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CURRENT TRENDS TOWARDS AN OCULAR DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Ophthalmic drug delivery is one of the challenging endeavors facing pharmaceutical scientist today. The structural and functional aspects of the eye render this organ highly impervious to foreign substances. A significant challenge to the formulator is to overcome the protective barriers of the eye without causing permanent tissue damage. The major problem encountered with topical administration is the rapid pre-corneal loss caused by naso-lacrymal drainage and high tear fluid turnover which leads to only 10% drug concentrations available at the site of actions. Poor bioavailability of drugs from ocular dosage forms is mainly due to the tear production, non-productive absorption, transient residence time, and impermeability of corneal epithelium. Most ocular treatments like eye drops and suspensions call for the topical administration of ophthalmic drugs to the tissues around the ocular cavity. These dosage forms are easy to instill but have the inherent drawback that the majority of the medication in them is immediately diluted. An update of current research advancement in ocular drug delivery necessitates and helps drug delivery scientists to modulate their think process and develop novel and safe drug delivery strategies. Current review intends to summarize the existing conventional formulations for ocular delivery and their advancements followed by current nanotechnology based formulation developments. Major improvements are required in each of the technologies discussed in this review.

KEYWORDS: Ophthalmic drug delivery, Iontophoresis, Drug delivery, Ocular inserts, Topical ocular.

1. INTRODUCTION

Many regions of the eye are relatively inaccessible to systematically administered drugs and as a result, topical drug delivery remains the preferred route in most cases. Drug may be delivered to treat the precorneal region for such infections as conjunctivitis and blepharitis, or to provide intraocular treatment via the cornea for diseases such as glaucoma and uveitis.[1] Approaches that have been attempted to increase the bioavailability and the duration of therapeutic action of ocular drugs can be divided into two categories. The first is based on the use of the 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. The bioavailability of ophthalmic drug is however, very poor due to efficient protective mechanisms of the eye, blinking, baseline and reflex lachrymation and drainage remove rapidly foreign substances, including drug, from the surface of the eye. Moreover, the anatomy, physiology and the barrier function of the cornea compromise the rapid absorption of drug.[2] Frequent instillation of the eye drop is necessary to maintain a therapeutic drug level in the tear film or at the site of action but the frequent use of highly concentrated solution may induce toxic side effects.[3] Topical instillation is the most widely preferred noninvasive route of drug administration to treat diseases affecting the anterior segment. Conventional dosage forms such as eye drops account for 90% of the marketed ophthalmic formulations. The reason may be attributed to ease of administration and patient compliance.[1,4] Nonetheless, the ocular bioavailability is very low with topical drop administration. Numerous anatomical and physiological constraints such as tear turnover, nasolachrymal drainage, reflex blinking, and ocular static and dynamic barriers pose a challenge and impede deeper ocular drug permeation.[5] Hence, less than 5% of topically applied dose reaches to deeper ocular tissues.[6] 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 pre-corneal drug loss. 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.

2. Anatomy and physiology of eye[7-10]

The human eye is essential sense organ of the body and its anatomy is quite complex. Eye is able to refract light and produce a focused image that can stimulate nervous system and enable the ability to see. The structure and different parts of the eye shown in figure 1 and 2.

2.1 Aqueous humour: It is a jelly like substance located in the anterior chamber of the eye.

2.2 Choroid: The choroid layer is located behind the retina and absorbs unused radiation.

2.3 Ciliary muscle: The ciliary muscle is a ring shaped muscle attached to iris. It is important because contraction and relaxation of the ciliary muscle controls the shape of the lens.

2.4 Cornea: Cornea is a clear transparent epithelial membrane. Light rays pass through the cornea to reach the retina. The cornea is convex anteriorly and is involved in refracting light rays to focus them on the retina.

2.5 Fovea: The fovea is a small depression (approx. 1.5mm in diameter) in the retina. This is the part of the retina in which high resolution vision of the fine details is possible.

2.6 Hyaloids: The hyaloids diaphragm divides the aqueous humour from the vitreous humour.

2.7 Iris: The iris is the visible colored part of the eye and extends anteriorly from the ciliary body, lying behind the cornea and in front of the lens. It divides the anterior segment of the eye into anterior and posterior chamber which contains aqueous fluid secreted by the ciliary body. The iris is supplied by parasympathetic and sympathetic nerves. Parasympathetic stimulation constructs the pupil and sympathetic stimulation dilates it.

2.8 Lens: The lens of the eye is flexible units that consist of layers of tissue enclosed in a tough capsule. It is suspended from the ciliary muscles by the zonule fibers.

2.9 Optic nerves: The optic nerve is the second cranial nerve and is responsible for vision. Each nerve contains approximately one millions fibers transmitting information from the rod and cone cells of the retina.

2.10 Papilla: The papilla is also known as the “blind spot” and is located at the position from which the optic nerve leaves the retina.

2.11 Pupil: The pupil is the aperture through which light and hence images we see and "perceive" enters the eye. This is informed by the iris. As the size of iris increases (or decreases) the size of the pupils decreases (or increase) correspondingly.

2.12 Retina: 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, then the hyaloids and finally the vitreous humour before reaching the retina. The retina contains photosensitive elements (called rods and cones) that convert the light they detect into nerve impulses that are then sent onto the brain along the optic nerve.

2.13 Sclera: The sclera is tough white sheath around the outside of the eye-ball. It consists of a membrane that maintains the shape of the eye and gives the attachment to the extrinsic muscle of the eye.

2.14 Vitreous humour: The vitreous humour (vitreous body) is a jelly like substances.

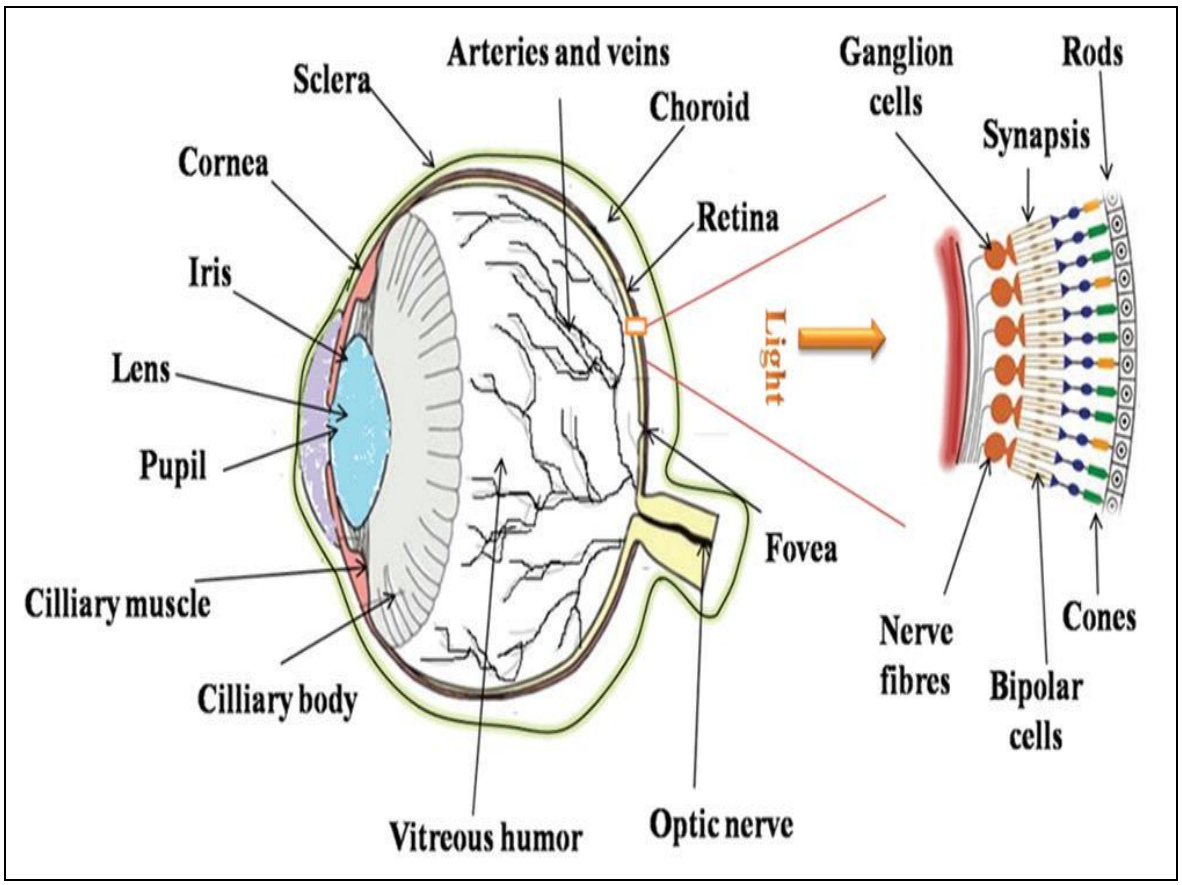

Fig. 1: Various parts of the eye.

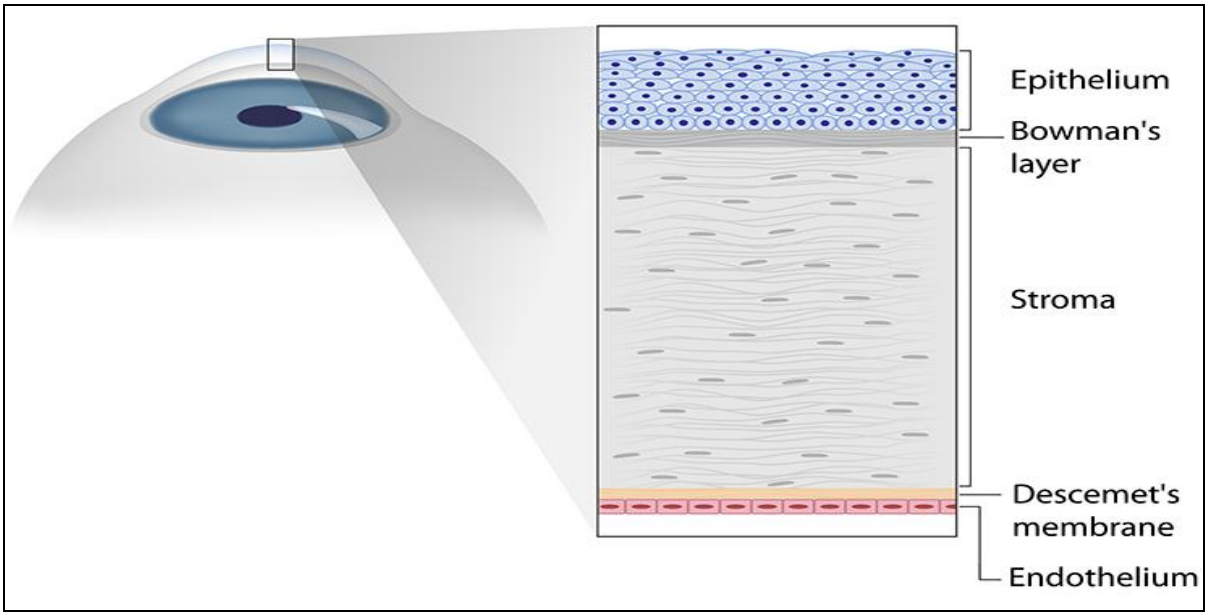

Fig. 2: The schematic structure of cornea.

3. Ophthalmic disoders[11-13]

- **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).

4. Advantages of ocular drug delivery systems

Various advantages of ocular drug delivery system are given below.

- 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 vascularisation. 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.

5. Disadvantages of ocular delivery system

Various disadvantages of ocular drug delivery system are given below.

- 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.[14,15]

6. Routes of administration into the eye

Compared with drug delivery to other parts of the body, ocular drug delivery must overcome important challenges posed by various ocular barriers. Many of these barriers are inherent and unique to ocular anatomy and physiology making it a challenge to deliver the appropriate dose at the appropriate place.[5,6] Ophthalmic drug delivery is used only for the treatment of local conditions of the eye and cannot be used as a portal of drug entry to the systemic circulation. Significant advances have been made to optimize the localized delivery of medication to the eye, so that the route is now associated with highly sophisticated drug delivery techniques. Some of these technologies are unique to the eye and many are also found in other delivery routes.[16]

6.1 Topical administration

Topical administration is employed mostly in the form of eye drops, ointments, gels, or emulsions, to treat anterior segment diseases. Topical application has remained the most preferred method due to the ease of administration and low cost. For most of the topically applied drugs, the site of action is usually different layers of the cornea, conjunctiva, sclera, and the other tissues of the anterior segment such as the iris and ciliary body (anterior uvea). Upon administration, precorneal factors and anatomical barriers negatively affect the bioavailability of topical formulations. Precorneal factors include solution drainage, blinking, tear film, tear turn over, and induced lacrimation. Human tear volume is estimated to be 7 µL,

and the cul-de-sac can transiently contain around 30 µL of fluid. However, tear film displays a rapid restoration time of 2 - 3 min, and most of the topically applied solutions are washed away within 15 - 30 sec. after instillation. Considering all the precorneal factors, contact time with the absorptive membranes is low, which is considered to be the primary reason for less than 5% of the applied dose reaching the intraocular tissues.

6.2 Systemic (Parenteral) administration

Following systemic administration, the blood-aqueous barrier and blood-retinal barrier are the major barriers for the anterior segment and posterior segment ocular drug delivery, respectively. Even though it is ideal to deliver the drug to the retina via systemic administration, it is still a challenge because of the blood-retina barrier, which strictly regulates drug permeation from blood to the retina. Hence, specific oral or intravenous targeting systems are needed to transport molecules through the choroid into deeper layers of the retina.

6.3 Oral administration

Oral delivery alone or in combination with topical delivery has been investigated for different reasons. Topical delivery alone failed to produce therapeutic concentrations in the posterior segment. Also, oral delivery was studied as a possible noninvasive and patient-preferred route to treat chronic retinal diseases as compared to the parenteral route. However, restricted accessibility to many of the targeted ocular tissues limits the utility of oral administration which necessitates high dosage to achieve significant therapeutic efficacy. Such doses can result in systemic side effects. Hence, parameters such as safety and toxicity need to be considered when trying to obtain a therapeutic response in the eye upon oral administration.

6.4 Periocular and intravitreal administration

Although not very appealing to patients, these routes are employed partly to overcome the inefficiency of topical and systemic delivery to the posterior segment. The periocular route includes subconjunctival, subtenons, retrobulbar, and peribulbar administration and is comparatively less invasive than the intravitreal route. Subconjunctival injection bypasses the conjunctival epithelial barrier, which is a rate-limiting barrier for the permeation of water-soluble drugs. Drug solutions are placed in close proximity to the sclera, which results in high retinal and vitreal concentrations.

Unlike periocular injections, the intravitreal injection offers distinct advantages as the molecules are directly inserted into the vitreous. This method involves injection of the solution containing the drug directly into the vitreous via pars plana using a 30-gauge needle. Unlike other routes, intravitreal injection delivers higher drug concentrations to the vitreous and retina. However, drug distribution in the vitreous is nonuniform. Small molecules can rapidly distribute through the vitreous, whereas the diffusion of larger molecules is restricted. This distribution also depends on the pathophysiological condition and molecular weight of the administered drug. Similarly, mobility of nanoparticles in the vitreous depends on their structure and surface charge[5,6,17] Some of routes of administration to the eye are shown in figure 3.

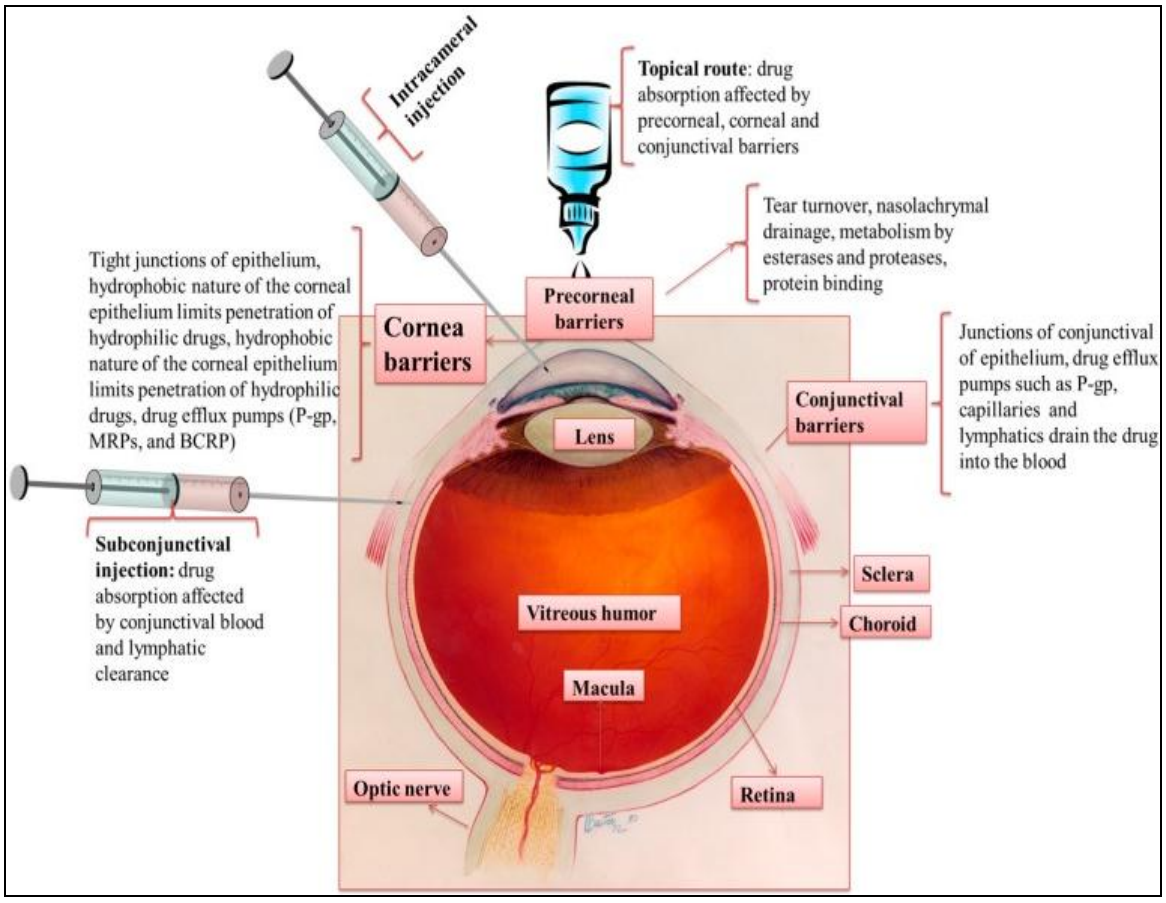

Fig. 3: Routes of administration for anterior segment drug delivery, ocular tissue barriers and clearance mechanisms that prevent drug absorption into the eye.

7. Barriers for ocular delivery:[18] The transport of fluids and solutes in the eye is controlled by several membranes and barriers. These barriers can hamper the delivery of topical ocular drugs (i.e., eye drops) and systemically (i.e., orally or intravenously) administered drugs. Topical ocular drugs, mostly given as eye drops, are the most frequently used dosage forms

for treating ocular diseases. The first barrier to cross for these drugs is the tear film, which rapidly removes instilled compounds from the eye, resulting in low bioavailability. Other membranous barriers are located in the cornea, the conjunctiva, the iris-ciliary body, and the retina. Depending on the physiochemical characteristics of the compounds, delivery of drugs can occur through the corneal route and/or the conjunctival/scleral route. The corneal route is the main route for delivery of drugs to the anterior chamber. Permeation of hydrophilic drugs and macromolecules through the corneal epithelium is limited by the presence of tight junctions between adjacent outer superficial epithelial cells. The abundant presence of hydrated collagen in the stroma may hamper the diffusion of highly lipophilic agents. The endothelium is more permeable and allows the passage of hydrophilic drugs and macromolecules between the aqueous and the stroma due to the presence of "leaky tight junctions" called desmosomes or macula adherents. The passage of topical ocular drugs through the corneal route depends on their lipophilicity, molecular weight, charge, and degree of ionization. Particularly, small lipophilic drugs can easily permeate through the cornea. After crossing the cornea, the drug diffuses into the aqueous and to the anterior uvea.

7.1 Drug loss from the ocular surface

After instillation, the flow of lacrimal fluid removes instilled compounds from the surface of the 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.

7.2 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.

7.3 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 uvea (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 thereafter distribution into the retina is limited by the RPE and retinal endothelia shown in table 1.

Table 1: Barriers for the ocular delivery.

	Conjunctiva	**Cornea**	**Sclera**
Surface area	17.65 ± 2.12 cm^2	1.04 ± 0.12	16 – 17
Thickness	-	0.57mm	0.4 -0.5 mm
Structural composition	Mucus membrane Epithelium Vasculature	5 layers Epithelium Bowman's membrane Stomata Descemet's membrane Endothelium	Collagen fibers Water Proteoglycans Monopoly saccharides Elastic fibers Fibroblast

8. Mechanism of ocular absorption[11,19,20]

The drug from the eye is absorbed by 2 routes i.e. by corneal route and by non corneal route shown in figure 4.

8.1 Corneal route

This is the major pathway of drug absorption for the topically applied formulation. The absorption of drug is occurring by two mechanism transcellular and paracellular diffusion. The hydrophilic drugs are absorbed by paracellular diffusion and most of the lipophilic drugs are absorbed by transcellular diffusion. Generally, corneal penetration is mainly governed by the lipophilicity of the drug but it is also affected by factors like solubility, molecular size and shape, charge and degree of ionization.

8.2 Non corneal route

The absorption is occurring through conjunctiva and sclera. There are three routes by which drugs can permeate through sclera.

a) Through the perivascular spaces.

b) Through the aqueous media of gel-like mucopolysaccharides.

c) Through the empty spaces within collagen network.

This route is considered to be non productive route as the most of the drug reaches to the systemic circulation before it reaches to the intraocular tissues. This route may be important for the hydrophilic compounds with large molecular weights such as timolol maleate and gentamicin.

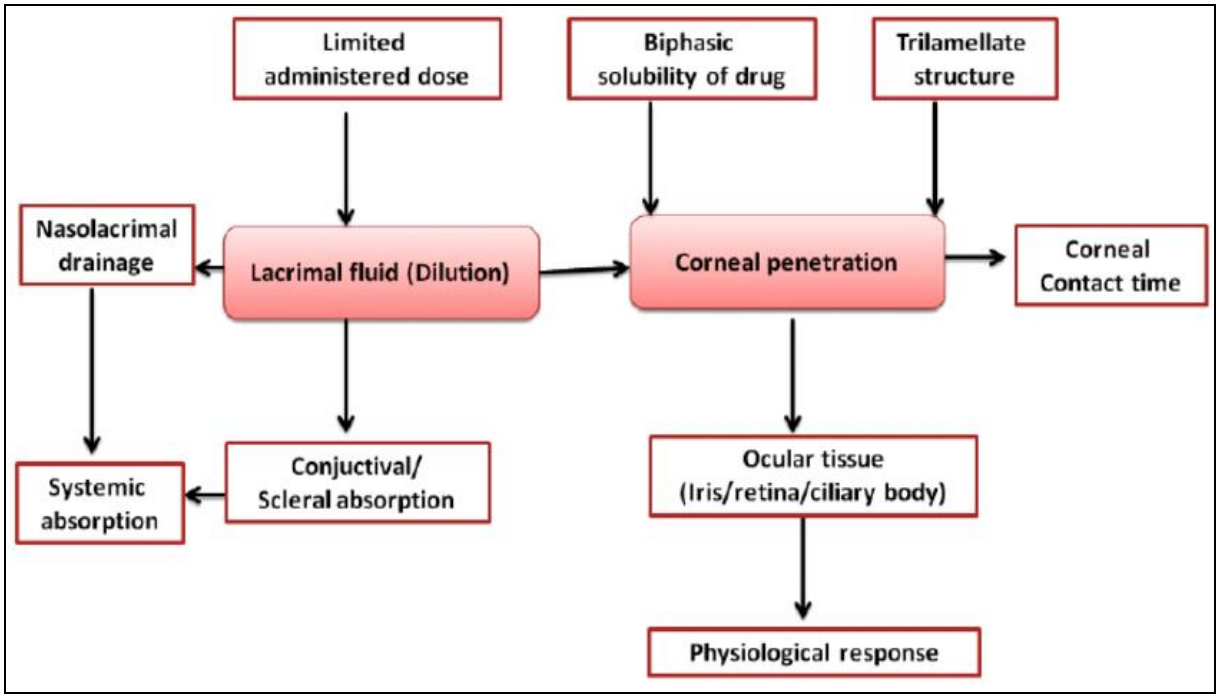

Fig. 4: Mechanism of ocular absorption.

9. Mechanism of drug release into the eye

The drug is released by three following mentioned mechanism:

i) Diffusion ii) Osmosis iii) Bioerosion

Diffusion: In the diffusion mechanism, release of the drug is continuously acted as predefined controllable manner. When ocular inserted into the eye, the fluid of eye enters into the insert and causes swelling of the polymer which leads to relaxation of chain and drug diffusion occur.

Osmosis: In the osmosis, the insert is divided into two parts as internal and external when eye fluid comes in contact with eye insert diffuse and stretched.

Bioerosion: When ocular insert comes in contact with tear fluid, it leads to release the drug in a sustained manner by erosion of matrix. The drug is available as dispersing in the ocular insert, through in the matrix it is believed that drug release in more in controlled form if it is available in the superficial concentrated in the matrix form.

10. Dosage forms applied to the eye

Common to all ophthalmic dosage forms is the critical requirement for sterility of the finished product as well as consideration of the sensitivity of ocular tissue to irritation.

10.1 Solutions

Ophthalmic solutions are sterile solutions intended for instillation in the eye shown in the figure 5.Included in this dosage form category are solid preparations that, when reconstituted according to the labelin structions, result in a solution. In addition to sterility, these dosage forms require the careful consideration of such other pharmaceutical factors as the need for antimicrobial agents, osmolarity, buffering, viscosity, and proper packaging. The corneal contact time of topical ophthalmic solutions increases with the viscosity of the formulations up to 20 centipoise (cP). Further increases result in reflex tearing and blinking in order to regain the original viscosity of the lacrimal fluid (1.05–5.97 cP). The bioavailability increase associated with this longer precorneal permanence allows the frequency of drug application to be reduced. Synthetic polymers, such as polyvinylalcohol (PVA), polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), polyacrylic acid (PAA), and many cellulose derivatives, are commonly employed as viscosity enhancers because of their physiologic compatibility and satisfactory physicochemical properties. Two of the major drawbacks of viscous and mucoadhesive formulations are blurring and an unpleasant sticky feeling in the eye. As consequence, patients may find compliance with treatment schedules difficult.[21 – 24]

10.2 Suspensions

Ophthalmic suspensions may be used to increase the corneal contact time of a drug substance and thus provide a more sustained action shown in the figure 5. Included in this dosage form category are those solid preparations that, when reconstituted according to the label instructions, result in a suspension. An ophthalmic suspension may be required when the active ingredient is insoluble in the desired vehicle or is unstable in solution.[25] Suspensions are required to be made with the insoluble drug in a micronized form to prevent irritation or scratching of the cornea.[21] Suspensions are commonly formulated by dispersing micronized drug powder (less than 10 μm in diameter) in a suitable aqueous vehicle size enhances the

ocular bioavailability. Unfortunately, a particle size above 10 μm in diameter may result in a foreign body sensation in the eye following ocular application, causing reflex tearing. A reduction in particle size generally improves the patient comfort and acceptability of suspension formulations.[16,22] Surfactants may be included in an ophthalmic suspension to disperse the drug effectively during manufacture and during product use. Nonionic surfactants are generally preferred because they tend to be less toxic. Viscosity-enhancing agents can be used to keep the particles suspended. Preparation of flocculated suspensions is not recommended because the larger flocs may irritate the eye.[23,24] Ophthalmic suspensions must possess the same characteristic of sterility as ophthalmic solutions, with proper consideration given also to preservation, osmolarity, buffering, viscosity and packaging. Additionally, ophthalmic suspensions must contain particles of such chemical characteristics and small dimensions that they are nonirritating to the eyes. The ophthalmic suspension must be appropriately formulated so that the suspended particles do not agglomerate into larger ones upon storage.

Fig. 5: Ophthalmic solution (solution and suspensions).

10.3 Ointment

The most commonly used semisolid preparation is ointments consisting of dispersion of a solid drug in an appropriate vehicle base shown in the figure 6. Semi-solids dosage forms are applied once or twice daily and provide sustained effects. The primary purpose of the ophthalmic ointment vehicle is to prolong drug contact time with the external ocular surface. But they present a disadvantage of causing blurring of vision and matting of eyelids. Ophthalmic gels are similar in viscosity and clinical usage to ophthalmic ointments. Pilopine HS is one of the ophthalmic preparations available in gel form and is intended to provide

sustained action of pilocarpine over a period of 24 hours. Semi-solids vehicles were found to prolong the ocular contact time of many drugs, which ultimately leads to an enhanced bioavailability.[26]

Fig. 6: Ophthalmic ointment apply to eye.

10.4 Gels

Ophthalmic gels are composed of mucoadhesive polymers that provide localized delivery of an active ingredient to the eye shown in the figure 7. Such polymers have a property known as bioadhesion meaning attachment of a drug carrier to a specific biological tissue. These polymers are able to extend the contact time of the drug with the biological tissues and thereby improve ocular bioavailability. The choice of the polymer plays a critical role in the release kinetics of the drug (s) from the dosage form. Several bioadhesive polymers are available with varying degree of mucoadhesive performance. Some examples are carboxymethylcellulose, carbopol, polycarbophil, and sodium alginate.[24]

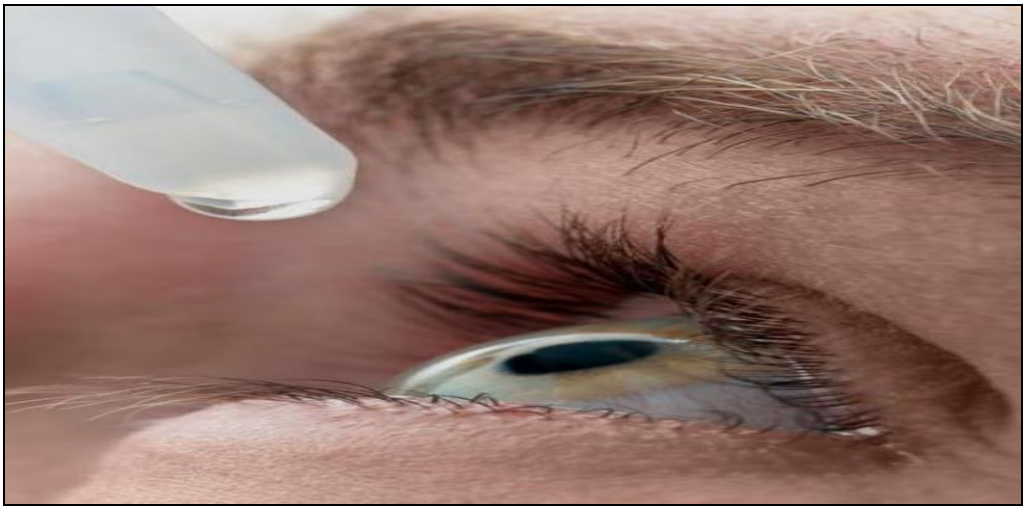

Fig. 7: Ophthalmic gels apply to eye.

10.5 Emulsions

Topical ophthalmic emulsions generally are prepared by dissolving or dispersing the active ingredient(s) into an oil phase, adding suitable emulsifying and suspending agents and mixing with water vigorously to form a uniform oil-in-water emulsion shown in the figure 8. Each phase is typically sterilized prior to or during charging into the mixing vessel. High-shear homogenation may be employed to reduce oil droplet size to sub-micron size which may improve the physical stability of the oil micelles so they do not coalesce. The resulting dosage form should contain small oil droplets, uniformly suspended. Limited aqueous solubility of the drug substance(s) is the most common rationale for developing an ophthalmic emulsion. The drug substance(s) can be added to the phase in which it is soluble at the beginning of the manufacturing process, or it can be added after the emulsion prepared by a suitable dispersion process. To prevent flocculation, creaming and coalescence of the emulsions, manufacturers commonly add surfactants to increase the kinetic stability of the emulsion so that the emulsion does not change significantly with time.[21,27]

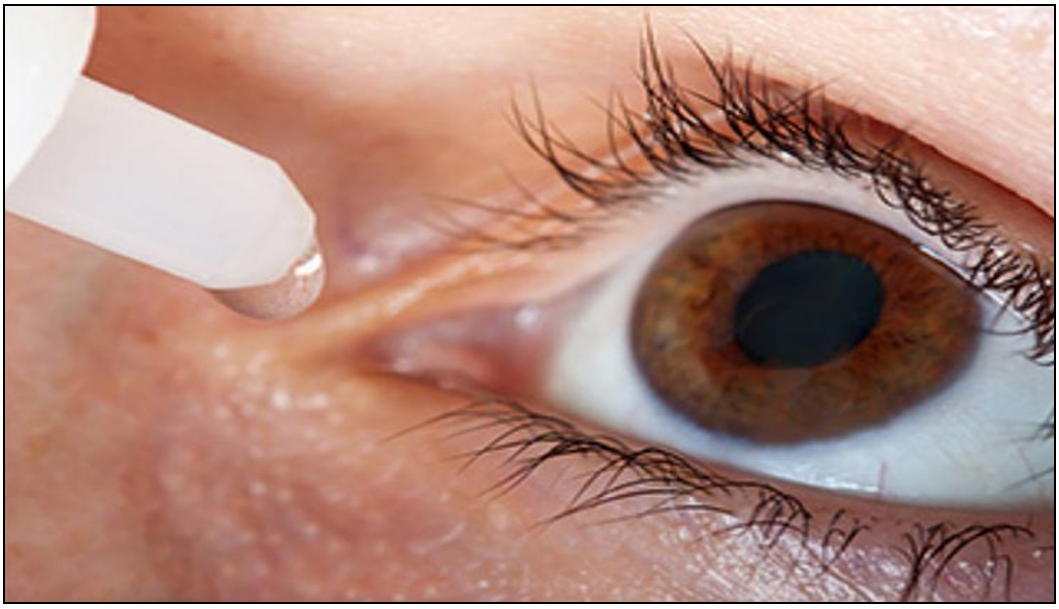

Fig. 8: Ophthalmic emulsions apply to eye.

10.6 Filter paper strips

Sodium fluoresce in and rose Bengal dyes are commercially available as drug impregnated filter paper strips shown in the figure 9. These dyes are used diagnostically to disclose corneal injuries and infections such as herpes simplex, and dry eye disorders.[26]

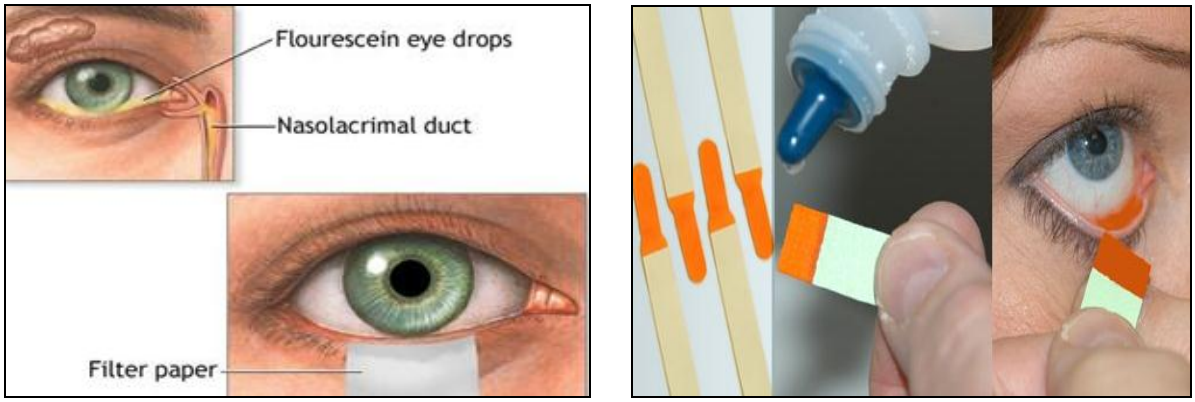

Fig. 9: Ophthalmic filter paper strips apply to eye.

10.7 Injections

While injections are considered a dosage form for nomenclature purposes, they are not treated as a dosage form in this paper shown in the figure 10. Instead, refer to the appropriate physical form, such as solution, suspension, etc., for general information.

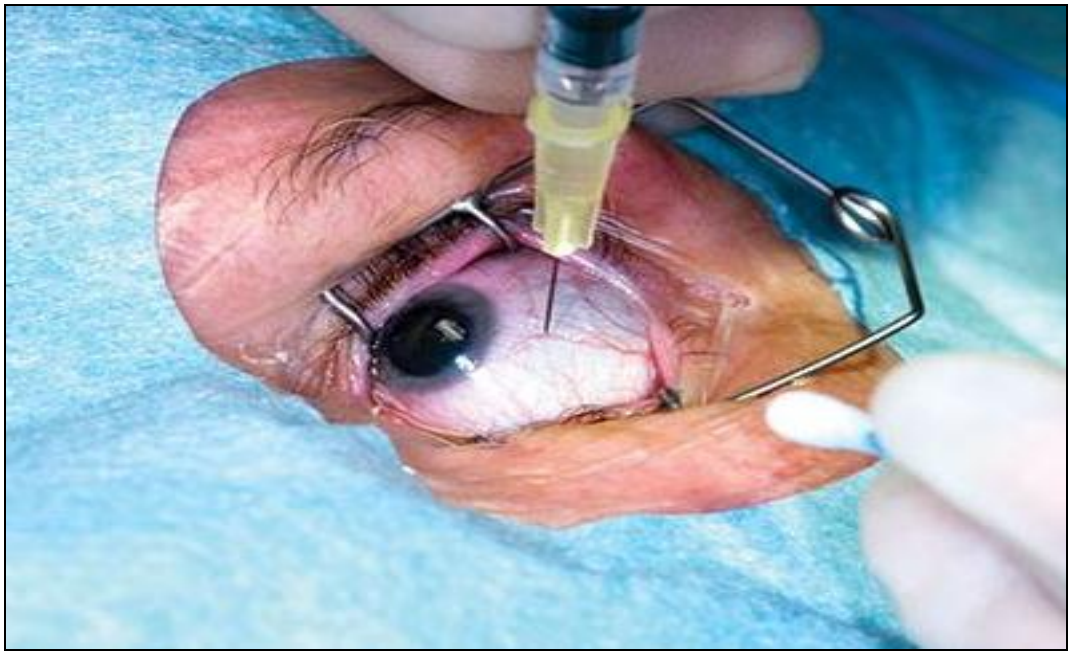

Fig. 10: Ophthalmic injection apply to eye.

10.8 Ocular inserts

Ocular inserts are solid dosage form and can overcome the disadvantage reported with traditional ophthalmic systems like aqueous solutions, suspensions and ointments. The typical pulse entry type drug release behavior observed with ocular aqueous solutions (eye drops), suspensions and ointments is replaced by more controlled, sustained and continuous drug delivery using a controlled release ocular drug delivery system. The eye drops provided pulse entry pattern of drug administration in the eye which is characterized by transient overdose, relatively short period of acceptable dosing, followed by prolonged periods of under dosing. The ocular inserts maintain an effective drug concentration in the target tissues and yet minimize the number of applications consonant with the function of controlled release systems. Limited popularity of ocular inserts has been attributed to psychological factors, such as reluctance of patients to abandon the traditional liquid and semisolid medications, and to occasional therapeutic failures (e.g. unnoticed expulsion from the eye, membrane ruptures etc.). A number of ocular inserts were prepared utilizing different techniques to make soluble, erodible, nonerodible, and hydrogel inserts.[28]

10.8.1 Contact lenses

Contact lenses can absorb water soluble drugs when soaked in drug solutions shown in the figure 11. These drug saturated contact lenses are placed in the eye for releasing the drug for long period of time. The hydrophilic contact lenses can be used to prolong the ocular

residence time of the drugs. In humans, the Bionite lens which was made from hydrophilic polymer (2-hydroxy ethyl methacrylate) has been shown to produce a greater penetration of fluorescein.[29]

Fig. 11: Ocular inserts contact lense.

10.9 Implants

Implants have been widely employed to extend the release of drugs in ocular fluids and tissues particularly in the posterior segment. Implants can be broadly classified into two categories based on their degradation properties: (1) biodegradable and (2) nonbiodegradable. With implants, the delivery rate could be modulated by varying polymer composition. Implants can be solids, semisolids or particulate-based delivery systems (4). Biodegradable polymers can be used to form solid or injectable implants, or they can be used to encapsulate particular systems as nano and microparticles. Particulate systems can be injected through thin needles and have different behavior and distribution in the ocular media depending on their size and composition. Polymers can be devised as viscous or semisolid materials that can be localized within the eye and used as a slow-release intraocular implant after a simple injection. Biodegradable polymers include poly lactic acid (PLA), poly glycolic acid (PGA), poly (lactic-coglycolic acid) (PLGA). Once implanted, bulk erosion occurs causing a burst of encapsulated drug. This phenomenon takes place following the cleavage of polymeric chains by enzymatic and nonenzymatic hydrolysis. These devices can be manufactured in various shapes including rods, plugs, pellets, discs, and sheets. Accordingly, they can be implanted into the anterior chamber, the vitreous cavity through the pars plana, or into the intrascleral space. Degradation of polycaprolactones (PCL) by cleavage of the esther bond produces small polymeric fragments that diffuse from the matrix and undergo phagocytosis. Drug

release from PCL porous reservoir can be obtained for more than 250 days with zero-order kinetics. Polyanhydrides are degraded by surface erosion and have very good biocompatibility.[30,31]

10.10 Drug device combination products

An ophthalmic drug device combination product is constituted, in most cases, of two components. One is a pharmaceutical dosage form containing the active ingredient(s) and the other is a device that will activate, or facilitate the penetration of the active ingredient(s) from the dosage form into a particular region of the eye. Some examples of these devices are those that generate waveforms (heat or light). One ophthalmic drug device combination product recently approved by FDA is verteporfin for injection, which is associated with a nonthermal red light activation used in the treatment of age-related macular degeneration.[32]

11. Novel ophthalmic dosage forms: (Nanotechnology based ocular drug delivery)

In a last few decades, many approaches have been utilized for the treatment of ocular diseases. Nanotechnology based ophthalmic formulations are one of the approaches which is currently being pursued for both anterior, as well as posterior segment drug delivery. Nanotechnology based systems with an appropriate particle size can be designed to ensure low irritation, adequate bioavailability, and ocular tissue compatibility. Several nanocarriers, such as nanoparticles, nanosuspensions, liposomes, nanomicelles and dendrimers have been developed for ocular drug delivery. Some of them have shown promising results for improving ocular bioavailability.

11.1 Colloidal systems

Colloidal dosage forms have been widely studied and employed in the field of ocular drug delivery. These dosage forms include liposomes, nanoparticles, microemulsions, nanoemulsions, etc. Advantages of colloidal dosage forms include sustained and controlled release of the drug at the targeted site, reduced frequency of administration, and ability to overcome blood-ocular barriers.[6] Encapsulation of drugs in these colloidal carriers can also significantly enhance permeation across the membrane and prevent degradation by the ocular enzymes. Such biodegradable carriers can be developed as an alternative to the implants prepared from nonbiodegradable polymers, which has to be removed surgically after a certain period of time.[33,34] Although very promising, commercial development of these colloidal systems remains limited because of the complexity of their manufacture, particularly in relation to stability problems during sterilization, which are not offset by substantial

improvements in pharmacokinetic and pharmacologic performance.[22] Temperatures required for autoclaving can cause irreversible damage to colloidal systems, while filtration is only applicable to microparticulates with a size less than 0.2 μm [23] shown in figure 12.

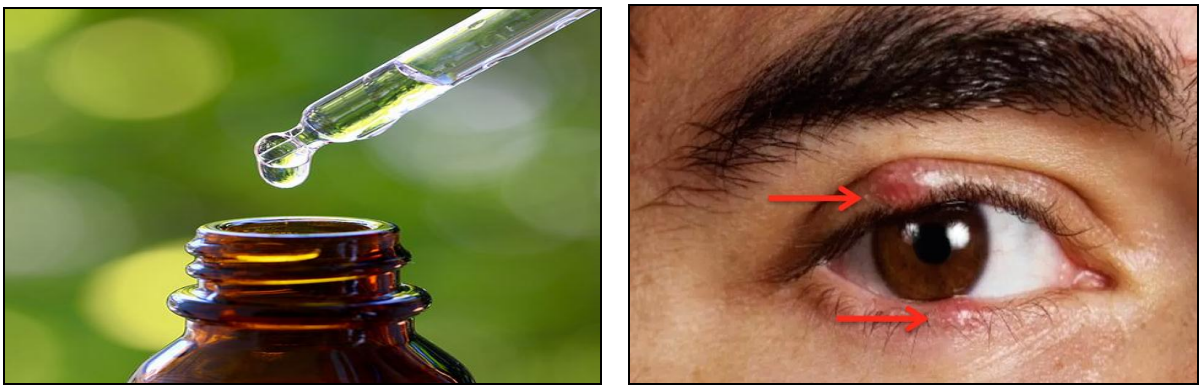

Fig. 12: Nanotechnology based ocular drug delivery.

11.2 Microemulsion

Due to their intrinsic properties and specific structures, microemulsions are a promising dosage form for the natural defense of the eye. Indeed, because they are prepared by inexpensive processes through auto emulsification or supply of energy and can be easily sterilized, they are stable and have a high capacity of dissolving the drugs shown in figure 13. The *in vivo* results and preliminary studies on healthy volunteers have shown a delayed effect and an increase in the bioavailability of the drug. The proposed mechanism is based on the adsorption of the nanodroplets representing the internal phase of the microemulsions, which constitutes a reservoir of the drug on the cornea and should then limit their drainage.[35,36]

Fig. 13: Microemulsion based ocular drug delivery.

11.3 Nanosuspensions

Nanosuspensions can be defined as sub-micron colloidal systems that consist of poorly watersoluble drug, suspended in an appropriate dispersion medium stabilized by surfactants shown in the figure 14. Usually nanosuspensions consist of colloidal carriers like polymeric resins which are inert in nature. They help in enhancement of drug solubility and thus bioavailability. Unlike microemulsions, they are non irritant. Charge on the surface of nanoparticles facilitates their adhesion to the cornea.[32]

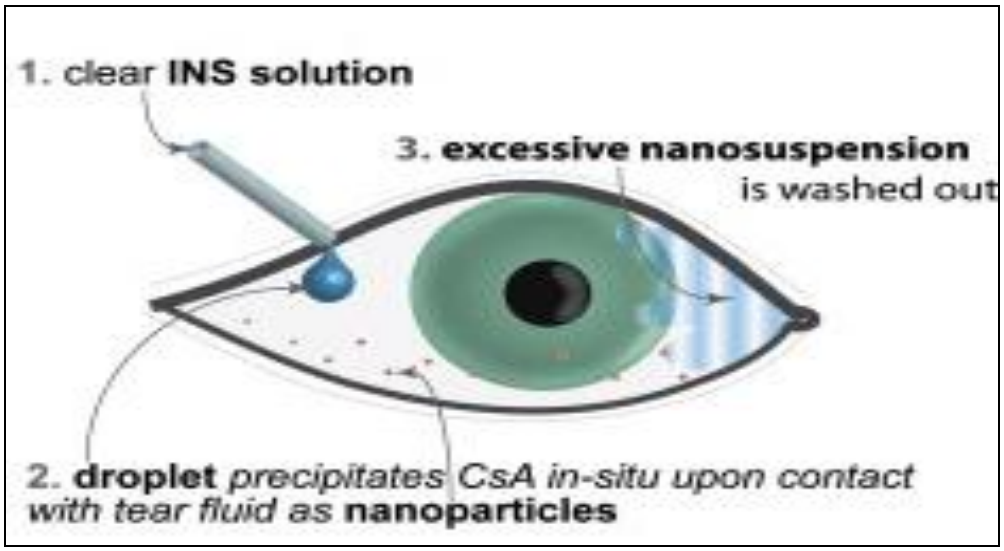

Fig. 14: Microemulsion based ocular drug delivery.

11.4 Hydrogels

Aqueous gels (hydrogels) consist of high molecular weight, hydrophilic, cross-linked polymer or co-polymers that form a three-dimensional network in water shown in the figure 15. These gels have been shown to combine significantly longer residence time in the cul-de sac with increased drug bioavailability. Typical gelling agents include cellulose derivatives, polyvinyl alcohol, hyaluronic acid and carbomer. The in situ forming gels are viscous liquids that shift to a gel phase upon exposure to physiological conditions. These systems are more acceptable for patients since they are administered into the eye as a solution, after which they undergo transition into a gel. Studies have shown that the precorneal residence times of some in situ gelling system can be several hours.[38,39] The polymers used for these gelling system exhibit reversible phase transitions. The change in viscosity can be due to a change in pH, temperature or ionic strength.[37] *In situ* gel forming materials include gallan gum, poloxamer and cellulose acetate phthalate latex.

Fig. 15: Hydrogel pad based ocular drug delivery.

11.5 Nanoparticles and Microparticles

Particulate polymeric drug delivery systems include micro and nanoparticles. The upper size limit for microparticles for ophthalmic administration is about 5-10 mm. Above this size, a scratching feeling in the eye can result after ocular application. Microspheres and nanoparticles represent promising drug carriers for ophthalmic application. The binding of the drug depends on the physicochemical properties of the drugs, as well as of the nano- or micro-particle polymer. After optimal drug binding to these particles, the drug absorption in the eye is enhanced significantly in comparison to eye drops. Particulates such as nanoparticles, nanocapsules, submicron emulsions, nanosuspensions improved the bioavailability of ocularly applied drugs.[40-42]

11.6 Liposomes

Liposomes are phospholipid-lipid vesicles for targeting drugs to the specific sites in the body. They provide controlled and selective drug delivery and improved bioavailability and their potential in ocular drug delivery appears greater for lipophilic than hydrophilic compounds. Liposomes offer the advantage of being completely biodegradable and relatively nontoxic but are less stable than particulate polymeric drug delivery systems. Liposomes were found to be a potential delivery system for administration of a number of drugs to the eye.[43 – 44]

11.7 Niosomes

In order to circumvent the limitations of liposomes, such as chemical instability, oxidative degradation of phospholipids, cost and purity of natural phospholipids, niosomes have been

developed as they are chemically stable compared to liposomes and can entrap both hydrophilic and hydrophobic drugs. They are nontoxic and do not require special handling techniques.[45]

11.8 Microneedle

Microneedle had shown prominent in vitro penetration into sclera and rapid dissolution of coating solution after insertion while in vivo drug level was found to be significantly higher than the level observed following topical drug administration like pilocarpine.

11.9 Dendrimer

Dendrimers can successfully used for different routes of drug administration and have better water-solubility, bioavailability and biocompatibility shown in the figure 16. It's based on the influence of size, molecular weight and number of amine, carboxylate and hydroxyl surface groups in several series of dendrimers. The residence time was longer for the solutions containing dendrimers with carboxylic and hydroxyl surface groups.[48,49]

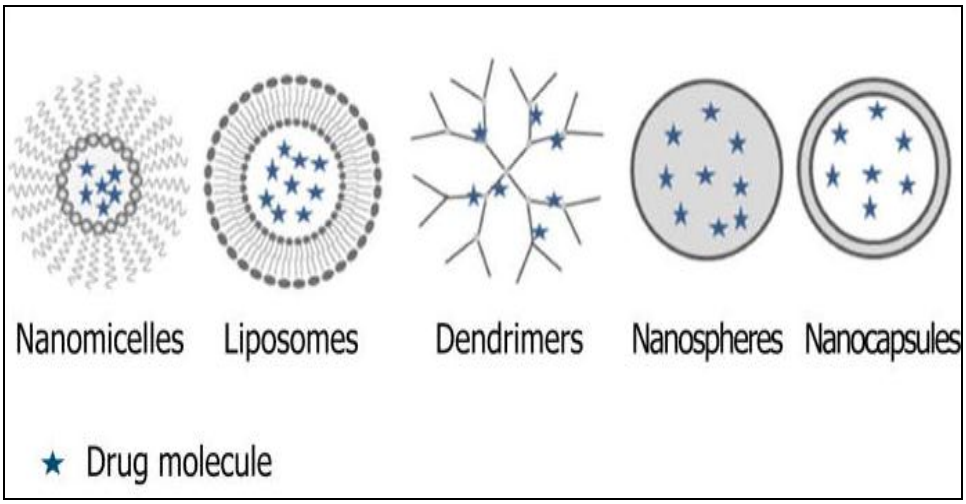

Fig. 16: Nanotechnology based ocular drug delivery.

11.10 Ocular iontophoresis

Iontophoresis is the process in which direct current drives ions into cells or tissues. When iontophoresis is used for drug delivery, the ions of importance are charged molecules of the drug.[46] If the drug molecules carry a positive charge, they are driven into the tissues at the anode; if negatively charged, at the cathode shown in the figure 17. Ocular iontophoresis offers a drug delivery system that is fast, painless and safe; and in most cases, it results in the delivery of a high concentration of the drug to a specific site. Increased incidence of bacterial

keratitis, frequently resulting in corneal scarring, offers a clinical condition that may benefit from drug delivery by iontophoresis. Iontophoretic application of antibiotics may enhance their bactericidal activity and reduce the severity of disease; similar application of anti-inflammatory agents could prevent or reduce vision threatening side effects.[47] But the role of iontophoresis in clinical ophthalmology remains to be identified.

Fig. 17: Treatment via ocular ionotophoresis.

11.11 Ultrasound

Ultrasound-mediated drug delivery has also received attention in recent years shown in the figure 18. Delivery of beta-blockers such as atenolol and timolol, was attempted with ultrasound application (20 kHz for 1 h) across cornea in the treatment of glaucoma. Corneal permeability of these compounds has been significantly enhanced with ultrasound.[50]

Fig. 18: Treatment via ocular ultrasound.

12. CONCLUSION

A few new products have been commercialized as a result of the research into the ophthalmic drug delivery. An ideal system should be able to achieve an effective drug concentration at the target tissue, while minimizing systemic exposure. In addition, the system should be comfortable and easy to use. Major improvements are required in each of the technologies discussed in this review. An ideal ophthalmic formulations should be able to achieve an effective drug concentration at the target tissue for an extended period of time, while minimizing systemic exposure. However, all systems have disadvantages associated with them. Hence there is a need for polymer pattern in which drug could be trapped physically to prolong drug residence time from corneal surface and preserve visual activity. It has been found from literature survey that ocular delivery based formulations have great applications for local treatment of eye disease with relatively lesser side effects as compared to other route of drug delivery. The novel advanced delivery systems offer more protective and effective mean of therapy for the nearly inaccessible diseases or syndromes of eyes. Progress in the field of ocular drug delivery has been established recently with controlled loading and sustained release.

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