A REVIEW ON OCULAR DRUG DELIVERY SYSTEM

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ABSTRACT

The purpose of this review is giving a current update of the knowledge in this field of ocular drug delivery .The ocular drug delivery has been a major challenge to drug delivery scientists mainly due to its unique anatomy and physiology. One of the major problem encountered by the conventional ocular dosage forms include the rapid precorneal drug loss due to its nasolacrimal drainage ,tear turnovers and drug dilution resulting in poor bioavailability .These efforts lead to development of novel drug delivery dosage forms such as nanoparticles,liposome ,ocuserts,and mucoadhesive formulations.Controlled drug delivery system offer many advantage such as improving drug bioavailability ,reducing toxicity and decreasing dosage frequency .Designing noninvasive sustained drug delivery system and exploring the feasibility of topical applications to deliver drug to the posterior segment may drastically improve drug delivery in the years to come.

Key words: *ocular drug delivery ,conventional ocular dosage forms,novel drug delivery system nanoparticles,liposome ,mucoadhesive formulation ,controlled drug delivery system*

INTRODUCTION

Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientist. The anatomy, physiology, and biochemistry of the eye render this organ highly impervious to foreign substances. The eye is a complex organ with an unique anatomy and physiology. The structure of eye can be divided into two main parts: anterior segment and posterior segment (Figure 1).The anterior and posterior segment of eye is affected by various vision threatening diseases. Diseases affecting anterior segment include, but not limited to glaucoma, allergic conjunctivitis, anterior uveitis and cataract. While, age related macular degeneration and diabetic retinopathy are the most prevalent diseases affecting posterior segment of the eye.[1]The anatomy of the eye makes it a challenge to deliver therapeutic agents. Due to the blood-retinal barrier (BRB), the eye is resistant to exposure of foreign substances, and pharmaceutical agents trying to reach the intended ocular tissues.[2,3]

The eye offers multiple entry routes through which ocular drugs may be delivered (for review Kang-Mieler et al.)[4] Delivery to the anterior segment of the eye may be achieved through topical and subconjunctival routes, or injected intracamerally. Posterior segment delivery can be achieved topically, systemically, and periocularly (i.e., through sub-Tenon's), via the suprachoroidal space, and via intraocular (i.e., intravitreal) injections. Success of therapeutic drug delivery depends on the delivery site,tissue barriers, and the type of pharmacological agents involved.[5]

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.[6,7] 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 impose a challenge and impede deeper ocular drug permeation.[8] Hence,less than 5% of topically applied dose reaches to deeper ocular tissues.[9]

To overcome the ocular drug delivery barriers and improve ocular bioavailability, various conventional and novel drug delivery systems have been developed such as emulsion, ointments, suspensions, aqueous gels liposomes, dendrimers., contact lenses, microneedles, and in situ thermosensitive gels for the earlier mention ocular diseases. Advances in biomaterials and nanotechnology have led to major growth in research of biodegradable microparticles and nanoparticles, hydrogels and ocular implants, all of which may contain ocular pharmacologic agents thereby providing improved delivery of a variety of medications.Furthermore, sustained release drug therapies may improve the side effects associated with current clinical treatments and lower the overall socio-economic impact of ocular diseases.[10] This review will provide an overview on various conventional and novel ophthalmic drug delivery systems developed to deliver drug to diseased ocular tissues for the treatment of ocular diseases.

OVERVIEW ON ANATOMY AND PHYSIOLOGY OF HUMAN EYE:

Clinically, the eye can be considered to be composed of two segments:

(a) Anterior segment
(b) Posterior segment

Anterior segment consist of front one-third of eye that mainly includes pupil, cornea, iris, ciliary body, aqueous humor, and lens while the posterior segment consists of the back two-thirds of the eye that includes vitreous humor, retina, choroid, macula, and optic nerve.(fig:1)[11,12]

PUPIL: A small opening in the iris is known as a pupil. Its size is controlled with the help of iris. It controls the amount of light that enters the eye.

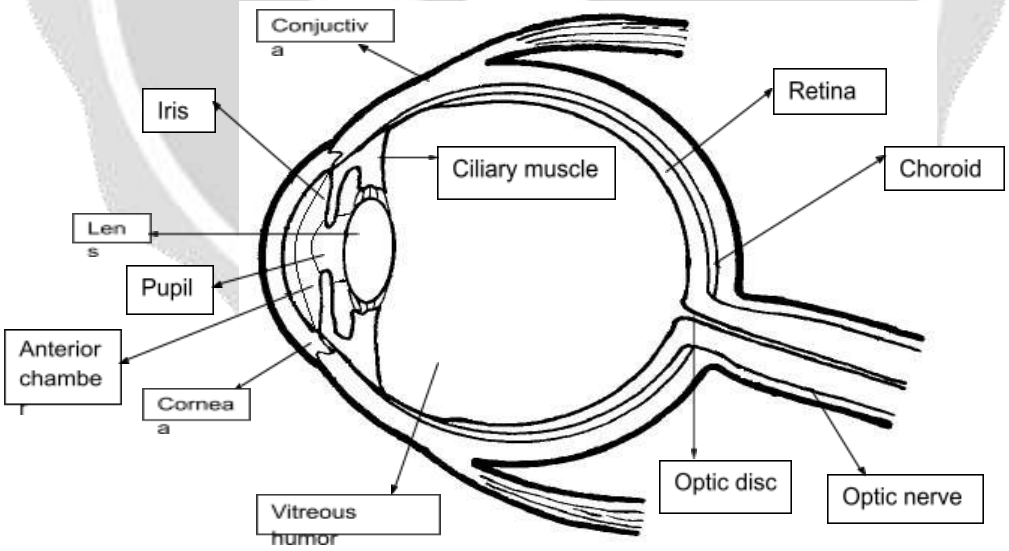


Figure 1; Structure of Human Eye

CORNEA: The cornea is the clear, dome-shaped covering at the front of the eye that lets in light. The cornea covers the pupil and the iris[13].It does not contain any blood vessels. The cornea has five layers antero-posteriorly (Figure 2):

1. Epithelium and its basement membrane –stratified squamous type of epithelium with five to six cell layers of regular arrangement.
2. Bowman's layer – homogeneous sheet of modified stroma.
3. Stroma – consists of approximately 90% of total corneal thickness. Consists of lamellae of collagen, cells and ground substance.

4.Descemet's membrane– the basement membrane of the endothelium.

5. Endothelium – a single layer of cells lining the inner surface of Descemet's membrane.

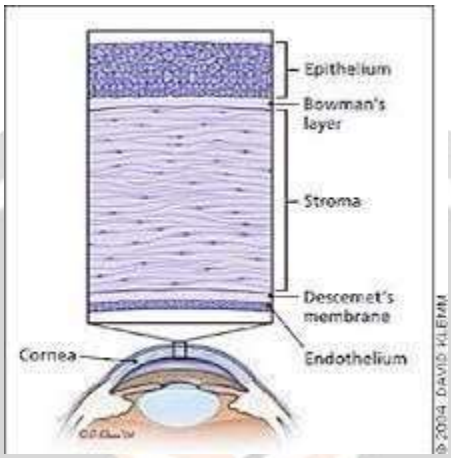


Figure 2:Different layers of Cornea.

SCLERA: The sclera is the tough, white connective tissue that covers most of the outside of the eyeball. The sclera is seen as the white portion of the eye and serves as the protective covering. The optic nerve and blood vessels pass through the sclera in the back of the eye.

IRIS: The iris is the thin, muscular, colored part of the eye. It is located at the front (anterior) of the eye,between the cornea and the lens.[14] The iris opens and closes the pupil (the small central opening) to change the amount of light entering the eye.

CILIARY BODY: The ciliary body lies just behind the iris and extends forward from the choroid. It is the muscular ring of tissue that helps the eye focus. It changes the shape of the lens so it can focus on near or far objects.[15].The ciliary body contains cells that make aqueous humor, which is the clear fluid in the front of the eye between the cornea and lens.

LENS: The lens is a transparent structure in the inner part of the eye, which lies directly behind the cornea and iris.The lens changes shape to allow the eye to focus on objects. The lens focuses light rays on the retina.[16]

THE AQUEOUS HUMOUR: The aqueous humour is an optically clear solution of electrolytes (in water) that fills the space between the cornea and the lens. Normal volume is 0.3 ml. Its function is to nourish the lens and cornea.

VITREOUS HUMOUR: Is a transparent gel consisting of a three-dimensional network of collagen fibres with the interspaces filled with polymerized hyaluronic acid molecules and water. It fills the space between the posterior surface of the lens, ciliary body and retina.

RETINA: It is a light-sensitive layer that consists of numerous nerve cells. It converts images formed by the lens into electrical impulses. These electrical impulses are then transmitted to the brain through optic nerves.
There are two main types of photoreceptors in the retina – the rods and the cones. In the fovea centralis the only photoreceptors are cones, which are responsible for acute vision (visual details) and colour vision. The rods are responsible for vision in poor (dim) light and for the wide field of vision.

CHOROID: The choroid, also known as the choroidea or choroid coat, is a part of the uvea, the vascular layer of the eye, and contains connective tissues, and lies between the retina and the sclera. The choroid provides oxygen and nourishment to the outer layers of the retina. Along with the ciliary body and iris, the choroid forms the uveal tract.

CONJUCTIVA: The conjunctiva is involved in the formation and maintenance of the precorneal tear film and in the protection of the eye.It is a thin, vascularised mucous membrane that lines the posterior surface of the eyelids and outer region of the cornea.The conjuctival epithelium differs somewhat from that of the cornea,in that it is thicker and possesses mucus-secreting goblet cells. The human conjuctiva is between 2 to 30 time more permeable to drugs than the cornea and it is proposed that loss by this route is a major path for drug clearance.[17]

OPTIC NERVE: The optic nerve is a bundle of more than 1 million nerve fibers. Also known as the second cranial nerve or cranial nerve II (CNII).It transmits sensory information for vision in the form of electrical impulses from the eye to the brain.[18]

BARRIERS TO OCULAR DRUG DELIVERY

The reason why it is difficult to achieve relevant therapeutic doses within the eye is primarily due to the presence of multiple barriers. These barriers can be broadly classified as anatomical barriers and physiological barriers .

Anatomical barriers:

When a dosage form is topically administered there are two routes of entry, either through the cornea or via the non-corneal route. The cornea is a very tight multilayered tissue that is mainly composed of five sections: epithelium, bowman's membrane, stroma, descemet's membrane and endothelium. Out of these it's the epithelium which acts as the principal barrier. These 5-6 layers of columnar epithelial cells with very tight junctions create high paracellular resistance of 12-16 kΩ.cm.[19] It acts as a major barrier to hydrophilic drug transport through intercellular spaces. On the other hand stroma, which consists of multiple layers of hexagonally arranged collagen fibers containing aqueous pores or channels allow hydrophilic drugs to easily pass through but it acts as a significant barrier for lipophilic drugs. Thus for a drug to have optimum bioavailability, it should have the right balance between lipophilicity and hydrophilicity. The remaining layers are leaky and do not act as significant barriers.
Non-corneal route bypasses the cornea and involves movement across conjunctiva and sclera. This route is important especially for large and hydrophilic molecules such as peptides, proteins and siRNA.[20] The conjunctiva is more permeable than cornea especially for hydrophilic molecules due to much lower expression of tight junction proteins relative to corneal epithelium.

Physiological barriers

The eye's primary line of defense is its tear film. Bioavailability of topically administered drugs is further reduced by precorneal factors such as solution drainage,tear dilution, tear turnover, and increased lacrimation [21].The lacrimal fluid is an isotonic aqueous solution containing a mixture of proteins (such as lysozyme) as well as lipids. Following topical application, lacrimation is significantly increased leading to dilution of administered dose. This in turn lowers drug concentration leading to diminished drug absorption. Rapid clearance from the precorneal area by lacrimation and through nasolacrimal drainage and spillage further reduces contact time between the tissue and drug molecules. This in turn lowers the exact time for absorption leading to reduced bioavailability.Thus drugs administered as eye drops need to be isotonic and nonirritating to prevent significant precorneal loss.

Drug and dosage form related factors

Solubility: Solubility is dependent on the pKa of the drug and pH of the solution. With these parameters one can determine the ratio of ionized to unionized molecules. Usually unionized molecules can readily permeate biological membranes. In case of ionized species, their charge can also affect permeability across the cornea. The corneal

epithelium bears a negative charge at the pH of lachrymal fluid and hence cationic species tend to penetrate at a faster rate to their anionic counterparts.

Lipophilicity: As previously mentioned, lipophilic drug tend to permeate easily through the epithelial layers of cornea. But the hydrophilicity of the inner layer of cornea (stroma) requires higher hydrophilicity for optimal permeation. Partition coefficient (Log P) value ranging from 2-4 is found to result in optimum corneal permeation.[22]

Molecular weight and size: The diameter of the tight junctions present on corneal epithelium is less than 2 nm. Thus, molecules having molecular weight less than 500 Dalton are able to permeate readily.[23]The conjunctiva has larger paracellular pore diameter thus allowing permeation of larger molecules such as small and medium size peptides (5000-10000 Daltons)[24]

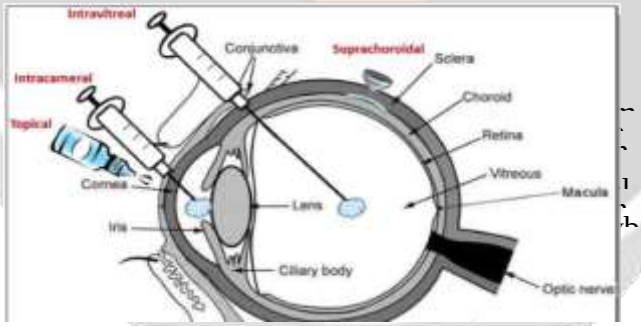
OCULAR DRUG DELIVERY ROUTES

There are several possible routes of drug delivery into the ocular tissues (Fig. 3). The selection of the route of administration depends primarily on the target tissue.

associated with topical administration is, A major fraction of drug is lost by lacrimation, tear dilution, nasolacrimal drainage and tear turnover. Such precorneal losses result in very low ocular bioavailability. Typically, less than 5% of the total administered dose reaches aqueous humor.[27]

Oral/ Systemic Administration:

Oral delivery or in combination with topical delivery[28] 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 injectable route.These include various classes of drugs such as analgesics[29], antibiotics, antivirals, antineoplastic agents, and omega-6 fatty acids[30].A major drawback associated with systemic administration is only 1–2% of administered drug reaches to vitreous cavity.



Intra Vitreal Injection:

Intravitreal injection (IVI) involves delivering of the drug formulation directly into the vitreous humor through pars plana. This method provides direct access to the vitreous and avoids both the cornea and also the sclera blood vessels. Formulations such as solution, suspension or a depot formulation can be administered through this route.A volume between 20-100 microliter can be injected .Unlike other routes, intravitreal injection offers higher drug concentrations in vitreous and retina.

Intracameral injections:

Intracameral route is similar to intravitreal injections but this injection delivers drug to the anterior chamber,with very limited access to the posterior segment. It is generally employed for anterior segment procedures such as

cataract surgery.[31] It is an efficient and often a more cost-effective method of delivering antibiotics relative to topical antibiotics and antifungal agents.[32]

Sub-conjunctival injections:

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. This injection delivers the drug beneath the conjunctival membrane that lines the inner surface of eyelid.

Periocular route:

Periocular route has been considered as the most promising and efficient route for administering drugs to posterior eye segment. Periocular refers to the region surrounding the eye. It is a broad term which includes peribulbar, posterior juxtascleral, retrobulbar, subtenon and subconjunctival routes. Example: peril ocular steroid injection involves placement of steroid around the eye to treat intraocular inflammation or swelling of the eye.

Table 1:Summary of Routes of Administration and Benefits in Ocular Delivery

ROUTE	BENEFITS
Topical	High patient compliance, self-administrable and noninvasive
Oral/Systemic	Patient compliant and noninvasive route of administration
Intravitreal	Direct delivery to vitreous and retina, sustains drug levels, evades BRB
Intracameral	Provides higher drug levels in the anterior chamber, eliminates usage of topical drops, reduces corneal and systemic side effects seen with topical steroid therapy
Subconjunctival Ssubtenon	Delivery to anterior and posterior segment, site for depot formulations High vitreal drug levels, relatively noninvasive, fewer complications unlike intravitreal delivery.
Retrobulbar	Administer high local doses of anesthetics, more effective than peribulbar, minimal influence on IOP.
Posterior Juxtasceral	Safe for delivery of depot formulations, sustain drug levels up to 6 months to the macula, avoids risk of endophthalmitis and intraocular damage.

FORMULATION APPROACHES OF OCULAR DRUG DELIVERY SYSTEM

Conventional Ocular Drug Delivery System

There is a wide range of ophthalmic products available in the market out of which around 70% of prescriptions include conventional eye drops. The reasons may be due to ease of bulk scale manufacturing, high patient acceptability, drug product efficacy, stability and cost effectiveness.

Topical liquid/solution eye drops

Topical drops are the most convenient, safe, immediately active, patient compliant and noninvasive mode of ocular drug administration. Solutions/eye drops also have disadvantages: the very short time the solution stays at the eye surface, its poor bioavailability (a major portion, i.e., 75% is lost via nasolacrimal drainage), the instability of the dissolved drug and the necessity of using preservatives. A considerable disadvantage of using eye drops is the rapid elimination of the solution and their poor bioavailability.Therefore, to improve drug contact time, permeation and ocular bioavailability; various additives may be added to topical eye drops such as viscosity enhancers, permeation enhancers and cyclodextrins.[33]

Emulsions:

An emulsion based formulation approach offers an advantage to improve both solubility and bioavailability of drugs. There are two types of emulsions which are commercially exploited as vehicles for active pharmaceuticals: oil in water (o/w) and water in oil (w/o) emulsion systems. For ophthalmic drug delivery,o/w emulsion is common and widely preferred over w/o system. The reasons include less irritation and better ocular tolerance of o/w emulsion.[34] Some current examples of available medicines based on the technology of emulsion are the AzaSite®, Refresh Endura® and RestasisTM.[35-38]

Suspensions:

Suspension may be defined as dispersion of finely divided insoluble API in an aqueous solvent consisting of a suitable suspending and dispersing agent. In other words, the carrier solvent system is a saturated solution of API. Suspension particles retain in precorneal pocket and thereby improve drug contact time and duration of action relative to drug solution. Duration of drug action for suspension is particle size dependent. Smaller size particle replenishes the drug absorbed into ocular tissues from precorneal pocket. While on the other hand, larger particle size helps retain particles for longer time and slow drug dissolution. Thus, an optimal particle size is expected to result in optimum drug activity. Several suspension formulations are marketed worldwide to treat ocular bacterial infections. TobraDex suspension is one of the widely recommended commercial products for subjects responding to steroid therapy.[39]

Eye ointments

Ointments are usually formulated using mixtures of semisolid and solid hydrocarbons (paraffin) which have a melting or softening point close to body temperature and are nonirritating to the eye. Ointments may be simple bases, where the ointment forms one continuous phase, or compound bases where a two-phased system (e.g., an emulsion) is employed. The medicinal agent is added to the base either as a solution or as a finely micronized powder. Upon instillation in the eye, ointments break up into small droplets and remain as a depot of drug in the cul-de-sac for extended periods.Ointments are therefore useful in improving drug bioavailability and in sustaining drug release. Although safe and well-tolerated by the eye, ointments suffer with relatively poor patient compliance due to blurring of vision and occasional irritation.[40]

Novel Ocular Drug Delivery System

In the novel drug delivery system various approaches are used. These delivery systems delay the elimination of active ingredient from eye and also improve corneal penetration of drug molecule.[41]

VESICULAR SYSTEM

Liposomes:

Liposomes are the microscopic vesicles composed of one or more concentric lipid bilayers, separated by water or aqueous buffer compartments. Liposomes possess the ability to have an intimate contact with the corneal and conjunctival surfaces, which increases the probability of ocular drug absorption. [42] This ability is especially desirable for drugs that are poorly absorbed, the drugs with low partition coefficient, poor solubility, or those with medium to high molecular weights.[43] The size of liposomes usually range from 0.08 to 10.00 μm and based on the size and phospholipid bilayers, liposomes can be classified as small unilamellar vesicles (10–100 nm), large unilamellar vesicles (100–300 nm) and multilamellar vesicles (contains more than one bilayer).[44] For ophthalmic applications, liposomes represent ideal delivery systems due to excellent biocompatibility, cell membrane like structure and ability to encapsulate both hydrophilic and hydrophobic drugs. Formulated and evaluated soft contact lenses coated with ciprofloxacin entrapped in liposome.

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. Niosomes are bilayered structural vesicles made up of nonionic surfactant which are capable of encapsulating both lipophilic and hydrophilic compounds. Niosomes reduce the systemic drainage and improve the residence time, which leads to increase ocular bioavailability. They are nonbiodegradable and nonbiocompatible in nature. In a recent approach to deliver

cyclopentolate, niosomal formulation was developed. It released the drug independent of pH, resulting in significant enhancement of ocular bioavailability.

CONTROLED DRUG DELIVERY SYSTEM

Intraocular Implants:

Intraocular administration of the implants always requires minor surgery. In general, they are placed intravitreally, at the pars plana of the eye (posterior to the lens and anterior to the retina).[45-46] Although this is an invasive technique, the implants have the benefit of (1) by-passing the blood-ocular barriers to deliver constant therapeutic levels of drug directly to the site of action, (2) avoidance of the side effects associated with frequent systemic and intravitreal injections, and (3) smaller quantity of drug needed during the treatment. The ocular implants are classified as nonbiodegradable and biodegradable devices. Nonbiodegradable implants can provide more accurate control of drug release and longer release periods than the biodegradable polymers do, but the nonbiodegradable systems require surgical implant removal with the associated risks. The ocular implants are summarized in Table 2. Implants can be in the form of solid, semi-solid, or particulate-based delivery systems.[47]It is an alternative to repeated injections, because they increase half-life of the drug and may help to minimize peak plasma level; they might improve patient acceptance and compliance. It has disadvantages like side effects: the insertion of these devices is invasive and with associated ocular complications (retinal detachment and intravitreal hemorrhage for intravitreal implant).

Table 2:Description of current and potential ophthalmic implants

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

Dendrimers:

Dendrimers are characterized as nanosized, highly branched, star shaped polymeric systems. These branched polymeric systems are available in different molecular weights with terminal end amine, hydroxyl or carboxyl functional group[48].Selection of molecular weight, size, surface charge,molecular geometry and functional group are critical to deliver drugs. The highly branched structure of dendrimers allows incorporation of wide range of drugs, hydrophobic as well as hydrophilic.Poly (amidoamine) (PAMAM) dendrimers are widely employed in ocular drug delivery.[49]

Cyclodextrin:

Cyclodextrins (CDs) are cyclic oligosaccharides capable of forming inclusion complexes with many guest molecules.[50] CD complexes are reported to increase corneal permeation of drugs like dexamethasone, dexamethasone acetate, cyclosporine and pilocarpine resulted in higher bioavailability than the conventional eye drops.[51] Due to inclusion, the free drug is not available, so drugs with inherent irritant properties can be successfully delivered by this approach. CD molecules are inert in nature and were found to be non irritant to the human and

animal eye.[50]

Contact Lenses:

Contact lenses are thin, and curved shape plastic disks which are designed to cover the cornea.[52] After application, contact lens adheres to the film of tears over the cornea due to the surface tension. Drug loaded

contact lens have been developed for ocular delivery of numerous drugs such as β-blockers, antihistamines and antimicrobials. It is postulated that in presence of contact lens, drug molecules have longer residence time in the post-lens tear film which ultimately led to higher drug flux through cornea with less drug inflow into the nasolacrimal duct. Usually, drug is loaded into contact lens by soaking them in drug solutions. These soaked contact lenses demonstrated higher efficiency in delivering drug compared to conventional eye drops.

Collagen Shield:

Collagen shield basically consist of cross linked collagen, fabricated with foetal- calf skin tissue and developed as a corneal bandage to promote wound healing. Topically applied antibiotic conjugated with the shield is used to promote healing of corneal ulcers.Because of its structural stability, good biocompatibility and biological inertness, collagen film proved as a potential carrier for ophthalmic drug delivery system. Collagen ophthalmic inserts are available for delivery of pilocarpine to the eye.[53]

Figure 4:Collagen Shield

Microemulsion:

Microemulsion is stable dispersions of water and oil, facilitated by a combination of surfactant and co-surfactant in a manner to reduce interfacial tension. Microemulsion improves the ocular bioavailability of the drug and reduces frequency of the administration. These systems are usually characterized by higher thermodynamic stability, small droplet size (~100 nm), and clear appearance.[54] An oil in water system consisting of pilocarpine using lecithin, propylene glycol, PEG 200 as surfactant/co surfactants, and isopropyl myristate as the oil phase has been designed, which is nonirritating to the rabbit animal model. Such formulations often provide sustained drug release, thereby reducing frequency of the drug administration.

Nanosuspension:

This can be defined as sub-micron colloidal system which consists of poorly water-soluble drug, suspended in an appropriate dispersion medium stabilized by surfactants. Nanosuspension usually consists of colloidal carriers like polymeric resins which are inert in nature. Nanosuspension improves the ocular bioavailability of the drug by prolonging the contact time. Charge on the surface of nanoparticles facilitates its adhesion to the cornea[55]. It provides several advantages such as sterilization, ease of eye drop formulation, less irritation, increase precorneal residence time and enhancement in ocular bioavailability of drugs which are insoluble in tear fluid.[56]

Microneedles:

Microneedles enable minimally invasive delivery of free or encapsulated drug. Clearside Biomedical (Alpharetta, GA, USA) developed a microneedle and injector that administers a suprachoroidal injection of corticosteroid triamcinolone acetonide (CLS-TA), which is Clearside Biomedical's proprietary suspension of TA. The injector allows for consistent insertion of microneedle into the suprachoroidal space. Thus, this method reduces the risks commonly associated with intravitreal injections, including potential for retinal damage.[57]. Due to the small surface

area of the microneedle, this system is limited to small molecules and microneedles cannot always deliver a therapeutic dose.

Mucoadhesive polymers/ Dosage forms:

This approach relies on vehicles containing polymers which will attach, via noncovalent bonds, to conjunctival mucin. Mucoadhesive polymers are usually macromolecular hydrocolloids with numerous hydrophilic functional groups such as carboxyl-,hydroxyl-, amide and sulphate, capable of establishing electrostatic interactions. The bioadhesive dosage form showed more bioavailability of the drug as compared to conventional dosage forms. Thermes et al evaluated the effect of polyacrylic acid as a bioadhesive polymer on the ocular bioavailability of timolol. It was found that polyacrylic acid prolonged the effect of timolol. Subsequently, several natural and synthetic polymers have been screened for their ability to adhere to mucin epithelial surfaces; however, little attention has been paid to their use in ophthalmic drug delivery.[58]

Ocular Insert:

The ocular inserts overcome this disadvantage by providing with more controlled, sustained, and continuous drug delivery by maintaining an effective drug concentration in the target tissues and yet minimizing the number of applications. It causes accurate dosing of the drug. It has disadvantages like patient incompliance, difficulty with self-insertion, foreign body sensation, and inadvertent loss from the eye. A number of ocular inserts were prepared utilizing different techniques to make soluble, erodible, nonerodible, and hydrogel inserts [Table 3]

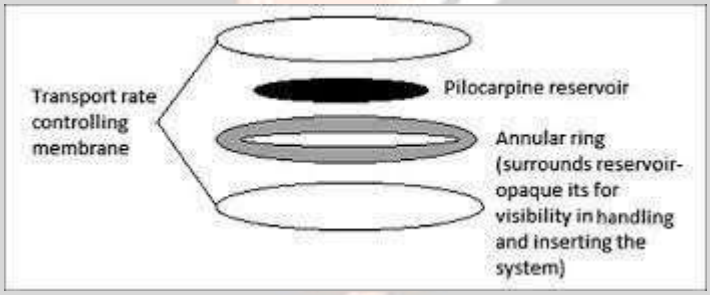


Figure 5:Ocusert

Table 3:Various types of ophthalmic inserts.

Types	Description
Erodible inserts	The fabrication polymer is hydrophobic but biodegradable. Drug is released through the erosion of the surface of the insert.
Soluble inserts	The fabrication polymer is hydrophilic and water soluble.
	Drug release characteristics:Diffusion control for soluble drugs.Dissolution control for less soluble drugs
Hydrophilic but water insoluble Inserts	The fabrication polymer is hydrophilic but water-insoluble . Drug release characteristics: Diffusion control for soluble drugs Dissolution control for less soluble drugs
Inserts using osmotic system	A polymeric matrix in which the drug is dispersed as discrete small domains. Upon placement in the cul-de-sac, tears are imbibed into the matrix because of an osmotic pressure gradient created by the drug, where upon the drug is dissolved and released

Membrane-controll ed diffusional inserts	The drug core is surrounded by a hydrophobic polymer membrane; this controls the diffusion of the drug from the core to the outside

In-situ gelling System/Phase transition System:

In-situ hydrogels refer to the polymeric solutions which undergo sol-gel phase transition to form viscoelastic gel in response to environmental stimuli. Gel formulations usually incorporate various phase changing polymers, i.e., after administration, polymer phase changes into semi-solid or solid matrix in order to achieve sustained drug delivery. This change in polymer phase maybe, ion concentration, pH or temperature dependent.[59] . Fluids showing viscoelastic nature are preferred for the usage in gel forming systems. Such systems containing hyaluronic acid, polyacrylic acid and/or chitosan are able to maintain high viscosity under conditions of low shear and low viscosity under high shear rate allowing ease of formulation and application along with sustained delivery.Hydrogels are the polymeric networks that are hydrophilic in nature. These polymers can incorporate large quantities of water and biological fluids into a swollen cross-linked gel system. The hydrogels have the ability to retain hydrophobic and hydrophilic agents both small as well as macromolecules. The polymer network regulates permeation and diffusion characteristics. These polymers can be biodegradable or non-biodegradable and also bio-compatible based on the gelling material. Polysaccharides have been widely used in hydrogels and are considered to be more advantageous over synthetic polymers.[60]

Ocular Iontophoresis:

Iontophoresis is a noninvasive method of transferring ionized drugs through membranes with low electrical current[61-62].The drugs are moved across the membranes by two mechanisms: migration and electro-osmosis.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.[63] If the drug molecules carry a positive charge, they are driven into the tissues at the anode; if negatively charged, at the cathode. 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. 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.

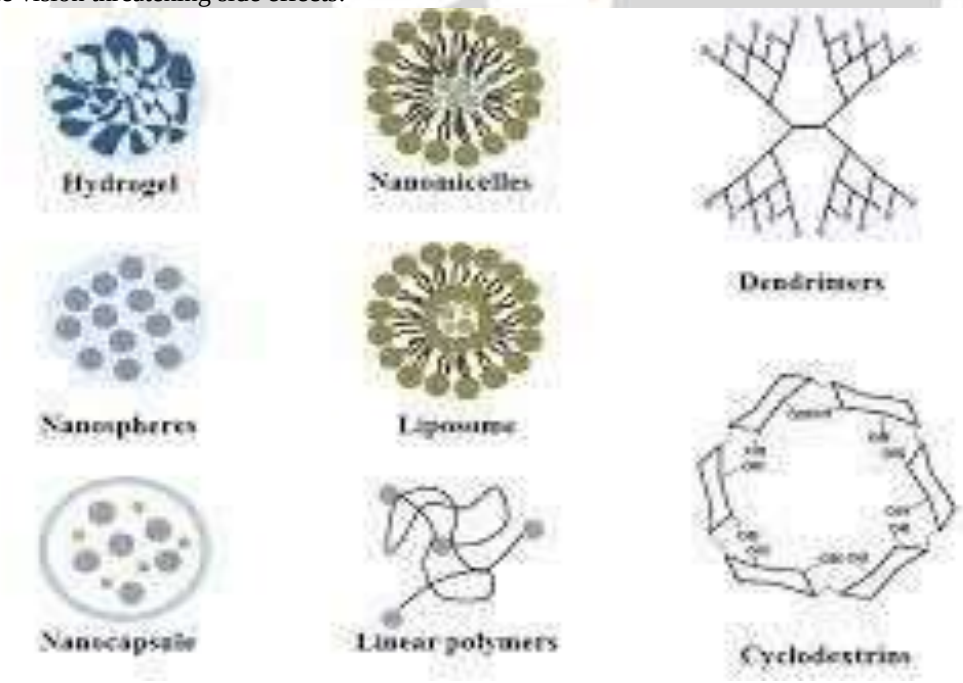


Figure 6:Novel Drug Delivery System

PARTICULATES (NANOPARTICLES AND MICROPARTICLES)

Nanoparticles:

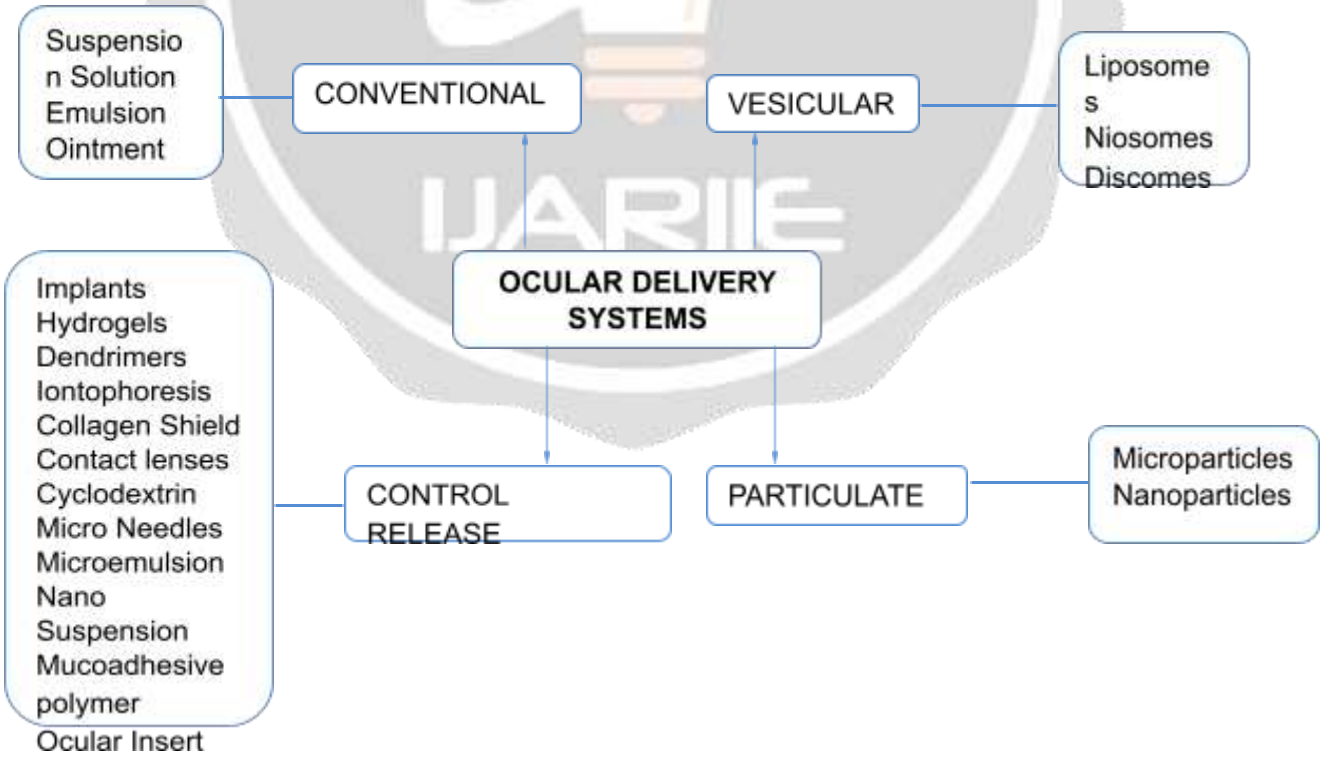
Nanoparticles are colloidal carriers with a size range of 10 to 1000 nm. For ophthalmic delivery, nanoparticles are generally composed of lipids, proteins, natural or synthetic polymers such as albumin, sodium alginate, chitosan, poly (lactide-co-glycolide) (PLGA), polylactic acid (PLA) and polycaprolactone. Drug loaded nanoparticles can be nanocapsules or nanospheres (Figure 6). In nanocapsules, drug is enclosed inside the polymeric shell while in nanospheres; drug is uniformly distributed throughout polymeric matrix.

Nanoparticles represents a promising candidate for ocular drug delivery because of small size leading to low irritation and sustained release property avoiding frequent administration. However, like aqueous solutions, nanoparticles may be eliminated rapidly from precorneal pocket. Hence, for topical administration nanoparticles with mucoadhesive properties have been developed to improve precorneal residence time[64]. Polyethylene glycol (PEG), chitosan and hyaluronic acid are commonly employed to improve precorneal residence time of nanoparticles.

Microparticles:

Microparticles are drug-containing, micron-sized polymeric particles suspended in a liquid medium. Drugs can be physically dispersed in the polymer matrix or covalently bound to the polymer backbone.[65] Upon topical instillation, the particles reside in the ocular cul-de-sac, and the drug is released from the particles through diffusion, chemical reaction, and/or polymer degradation. Microparticles improve precorneal residence time, which leads to continuous and sustain release of the drug. Hence, improved ocular bioavailability of the drug and reduced dosing frequency. It causes irritation to the eye because of the large particle size. Biodegradation, bioadhesion, and biocompatibility are the desired properties for the fabrication polymers of ophthalmic microparticles. The following are examples of published biodegradable microparticles,

- Microspheres of methylprednisolone chemically linked to hyaluronate esters; • Pilocarpine-loaded albumin or gelatin microspheres;
- Acyclovir-loaded chitosan microspheres.



Flow chart of Different drug delivery systems for ocular therapy

CONCLUSION

Drug delivery to targeted ocular tissues has been a major challenge to ocular scientist ,for decades .Over last several years ,attempts have been made to improve ocular bioavailability through manipulation of product formulation such as viscosity enhancer and application of mucoadhesive polymers. A few new products have been commercialized as a result of the research into ophthalmic drug delivery .The performance of these new products ,however ,is still far from being perfect. Major improvement are required in each of the technologies discussed in this review .Some approaches are relatively easy to manufacture ,but are limited in their ability to provide sustained drug release .Other approaches are promising with regard to sustained drug release but are difficult to manufacture. However ,there is still need of developing a carrier system which could reach targeted ocular tissue ,including back of the eye tissue.With the current pace of ocular research and efforts being made and put in,it is expected to result in a topical drop formulation that retains high precorneal residence time ,avoids non-specific drug tissue accumulation and deliver therapeutic drug levels into targeted ocular tissue.

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61}Fig 1: Structure of human eye :https://encrypted-tbn0.gstatic.com/images?q=tbn:ANd9GcR5bhCMqsacIBcdolD0e7hgxJBtX5_ DmgR0xg&usqp=CAU

62}Fig 2: Different layer of cornea:https://www.researchgate.net/figure/Corneal-layers-from-anterior-to-posterior-layer-21_fig1_283 345238

63}Fig 3: Route of ocular drug delivery:https://www.researchgate.net/figure/Routes-of-ocular-drug-delivery-14_fig1_344870172

64}Fig 4: Collagen shield:https://images.app.goo.gl/82EBEcxdgNk3eaGB8

65}Fig 5: various types of ophthalmic inserts:https://images.app.goo.gl/m6r4R2WcdsMr4EjHA

66}Fig 6: Novel drug delivery systems:https://images.app.goo.gl/BZHX3nXVMpwxSYu99