retina is not just to be the screen onto which an image may be formed but also to collect the information contained in that image and transmit it to the brain in a suitable form for use by the body. The retinal "screen" is therefore a light sensitive structure lining the interior ofthe eye. It contains photosensitive cells (called rods and cones) and their associated nerve fibers that convert the light they detect into nerve impulses that are then sent onto the brain along the optic nerve.

K. Macula

The center of the retina is called the macula. The macula contains a high concentration of photoreceptor cells which convert light into nerve signals. Because of the high concentration of photoreceptors, we are able to see fine details such as newsprint with the macula. At the very center of the macula is the fovea, the site of our sharpest vision.

L. Choroid

The choroid layer is located behind the retina and absorbs unused radiation and nourishes the outer portions of the retina. It is a thin, highly vascular (i.e. it contains blood vessels) membrane that is dark brown in colour and contains a pigment that absorbs excess light and so prevents blurred vision (due to too much light on the retina). The choroid has one of the highest blood flows in the body. The choroid is loosely attached to the inner surface of the sclera by the lamina fusa.

M. Optic nerve

The optic nerve (a bundle of over 1 million nerve fibers) is responsible for transmitting nerve signals from the eye to the brain. These nerve signals contain information on an image for processing by the brain. The front surface of the optic nerve, which is visible on the retina, is called the optic disk.

Accessory organs of the eye:

The eye is protected by several structures.

- Eyebrows
- Eyelids and eyelashes
- Lacrimal apparatus

Eyebrows protect the anterior aspect of eyeball from sweat, dust and foreign bodies. The eyelids have various layers of tissue including conjunctiva which protects the delicate cornea and front of the eye. When eye drops are administered, they are placed in lower conjunctival sac. The lacrimal glands secrete tears composed of water, mineral salts, antibodies

and lysozyme, a bactericidal enzyme. Drainage of the eye drops through nasolacrimal system into gastrointestinal tract begins immediately on instillation. This takes place when either reflex tearing or the dosage form causes volume of fluid in peripheral tissue to exceed the normal lacrimal volume of 7-10 µl. The excess fluid volume enters the superior and inferior lacrimal puncta, moves down the canalicula into the lacrimal sac, and continues into the gastrointestinal tract [13].

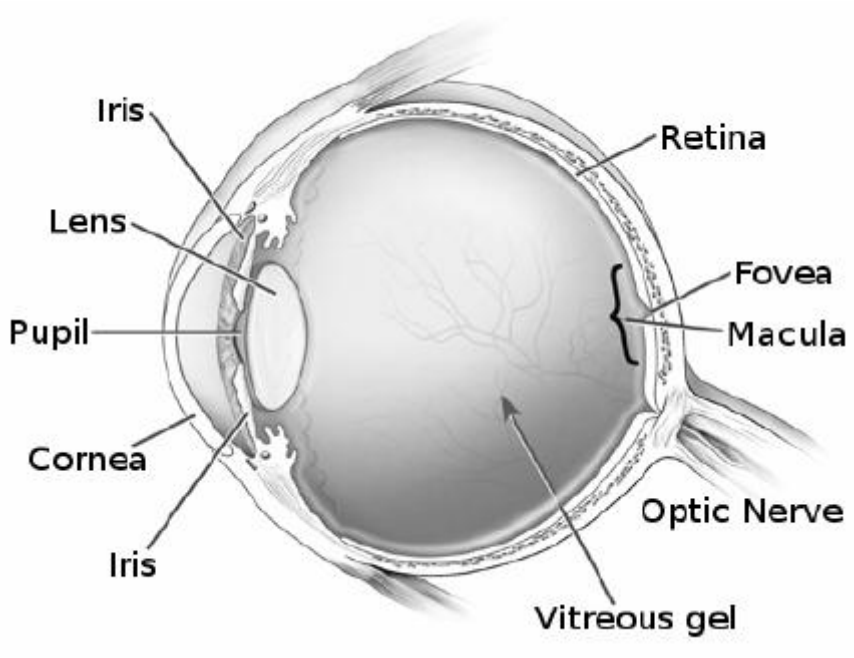

Figure.1; Structure of Eye (copied from google.co.in)

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.m 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.

BARRIERS FOR OCULAR DELIVERY

Drug loss from the ocular surface

After instillation, the flow of lacrimal fluid removes instilled compounds from the surface of eye. Even though the lacrimal turnover rate is only about 1 µl/min the excess volume of the instilled fluid is flown to the nasolacrimal duct rapidly in a couple of minutes. Another source of non-productive drug removal is its systemic absorption instead of ocular absorption. Systemic absorption may take place either directly from the conjunctival sac via local blood capillaries or after the solution flow to the nasal cavity.

Lacrimal fluid-eye barriers

Corneal epithelium limits drug absorption from the lacrimal fluid into the eye. The corneal epithelial cells form tight junctions that limit the paracellular drug permeation. Therefore, lipophilic drugs have typically at least an order of magnitude higher permeability in the cornea than the hydrophilic drugs. In general, the conjunctiva is leakier epithelium

than the cornea and its surface area is also nearly 20 times greater than that of the cornea.

Blood-ocular barriers

The eye is protected from the xenobiotics in the blood stream by blood-ocular barriers. These barriers have two parts: blood-aqueous barrier and blood-retina barrier. The anterior blood-eye barrier is composed of the endothelial cells in the uveam (The middle layer of the eye beneath the the sclera. It consists of the iris, ciliary body, and choroid). This barrier prevents the access of plasma albumin into the aqueous humor, and also limits the access of hydrophilic drugs from plasma into the aqueous humor. The posterior barrier between blood stream and eye is comprised of retinal pigment epithelium (RPE) and the tight walls of retinal capillaries. Unlike retinal capillaries the vasculature of the choroid has extensive blood flow and leaky walls. Drugs easily gain access to the choroidal extra vascular space, but there after distribution into the retina is limited by the RPE and retinal endothelia.

MECHANISM OF OCULAR DRUG ABSORPTION

Drugs administered by instillation must penetrate the eye and do so primarily through the cornea followed by the non-corneal routes. These non-corneal routes involve drug diffusion across the conjunctiva and sclera and appear to be particularly important for drugs that are poorly absorbed across the cornea [14].

Corneal permeation

The permeation of drugs across the corneal membrane occurs from the precorneal space.

Various Barrieirs to drug Absorption:

In tears have a direct bearing on efficiency of drug absorption into the inner eye. The productive absorption of most ophthalmic drugs results from diffusional process across corneal membrane. The efficiency of absorption process is a function of rate and extent at which the transport processes of eye. The flux of any drug molecule across the biological membrane depends on the physicochemical properties of the permeating molecule and its interaction with the membrane. The extent to which the transport or absorption process occurs is also function of physiological mechanism of precorneal fluid drainage or turnover. In terms of transcorneal drug permeation, the cornea can be considered to consist of three primary layers (epithelium, stroma and endothelium). The epithelium and endothelium contain on the order of a 100 fold greater amount of lipid material than the stroma. Consequently, depending on the physicochemical properties of a diffusing drug, the resistance offered by the individual layers varies greatly. Epithelium, being lipodal, represents a diffusional barrier offering high resistance to ionic or other aqueous soluble or polar species. In contrast, compounds with relatively low polarity encounter a greater diffusional resistance in the hydrophilic stroma layer. This frequently cited concept of drug permeation across the corneal membrane ism referred to as “differential solubility concept”.

Non-corneal permeation

Primary mechanism of drug permeation is the sclera is likely to be diffusion across the intercellular aqueous media in the case of structurally similar corneal stroma. Therefore the possibility of partitioning mechanism cannot be eliminated. Although like cornea, the conjunctiva is composed of an epithelial layer covering an underlying stroma, the conjunctival epithelium offers substantially less resistance than does the corneal epithelium.

CLASSIFICATION OF OPHTHALMIC INSERTS

The classification of ophthalmic inserts is [15]

Based upon their solubility behaviour

Insoluble

- Diffusion
- Osmotic and
- Contact lens

Soluble

- Based on natural polymers e.g. collagen.
- Based on synthetic or semi synthetic polymers e.g. cellulose derivatives like HPMC, HPC, MC etc.

Insoluble ocuserts [16]

Only the insoluble types can usually deliver drugs by a variety of method sat controlled, predetermined rate, but need removal from the eye when empty. Insoluble ocuserts can be classified into two categories:

Reservoir system

In this system the drug released either by diffusion or by an osmotic process. It contains, respectively, a liquid, a gel, a colloid, a semisolid, a solid matrix, or a carrier containing drug.

Diffusional insert or ocuserts

Based on porous membrane ocuserts system is a novel ocular drug delivery system. From diffusional inserts/Ocusert drug release is based on a diffusional release mechanism.

Osmotic inserts

The osmotic inserts are usually composed of a central part bounded by a peripheral part and are of two types:

Type 1; The central part is composed of a single reservoir of a drug surrounded by the polymer as discrete small deposits, with or without an additional osmotic solute dispersed throughout a polymeric matrix. An insoluble semipermeable polymer film comprised the second peripheral part of these inserts. In the form of apertures, the osmotic pressure against the polymer matrix causes its rupture. Near the surface of the device drug is then released through these apertures from the deposits.

Type 2; The central part is composed of two different compartments. In two separate compartments the drug and osmotic solutes are placed, the drug reservoir being surrounded by an elastic impermeable membrane and by a semi-permeable membrane the osmotic solute reservoir surrounded. The second peripheral part of this type is similar to type 1.

Matrix systems

The second category matrix system is mainly represented by contact lenses and particular group of insoluble ophthalmic devices. It forms a three dimensional network or matrix capable of retaining water, aqueous drug solution or solid components and consist of covalent cross-linked hydrophilic or hydrophobic polymer. Contact lenses Contact lenses are initially used for vision correction. The possibility of correcting vision and releasing drug simultaneously the main advantage of this system. Refojo has proposed a subdivision of contact lenses into 5 parts.

- Rigid
- Semi-rigid
- Elastomeric
- Soft hydrophilic
- Bio-polymeric

Soluble ocuserts

Soluble (S) inserts normally defined as erodible (E), monolithic polymeric devices that releasing the drug and do not need removal while undergo gradual dissolution. Through polymer swelling true dissolution occurs mainly, while to a chemical or enzymatic hydrolytic process erosion corresponds. In swelling-controlled devices in a glassy polymer, the active agent is homogeneously dispersed. Water from the tear fluid begins to penetrate the matrix when the insert is placed in the eye, then by releasing their drug content, swelling and consequently polymer chain relaxation and drug diffusion take place. They do not need to be removed from their site of application is the main advantage of this system [17].

Natural polymers

To produce soluble ophthalmic inserts natural polymer used is preferably collagen. The therapeutic agent is preferably absorbed by soaking the insert in a solution containing the drug, drying, and re-hydrating it before use on the eye. On the concentration of the drug solution into which the composite is soaked as well as the duration of the soaking and the amount of binding agent present the amount of drug loaded will depend. As the collagen dissolves, the drug is gradually released from the interstics between the collagen molecules [17].

Synthetic and semi-synthetic polymer

This is based upon use of polymers i.e. semi-synthetic polymers (e.g., cellulose derivatives) and synthetic polymers i.e. polyvinyl alcohol. By using Eudragit, a polymer usually used for enteric coating or as a coating agent of the insert, a decreased release rate can be obtained [17].

Bio-erodible ocular inserts

These inserts are formed by bio-erodible polymers (e.g., cross-linked gelatin derivatives, polyester derivatives) which undergo hydrolysis of chemical bonds and hence dissolution. The great advantage of these bio-erodible polymers is the possibility of modulating their erosion rate by modifying their final structure during synthesis and by addition of anionic or cationic surfactants. Some important ocular inserts which are available commercially (SODI) or in advanced state of development (collagen shields, Ocufit and Minidisc) [17].

Soluble ophthalmic drug insert

Soluble ophthalmic drug insert (SODI) is a small oval wafer, which was developed by soviet scientists for cosmonauts who could not use eye drops in weightless conditions.

Collagen shields

Collagen is the structural protein of bones, tendons, ligaments, and skin and comprises more than 25% of the total body protein in mammals. This protein has several biomedical applications which is derived from intestinal collagen and the main application of which is probably catgut suture.

LITERATURE REVIEW

Novel drug delivery systems

Lipid nanoparticles functionalized with ligands such as chitosan and poly (ethylene) glycol and polymeric melt extruded films were developed and targeted for posterior segment ocular tissues using various model drugs [18,19]. Novasorb® is a patented drug delivery platform. The cationicemulsion which is based on electrostatic attraction with negatively charged ocular surface improving absorption of lipophilic drugs. Novasorb takes advantage of the negatively charged mucin layer and enables the drug to retain at the site for longer periods of time [20]. Cationorm®, a drug-free and preservative free cationic emulsion developed by Novagali using oleylamine (cationic emulsifier) is indicated for mild dry eye syndrome launched in Europe. Refresh dry eye therapy®, Soothe® XP emollient and Lipimix™ are placebo emulsions used for the treatment of dry eye syndrome. Cyclosporine A and latanoprost cationic emulsions are currently in phase III clinical trials. Tear Again® is a liposomal spray for dry eye syndrome [21]. Durasite® DDS polycarbophil based aqueous solution with innate ability for hydrogen-bonding with the mucus, cornealand conjunctival epitheliums, to provide the sustained effect [22,23]. Durasite consists of polymeric matrix as drug carrier and so used as a vehicle for delivery of small molecules to the target efficiently. Visudyne® 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 [24].

Punctual plugs are being developed by Mati therapeutics using model drugs latanoprost and olopatadine for glaucoma and allergy relief. Phase 2 clinical studies demonstrated the efficacy and safety in subjects with open angle glaucoma and ocular hypertension [25]. Intracanalicular inserts loaded with travoprost is being developed by ocular therapeutix for the treatment of glaucoma and ocular hypertension. The insert could deliver drug onto the ocular surface for 3 months. If approved, insert may become first non-invasive sustained release product for glaucoma [26]. LX201 is a silicone matrix episcleral implant designed to deliver cyclosporine A to the ocular surface for one year. Each implant is 0.08 inches wide and 0.04 inches high [27]. An episcleral implant developed by 3T Ophthalmics can be re-filled with drugs in any form, such as a solution, gel or matrix [28,29]. In pre-clinical studies with model drug (sodium fluorescein), the episcleral implant delivered high levels in the retina and posterior vitreous [30].

Sustained release drug delivery

Evaluation of the eye targeting drugs' pharmacokinetic profile in human subjects is not practically possible. Because frequent samplings of drug from eye chambers is very dangerous and usually not recommended. Especially, the aqueous and vitreous humor are not good places to collect samples from [6]. Hence, most of the studies are conducted in small animals and correlated to humans. Large experimental groups of animals are needed considering the sample volume and number of samples need to be taken for estimation of peak concentration in tissue and time to achieve maximum concentration in tissue. As patient acceptance is less regarding multiple drug dosages, sustained release formulations are being developed [31]. Several studies are already available where sustained release dosage forms are developed [13]. But these formulations need further techniques to study continuous drug release profile. As sustained release dosage forms are promising in other fields, the same were being developed in ocular diseases [32-33]. Subconjunctival erodible sustained release implant (Durasert™) is being developed by psivida corp which is under safety and efficacy testing (phase I/II clinical trial) in patients with elevated intraocular pressure [34]. A microelectromechanical systems (MEMS) drug delivery device is investigated for the treatment of chronic and refractory ocular diseases with nanoliter sized doses until refilled [35]. The Replenish, Inc ophthalmic micro pump system is comprised of four sub systems namely Anterior microPump™ (glaucoma), Posterior MicroPump™ (retinal complications), Eye link™ and drug refill system™ [36]. Cortiject® developed by Novagali Pharma is emulsion encapsulating corticosteroid prodrug with activated tissue targeting mechanism. Dexamethasone (DEX) palmitate prodrug released is deesterified by esterase enzyme in the retinal tissue and activated to DEX. Sustained release effect can be provided from 6-9 months following single injection into vitreous body. Cortiject is under the phase I/II development [37,38]. Carotuximab, (DE-122) an anti-endoglin antibody is being developed by Santen pharmaceuticals as an intravitreal injection for the treatment of age related macular degeneration [39]. Novel refillable intraocular drug delivery device is manufactured by hot melt extrusion of Bionate II® (DSM), a polycarbonate urethane. *In vitro* results indicated biocompatibility with ocular tissues. *In vivo* histology studies demonstrated that drug levels can be maintained in the retina greater than 3 months without any signs of inflammation [40,41]. Neurotech Pharmaceuticals, Inc has been developing "Encapsulated Cell Technology", which provides extracellular delivery of CNTF through long-term and stable intraocular release at constant doses through a device implanted in the vitreous [42]. Icon Bioscience, Inc. is developing IBI-10090 (Dexycu) containing dexamethasone using Verisome™ sustained drug delivery platform technology following injection into anterior chamber. Dexycu has undergone Phase III clinical trials [43]. For the better advancement of ocular drug delivery, bioavailability of the therapeutic compounds need to be evaluated critically. The bioavailability and bioequivalence issues will impede the drug development and can be a huge burden to drug market [44-45]. Selection of appropriate compartmental model needs to be developed for eye targeting drug formulations. Because there are limitations with obtaining precise data to study

local drug distribution in various chambers of the eye. At the same time, drug elimination from different parts of the eye effect drug concentration at target.

CONCLUSION

Ocular inserts, collagen shields, ocular films, disposable contact lenses, and other novel drug delivery technologies including hiosomes 20 and nanoparticles are included in the new ophthalmic delivery system. Combining medication delivery systems is a more recent approach that aims to boost a drug's therapeutic response. A better dose form for topical ophthalmic administration may result from this. Only a few of these drug delivery systems' products have reached the market. An ideal system would have minimal systemic effects and prolonged effective medication concentration at the target tissue. Any comfortable ophthalmic drug delivery system must take the needs of the patient into consideration when designing it. Each system needs major improvements, such as more sustained drug release, large-scale manufacturing, and stability. Combining medication delivery methods could provide a new direction for enhancing a system's ineffective therapeutic response. They can work around restrictions and combine the benefits of many systems. Drug delivery to the posterior segment ocular tissues of eye presents significant confrontations to drugs/drug candidates. Topical application is not yet promising and needs to be addressed with novel drug delivery platforms developed with integration of multi-disciplinary technologies encompassing biomedical engineering and nanotechnology.

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