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Review article

Recent Research Innovations In Drug Delivery 'Through And To' Ocular Route

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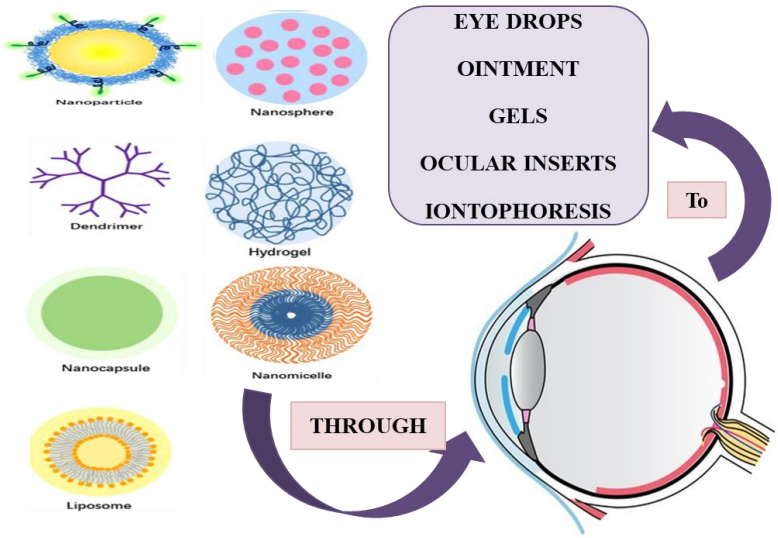
ABSTRACT: Delivery of Drug molecules to the brain is alwaysa challenging task. The main aim of this review is to explorethe ocular route as a powerful region and focus on the various Nano-formulations. Various efforts in ocular drug delivery have been made to improve the bioavailability and to prolong the residence time of topically applied drugs to the eye. Poor bioavailability of drugs from ocular dosage form is mainly due to the tear production, non-productive absorption, transient residence time, and impermeability of corneal epithelium. Though the topical and local application are still an acceptable and preferred way to achieve a therapeutic level of drugs that are used to treat ocular disorders, the primitive ophthalmic solution, suspension, and ointment dosage form are no longer sufficient to combat various ocular diseases. This article reviews the constraints with conventional ocular therapy and explores various novel approaches to improve ocular bioavailability of the drugs, advantages of vesicular approach and the future challenges to render the vesicular system more effective.

KEYWORDS: Ocular, Nano-formulations, Conventional, Through and To, blood supply, nerve supply..

GRAPHICAL ABSTRACT:



1. Introduction

Conventional dosage forms had been used for the management and treatment of various ocular disorders. The conventional dosage forms employed for the management of eye diseases include solutions, suspensions, emulsions, ointments, lotions,

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ocular inserts, contact lenses, paper strips, collagen shields and ophthalmic rods. It is usual that water-soluble drugs are delivered through topical administration in an aqueous solution. The problem associated with conventional dosage forms is that these are unable to cross static and dynamic barriers of the eye to treat posterior segment eye diseases so the conventional dosage forms cannot be targeted efficiently to the posterior segment of the eye[1]. The major deficiencies of these conventional dosage forms include poor ocular drug bioavailability, pulse-drug entry after topical administration, systemic exposure because of nasolacrimal duct drainage, and a lack of effective systems for drug delivery to the posterior segment of ocular tissue. Poor ocular drug bioavailability is the result of ocular anatomical and physiological constraints, which include the relative impermeability of the corneal epithelial membrane, tear dynamics, nasolacrimal drainage, and the high efficiency of the blood-ocular barrier [1].Ocular drug delivery for the treatment of various anterior and posterior eye diseases has been a challenge due to the critical micro-environment that exists in the eye and blood-ocular barriers (blood-aqueous and blood-retinal barrier). The first challenge to delivery is tear drainage which occur in the pre-corneal area (conjunctiva and eyelids) at almost 1.45 min_1, which causes more than 100-folds higher elimination of topically applied drug or drug carrier compared to absorption rate. This problem is especially evident in case of hydrophilic nano-carriers.The principal challenge in advancing therapeutics for treating diseases of the front as well as back of the eye is attainment of effective drug concentration at the drug target for prolonged periods of timeand minimizing any side effects.

Drug bioavailability in the anterior and posterior segments is very limited. Key reasons for such low bioavailability include short precorneal residence time of an eye drop as well as multiple permeability barriers that a drug has to cross beforereaching target eye tissues.The key challenge to overcome is short precorneal residence time. Corneal permeability, however, is critical for topically applied drugs targeting tissues of the anterior segment of the eye, including aqueous humor, iris, ciliary body and the lens. The conjunctiva is another barrier that limits drug permeability due to the presence of tight junctions and multicellular architecture [2].

It has been studied that 1.5 billion of the population was suffering from Central nervous system (CNS) disorder. Blood-brain barrier (BBB) is main obstacle in distribution of CNS drugs [3].The unique anatomy, the physiology of the eyemake it difficult to achieve an effective drug concentration at the target site [4].In general, the major problem in ocular therapeutics is to maintain an effective drug concentration at the site of action for an appropriate period of time, in order to achieve the expected pharmacological response[5].

The eye is a unique organ from the anatomical and physiological point of view, in that it contains several highly different structures with specific physiologic function.The retina with the optic nerve, an extension of the diencephalon of the central nervous system, has a very specific function in the visual perception and transduction phenomena [6].Eye is the most simply reachable site for topical administration of a medication. Drugs are commonly applied to the ocular system for a localized action on the surface or in the interior of the eye[7].Most of the topically applied drugs are washed off from the eye by various mechanisms (lacrimation, tear dilution and tear turnover) resulting in low ocular bioavailability of drugs. Insight into various membrane transporters/receptors present on

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the eye opened a new window of opportunities. Especially polar drug molecules, which fail to permeate ocular barriers, can be conveniently delivered via transporter/receptor targeted drug delivery systems [8].Most of the dose that is not washed out is systemically absorbed through the conjunctiva and nasal fluids and also through lacrimal drainage, pharynx, gastrointestinal tract, skin, aqueous humor, and inner ocular tissues, ultimately to be eliminated by metabolic processes [9]. For effective systemic delivery, a relatively high drug concentration must circulate in the plasma to achieve a therapeutic dose within the eye[10].Current trends in ocular therapeutics and drug delivery suggest that the existing dosage forms will be replaced by novel drug delivery systems that offer improved biopharmaceutical properties with the capability to deliver therapeutic agents more precisely to targeted receptors in the eye in a predictable manner [11].

1.1. ADVANTAGES OF OCULAR TO BRAIN DELIVERY

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 vascularization. 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[7].
Helps accurate dosing.
Overcome the side-effect of pulsed dosing produced by conventional systems.
Provide sustained and controlled drug delivery.
Increase the ocular bioavailability of drug by increasing the corneal contact time. This can be achieved by effective adherence to the corneal surface.
Provide targeting within the ocular globe so as to prevent the loss to other ocular tissues.
Circumvent the protective barriers like drainage, lacrimation and conjunctival absorption.
Provide comfort, better compliance to the patient and to improve therapeutic performance of drug.
Provide better housing of delivery system[12].

1.2. LIMITATIONS OF OCULAR TO BRAIN DELIVERY

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 [7].
Dosage form cannot be terminated during an emergency.
Interference with vision.
Difficulty in placement and removal.
Occasional loss during sleep or while rubbing eyes. Ration of the therapeutic effect resulting in a frequent dosing regimen.

2. REASONS FOR DEVELOPMENT OF OCULAR TO BRAIN TARGETED DRUG DELIVERY SYSTEMS

2.1 ANATOMY AND PHYSIOLOGY OF EYE[6]

The eye is essentially a globe suspended in the ocular orbit, specialized for sight through an arrangement of multiple tissues

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that function to focus, transmit and detect incoming light. Anatomy of eye as shown below figure.

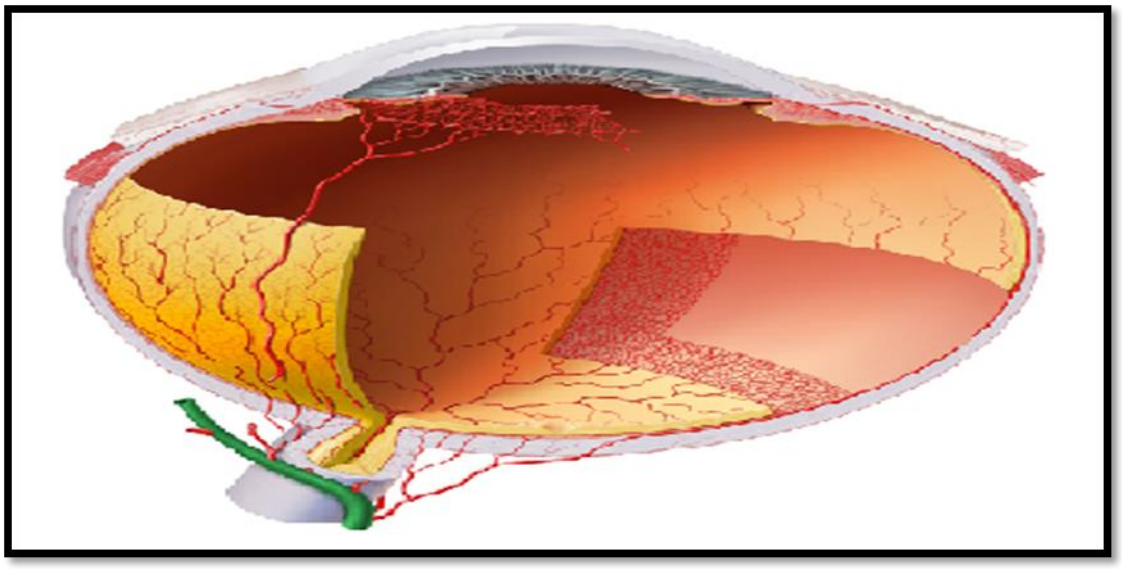

Fig. 1. Anatomy of human eye [42]

It is a spherical structure with a wall consisting of three layers:

1. Outer sclera
2. Middle choroids layer
3. The inner retina

Sclera: The sclera is commonly known as "the white of the eye." It is the tough, opaque tissue that serves as the eye's protective outer coat. Six tiny muscles connect to it around the eye and control the eye's movements. The optic nerve is attached to the sclera at the very back of the eye.

In children, the sclera is thinner and more translucent, allowing the underlying tissue to show through and giving it a bluish cast. As we age, the sclera tends to become more yellow.

Choroid layer: The choroid is the highly vascularized layer lying between the retina pigment epithelium layer and the sclera, with its primary function being the delivery of oxygenand nutrients fromthe blood flow into the outer retina[13].

The choroid lies between the retina and sclera. It is composed of layers of blood vessels that nourish the back of the eye. The choroid connects with the ciliary body toward the front of the eye and is attached to edges of the optic nerve at the back of the eye. It is situated inside the sclera, contains many blood vessels and is modified at the front of eye as the pigmented iris. The biconvex lens is situated just behind the pupil. The chamber behind the lens is filled with the vitreous humor, a gelatinous substance occupying 80% of the eyeball. The anterior and posterior chambers are situated between the cornea and iris, and iris and lens, respectively and filled with aqueous humor. At the back of the eye is the light detecting retina.

The Cornea: The cornea is a non-vascularized barrier consisting of five to seven layers, which exhibits high resistance to passive diffusion of ions and molecules and withstands the intraocular pressure. This tissue has a smaller surface area compared to the conjunctiva which, moreover, is a leakier epithelium than the cornea [5].The cornea is the transparent, dome-shaped window covering the front of the eye. It is a powerful refracting surface, providing 2/3 of the eye's focusing power. Like the crystal on a watch, it gives us a clear window to look through. Because there are no blood vessels in the cornea, it is normally clear and has a shiny surface. The

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Table 1: Examples of nanotechnology based ocular drug delivery systems

Active Agent Ibuprofen	Drug Delivery System	References
Ciclosporin Diclofenac sodium	Solid lipid nanoparticles	[29,30]
Cyclosporin Dexamethasone Pilocarpine	Nanoemulsions	[31,32]
Dexamethasone	Micelles	[33]
Flurbiprofen	Nanosuspension	[34]
Timolol maleate	Discosomes	[35]
Pilocarpine nitrate Dexamethasone	2-hydroxypropyl-â-Cyclodextrins	[36,37]
Acetazolamide Inulin Oligonucleotides Pilocarpine hydrochloride Diclofenac sodium	Liposomes	[38,39]
Tropicamide Pilocarpine nitrate	Dendrimers	[40]
Cyclopentolate	Niosomes	[41]

Table 2: Available ophthalmic products in market [1]

Brand name	**Drug**	**Dosage form**	**Uses**
Dichol	Carbachol	Sterile solution and prefilled syringes	In ophthalmic surgery
Refresh tears	Hydroxypropyl methylcellulose	Eye drops	In dryness of eye and as eye lubricant
Restasis	Cyclosporine	Emulsion	In dry eye
Refresh Classic	Artificial tear fluid	Single use vials	Relieves dry and irritated eyes
Ciplox	Ciprofloxacin	Eye drops	In eye infection and conjunctivitis
Geltear	Carbomer	Bioadhesive gel	As a lubricant, in buring,irritated an dried eye
Timolol xe	Timolol maleate	*In-situ* gel	For dried eye and Keratoconjuctivitis

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Acivir eye	Acyclovir	Ointment	For eye infection
Ocupol	Polymixin-B	Eye drops and ointment	In bacterial infection, corneal ulcer,
Pred Forte	Prednisolone acetate	Suspension	As anti-allergic and anti-inflammatory
Chloromycetin	Chlorampthenicol palmitate	Ointment	In conjunctivitis and eye inflammation
Betnisol N	Betamethasone	Eye drop	In eye infection
Dexcin	Dexamethasone	Eye drop	In eye infection

Table 3: Common ocular drugs: [9]

CATEGORY	DRUGS	INDICATIONS
Antibacterial (antibiotics)	Penicillins Cephalosporins Sulfonamides Tetracyclines Chloramphenicol Aminoglycosides Fluoroquinolones Vancomycin Macrolides	Used topically in prophylaxis (pre and postoperatively) and treatment of ocular bacterial infections. Used orally for the treatment of preseptal cellulitism e.g. amoxycillin with clavulonate, cefaclor Used intravenously for the treatment of orbital cellulitis e.g.gentamicin, cephalosporin, vancomycin, flagyl Can be injected intravitrally for the treatment of endophthalmitis
Antivirals	Acyclovir Trifluridine Ganciclovir	Inhibits viral DNA synthesis Block DNA synthesis, impair RNA replication Useful in CMV retinitis
Antifungal	Polyenes: E.g.Amphotericin B, Natamycin, nystatin Imidazoles: E.g. Miconazole, ketoconazole,fluconazole Flucytocine	Damage cell membrane of susceptible fungi Increase fungal cell membrane permeability Act by inhibiting DNA synthesis
Mydriatics and Cycloplegics	Tropicamide Homatropine Atropine	Corneal ulcer Uveitis Cycloplegic refraction
Antiglaucoma	Acetazoamide Prostaglandins	Reduce aqueous humour formation Increased aqueous out flow
Anti-inflammatory	Corticosteroid:	Allergic conjunctivitis,

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agents	Hydrocortisone cortisone prednisolone Triamcinolone Fluprednisolone Dexamethasone Betamethasone. NSAIDS	Scleritis, Uveitis, allergic keratitis After intraocular and extra ocular surgeries Posterior uveitis Optic neuritis Corneal graft rejection
Ocular Lubricants	Refresh tears Tears Naturale II Tear plus Moisol Dudrop	Ocular irritations in various diseases Dry eyes
Antihistaminic	Pyrilamine maleate, pheniraminemaleate, antazoline phosphate H1 antihistamine	Use in allergic conjunctivitis, irritation, pinguecula and pterygium Can cause sedation, mydriasis and increase IOP
Ocular diagnostic drugs	Fluorescein dye Rose bengal stain	stain corneal abrasions, applanation tonometry, detecting wound leak, NLD obstruction, fluorescein angiography severe dry eye, herpetic keratitis
Local anesthetics	propacaine, tetracaine Lidocaine bupivacaine	applanation tonometry, gonioscopy, removal of corneal foreign bodies, removal of sutures, examination of patients who cannot open eyes because of pain Cause anesthesia and akinesia for intraocular surgery
Ocular Toxicology	Topiramate	Causes acute angle-closure glaucoma (acute eye pain, redness, blurred vision, haloes) cause retinopathy (bull’s eye maculopathy)

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	Chloroquines	

adult cornea is only about 1/2 millimeter thick and is comprised of 5 layers: epithelium, Bowman's membrane, stroma, Descemet's membrane and the endothelium.The cornea is an optically transparent tissue that conveys images to the back of the eye and covers about one-sixth of the total surface area of the eye ball. The cornea is considered to be the main pathway for the permeation of drugs into the eye. It is 0.5 mm thick in the central region, increasing to approx. 0.7 mm at the periphery and composed of the five layers.

i. The Epithelium
ii. The Bowman's Membrane
iii. The stroma or Substantia Propria
iv. The Descemet's Membrane
v. The Corneal Endothelium

I. The Epithelium:-As the cornea's outermost region - comprising about 10 percent of the tissue's thickness - the epithelium functions primarily to: (1) block the passage of foreign material - such as dust or water - into the eye and other layers of the cornea (2) provide a smooth surface that absorbs oxygen and other needed cell nutrients that are contained in tears. This layer, which is about five cells deep, is filled with thousands of tiny nerve endings that make the cornea extremely sensitive to pain when rubbed or scratched.

II. The Bowman's Membrane: - This is an acellular homogenous sheet, about 8-14 μm thick. This is locatedbetween the basement membrane of the epithelium and the stroma.

III. The stroma or Substantia Propria: - It is located behind the epithelium and comprises about 90% of the cornea. It consists primarily of water (78%); layered protein fibers (16%) that give the cornea its strength, elasticity, and form; and cells that nourish it. The unique shape, arrangement, and spacing of the protein fibers are essential in producing the cornea's light-conducting transparency.

IV. The Descemet's Membrane: This is secreted by the endothelium, lies between the stroma and the endothelium.

V. The Corneal Endothelium: These single layers of cells are located between the stroma and the aqueous humor. Because the stroma tends to absorb water, the endothelium's primary task is to pump excess water out of the stroma. Without this pumping action, the stroma would swell with water, become hazy, and ultimately opaque.

The Conjunctiva:

It is basically involved in the formation and maintenance of the pre-corneal tear film and in the protection of the eye. It is thin, thevascularised mucous membrane that lines in the posterior surface of the eyelids and outer regions of the cornea. The human conjunctiva is 2 to 30 times more permeable to the drugs than the cornea and it had been proposed that loss by this route is a major path for drug clearance.

2.2. BLOOD SUPPLY EYE TO BRAIN

The blood supply to the optic nerve is complex and changes qualitatively along its course. Because of the varying nature of the vascular supply to the optic nerve, a wide variety of clinical syndromes may result from ischemia or infarction at each location. The vascular supply to the retinal ganglion cell axons as a function of location, starting at the retina, then the optic nerve head, the intra-orbital optic nerve, the optic canal, the intracranial optic nerve, and the chiasm and optic tract. The retinal circulation perfusing the retinal ganglion cells and their axons is that an inner retinal infarction the nerve head circulation is derived from two sources:

1. Central retinal artery is a branch of the intra-orbital ophthalmic artery, and enters the optic nerve during its intra-orbital cours.

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2. Posterior ciliary arteries provide the major blood supply to the optic nerve head. There are usually two posterior ciliary arteries, a medial and a lateral.

2.3. NERVE SUPPLY EYE TO BRAIN

The trigeminal nerve is the largest and most complex of the 12 cranial nerves (CNs). It supplies sensations to the face, mucous membranes, and other structures of the head. The cranial nerves are components of the peripheral nervous system, with the exception of cranial nerve II (optic nerve) which is not a true peripheral nerve but a neural tract of the diencephalon connecting the retina with the lateral geniculate nucleus both the optic nerve and the retina are part of the central nervous system (CNS) as shown in fig. 2. The axons of the remaining twelve nerves extend beyond the brain and consider in the part of the peripheral nervous system.The central ganglia of the cranial nerves or cranial nerve nuclei originate in the CNS, preferentially from the brainstem.

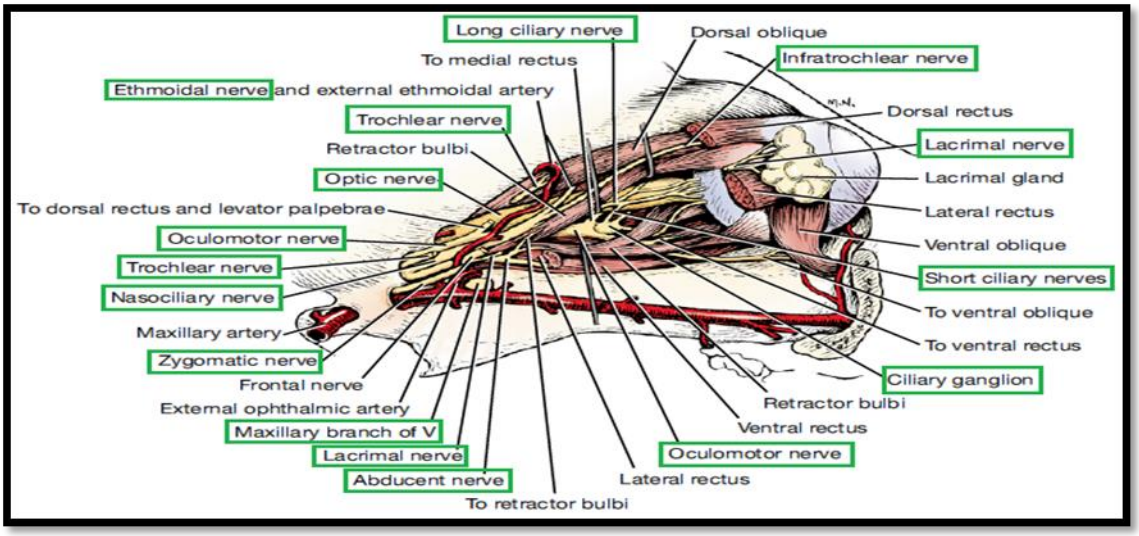

Fig. 2. Nerve supply of eye [44]

2.4. BARRIERS TO OCULAR DRUG DELIVERY

2.4.1. Tear film barrier: The main components of the tear film include mucin, water and lipid, and act a defensive barrier to the foreign-object access to the cornea and conjunctiva.

2.4.2. Corneal barrier:This is vascularand comprised of three major layers which are epithelium (multiple layers stacked on each other), stroma and endothelium (single layer). It acts as a barrier preventing the drug absorption from the lacrimal fluid into the anterior chamber after the topical administration.

2.4.3. Conjunctival barrier: This mucous membrane consist of conjunctival epithelium (2–3 layers thick), and an underlying vascularized connective tissue. Acts a barrier to the topically administered drugs and comparatively less-efficient to the corneal barrier.

2.4.4. Blood-aqueous barrier: This barrierlocated in the anterior segment of the eye and formed by the capillary endothelium in the iris, and the ciliary epithelium which both contain tight junctions. The barrier is relatively inefficient compared to the blood retinal barrier and small molecules can reach the aqueous humor by permeation through penetratedcapillaries in the ciliary processes.

2.4.5. Blood-retinal barrier (BRB): This barrier located in the posterior segment of the eye and formed by the retinal pigment

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epithelium (outer BRB) and the endothelial membrane of the retinal blood vessels (inner BRB), both contain tight junctions. The tight junctions restrict the entry of the drugs from the blood (systemic) into the retina/aqueous humor [14].

2.5. MECHANISM OF DRUG ABSORPTION

2.5.1. Corneal absorption:Maximum absorption takes place through the cornea, which leads the drug into aqueous humor.

2.5.2. Non-corneal absorption: The non-corneal route involves absorption across the sclera and conjunctiva, this route is not productive as it restrains the entry of drug into the intraocular tissues.

3. FORMULATION STRATEGIES FOR OCULARDRUG DELIVERY

‘THROUGH’

Ocular Iontophoresis

Ocular penetration enhancers

Periocular injection

Intravitreal injection

Subconjunctival Administration

Nanotechnology-based ocular drug delivery:

- Nanoparticles
- Solid lipid nanoparticles (SLNs)
- Liposomes
- Niosomes
- Nanosuspension
- Nanoemulsions
- Nanomicelles
- Nanogels
- Cubosomes
- Dendrimers

‘TO’

Eye drops

Gels

Emulsion

Suspensions

Prodrug

Ocular inserts

Collagen shields

2.5.3. Mechanism of controlled sustained drug release into the eye [12]

 The corneal absorption represents the major mechanism of absorption for the most conventional ocular therapeutic entities.

Passive Diffusion is the major mechanism of absorption for nor-erodible ocular insert with dispersed drug.

Controlled release can be further regulated by gradual dissolution of solid dispersed drug within this matrix as a result of inward diffusion ofanaqueous solution as shown in fig. 3.

3.1. APPROACHES ‘THROUGH’OCULAR DRUG DELIVERY

3.1.1. Ocular Iontophoresis: Iontophoresis is a modern non-invasive approach specifically designed for ocular drug delivery.Ocular iontophoresis overtures a drug-delivery system that is rapid, pain-free and secure; furthermore, in the majority of cases, it consequences in the delivery of a high concentration of the medicament to a particular site [15-17].Ocular iontophoresis has gained significant interest recently due to its noninvasive nature of delivery to both anterior and posterior segment. Iontophoresis is a noninvasive method of transferring ionized drugs through membranes with low electrical current. The drugs are moved across the membranes by two mechanisms: migration and electro-osmosis.Ocular iontophoresis is classified into transcorneal, corneoscleral, or trans-scleral iontophoresis [17].

3.1.2. Ocular penetration enhancers:They act by increasing corneal uptake by modifying the integrity of corneal epithelium. Chelating agents, preservatives, surfactants and bile salts were studied as possible penetration enhancers. But the

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effort was diminished due to the local toxicity associated with enhancers.

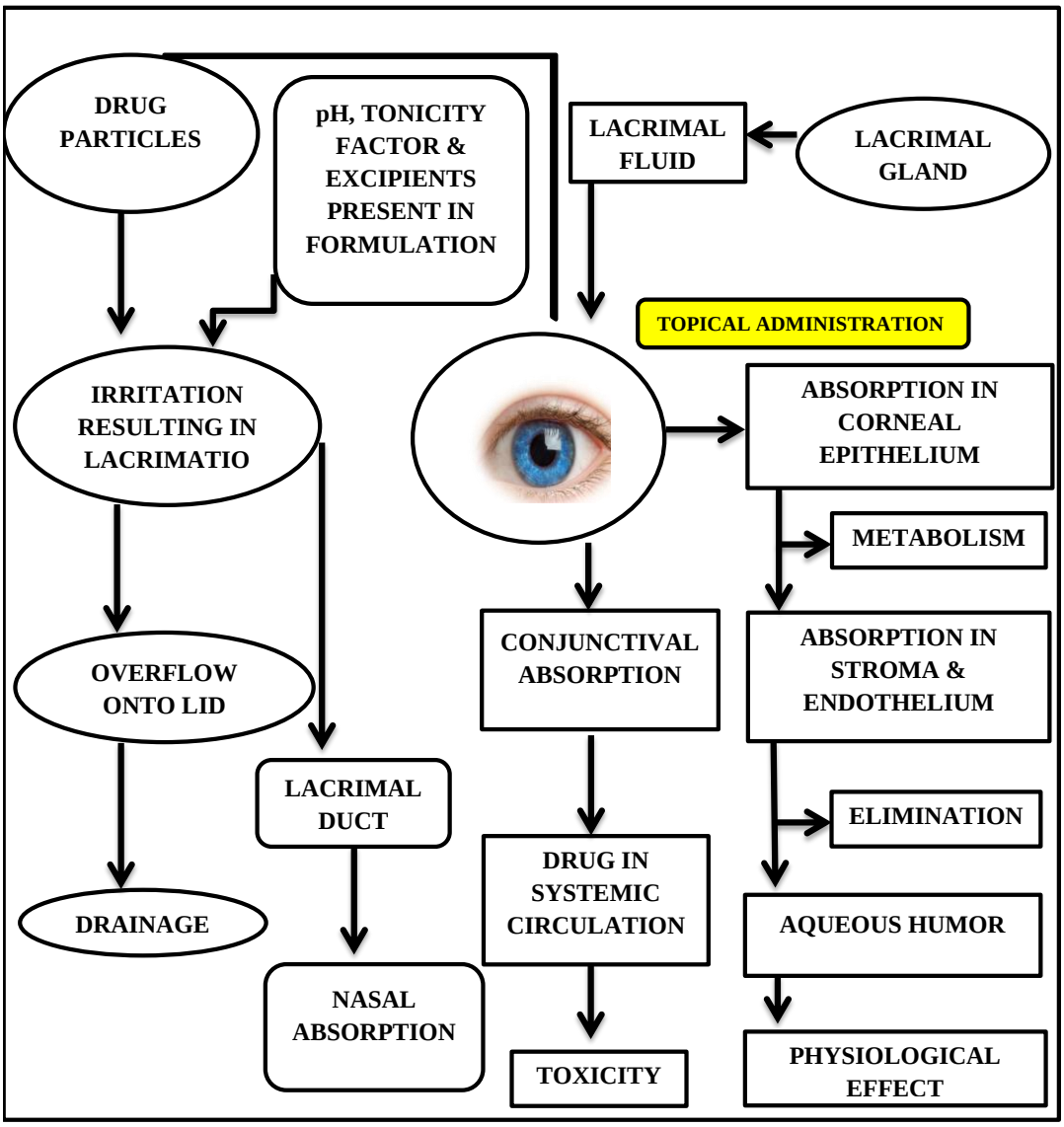

Fig. 3. Mechanism of controlled sustained drug release into the eye.

Penetration enhancers have also been reported to reduce the drop size of conventional ophthalmic solutions especially if they do not elicit local irritation [12, 16].

3.1.3. Periocular injection: Periocular injection includes a series of topical injections which are employed to overcome drawbacks of systemic administration and to increase the drug concentration in intraocular tissues. Periocular deliveriesthrough retro bulbar,peribulbar,sub-tenonand subconjunctivalinjectionarelessinvasivethan intravitreous injection. Drugsadministeredby Periocular deliveryroutes can reach theposteriorsegmentoftheeyebypenetrationof either corneal choroidorscleral.However,mostoftheseroutes suffer from greatdrawbackssuchasinefficiency inprolongingthe drug retention time[18].Drug solutions are placed near to the sclera, which results in high retinal and vitreal concentrations. It has advantages like

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improved drug absorption over systemically and topically delivered agents, more safety drug delivery to the posterior segment of the eye than systemic administration (no systemic toxicity), drug delivery to the target sites of the eye. Injections display first-order kinetics (this rapid rise may cause difficulties with toxicity, and drug efficacy can diminish as thedrug concentration falls below the targeted range) [17].

3.1.4. Intravitreal injection: Intravitreal injection is the most common administration route by injection of drug solution or suspension into the vitreous cavity through a 27- or 30-gauge needle. Usually a 20–100 µL volume solution can be directly injected into the vitreous cavity without discomfort. Intravitreal injections, which result in high local drug concentrations in the vitreous body and retina, can serve as an efficient route of administration for treating posterior eye diseases [18]

3.1.5. Subconjunctival Administration: One of the main routes of administration for ocular therapeutics is the subconjunctival pathway. Microspheres and implants have been developed and tested after subconjunctival administration. The advantage of this approach is that it may provide high drug levels for a long period in the extraocular area and its major disadvantage is its invasiveness [19].

3.1.6. Nanotechnology-based ocular drug delivery[20]: 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 [21].

3.1.6.1. Nanoparticles: As drug delivery systems, NPs can provide: (1) sustained delivery; (2) targeted delivery to specific cells or tissues; (3) improved delivery of both water-insoluble drugs and large biomolecule drugs, and (4) reduced side effects, minimizing toxicological reactions. Importantly, NPs can bypass biological barriers, especially blood-neural barriers including the BRB and the blood–brain barrier (BBB), which makes them exquisitely suitable for ocular diseases [20].

3.1.6.2. Solid lipid nanoparticles (SLNs): SLNs are the colloidal carrier systems composed of high melting point lipid as a solid core which is coated by aqueous surfactant. Due to low toxicity, simple preparation and large-scale production SLNs are the potential source for the variety of drugs. SLNs of solid lipid prepared with a photon correlation spectroscopy had diameter of about 50–1000 nm [22].

3.1.6.3. Liposomes: Liposomes are of the sizes 25–2500 nm. Liposomes are spherical vesicles composed of phospholipids and steroids (cholesterol) bilayers. These are biocompatible and biodegradable. Liposome may be unilamellar or multilamellar and have versatile drug loading properties.Hydrophilic and lipophilic drugs can be encapsulated in liposome, i.e., hydrophilic drugs in the core, whereas the lipophilic drugs in the bilayer. The drug is released by passive diffusion, vesicle disruption or by vesicle fusion [22].

3.1.6.4. Niosomes: Niosomes are bilayered nonionic surfactant vesicles chemically stable with the ability to carry both lipophilic and hydrophilic drugs. Niosomes are nonimmunogenetic, biodegradable and biocompatible, and show low toxicity due to their nonionic structure [23].

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3.1.6.5. Nanosuspension: Nanosuspensions are the biphasic colloidal dispersions, in which the pure drug particles are dispersed in an aqueous media. The nanosuspension provide an important and useful method for enhancing the bioavailability of poorly water-soluble drugs by reducing the particle size of the drug to submicron range and is stabilizeby polymers, surfactants or mixture of both. The surfactant added to the nanosuspension acts as a suspension agent [22].

3.1.6.6. Nanoemulsions:A clear or translucent emulsion containing droplet sizes typically below 200 nm. Nanoemulsions are thermodynamically unstable dispersions of oil and water that contain individual small droplets[22].

3.1.6.7. Nanomicelles:Nano-sizedmicelles have its vital importance and attention due to its ability to targetboth anterior segments related inflammation as well as a posteriorsegment of the eye. They are the colloidal dispersion of drugcarrier systems of size ranging 10 to 100 nm with a hydrophilic coronaand hydrophobic core. It may be noted that the hydrophobicity of adrug limits the possibility to formulate its clear solution in a concentrationsufficient to reach therapeutic levels in the ocular tissues[24].

3.1.6.8. Nanogels:Nanogels are defined as nanosized particles composed of a physically or chemically cross-linked polymer network which exhibits the ability to swell when in a 'good' solvent, typically water.Nanogels offer a unique platform for mucosal drug delivery as they can facilitate high drug loading capacities in addition to exhibiting excellent biocompatibility, enhanced colloidal stability and large surface areas with tunable chemical and physical properties[25].

3.1.6.9. Cubosomes:They are liquidcrystalline particles in nano size range (100–300 nm), usuallycomposed of amphiphilic lipids (Monoolein, and phytantriol) and withor without stabilizer/surfactant (Poloxomer 407).They are cubic structureswith numerous water channels within themselves. Hence, beingmade up of amphiphilic lipids and possessing aqueous channels, theycan resourcefully accommodate hydrophilic, lipophilic and amphiphilicmolecules with high loading efficiency [24].

3.1.6.10. Dendrimers:Dendrimers are macromolecular compounds from which someof highly branched, tree-like arms originate in a symmetric fashion, are consideras attractive for biomedical applications due to their unique physicochemical properties. As the dendrimer's size can be controlled based on the stepwise chemical synthetic processes of their generation, they can become similar in size to someof biological structures, such as G5 polyamidoamine dendrimers with the size of a hemoglobin molecule [18].

3.2. APPROACHES 'TO'OCULAR DRUG DELIVERY

3.2.1. Eye drop: Eye drops are the main form of topical administration due to good patient compliance and economic considerations. Drugs dissolved in eye drops are usually adsorbed by two routes: the corneal route (cornea, aqueous humor, intraocular tissue),and the conjunctiva route (conjunctiva, sclera, choroid, retina, vitreous body). Due to the corneal barrier and pre-corneal factors, less than 5% of totally administered drugs can reach the aqueous humor. As a result, eye drops have to be administered to maintained therapeutic drug concentrations[18].

3.2.2. Gels:Gel formation is an extreme case of viscosity enhancement through the use of viscosity enhancers. So the dosing frequency can be decreased to once a day [12].

3.2.3. Emulsion:An emulsion based formulation approach offers an advantage to improve both solubility and bioavailability of

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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 [26]. For ophthalmic drug delivery, o/w emulsion is common and widely preferred over w/o system. Several studies have demonstrated applicability of emulsions in improving precorneal residence time, drug corneal permeation, providing sustain drug release and thereby enhancing ocular bioavailability [27].

3.2.4. Suspensions:Suspensions are another class of non-invasive ocular topical drop drug carrier systems. Suspension defined as a 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 [28].

3.2.5. Prodrugs: Prodrugs enhance corneal drug permeability through modification of the hydrophilic or lipophilicity of the drug. The method includes modification of chemical structure of the drug molecule, thus making it selective, site specific and a safe ocular drug delivery system. Drugs with increased penetrability through prodrug formulations are epinephrine, phenylephrine, Timolol, and pilocarpine [12].Enzyme systems identified in ocular tissues include esterases, ketone reductase, and steroid 6-hydroxylase. Prodrug is considered as a new drug entity; so, extensive pharmacokinetic and pharmacologic information is required for proper design [17].

3.2.6. Ocular inserts:Ocular inserts are aseptic, thin, multilayered, drug loaded, solid or semisolid dosage forms placed into the cul-de-sac or conjunctival sac, whose dimension as well as build are specifically planned intended for ophthalmic application and can conquer the hindrance stated with traditional ophthalmic systems [1, 12, 15].

3.2.7. Collagen shield: Collagen is the structural protein of bones, tendons, ligaments and skin and comprises more than 25% of the total body protein in mammals. Collagen shields had been used in animal model and in humans (eg. Antibiotics, antiviral etc.,) or combination of these drugs often produces higher drug concentration in the cornea and aqueous humor when compared with eye drops and contact lens [12].

4. CONCLUSION

It can be concluded that eye is one of the most complex organs in the human body. Drug delivery to the posterior segment ocular tissues of eye presents collision among drugs/drug candidates. Effective management of ophthalmic diseases is challenging task for the pharmaceutical scientists because of complex nature of various diseases and the presence of ocular barriers. Topical application is not yet promising and needs to be addressed with novel drug delivery platforms as discussed in this review article. These non-conventional novel approaches like nanotechnology, microspheres, liposomes and iontophoresis offer effective delivery and further enhance the ocular absorption and reduce side effects. This review article offers ocular drug delivery as a unique carrier system for many pharmaceuticals. In future, much of the emphasis will be given to achieve non-invasive sustained drug release for eye disorders in both segments.

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5. References:

1. Pathak S, Chopra H Int J of Phar and Bio Sci :2230-7605.
2. Kompella1 UB, Kadam RS, Lee VHL (**2010**) NIH 1 : 435-56.
3. Thakur S, Sharma PK, Malviya R Annals of Pharmaco and Pharmaceut 2:1043.
4. Rupenthala ID *et al* (**2011**) International Journal of Pharmaceutics 411:69-77.
5. Alonso MJ *et al* (**2010**) Advanced Drug Delivery Reviews 62:100-17.
6. Khokhar P, Shukla V (**2014**) International Journal of Pharma Research & Review 3:29-41.
7. Ankit K *et al* (**2011**) European Journal of applied sciences 3: 86-92.
8. Costa VP, Marcelo LO, Freitas FR, Raul CM (**2012**) Pharmaceutics 4:252-275.
9. Morrison PW, Khutoryanskiy VV (**2014**) Ther Deliv 5: 297-315.
10. Washington N, Washington WC, Wilson CG (**2001**) Pharmaceutics: CRC Press: Boca Raton, Florida.
11. Kaur IP *et al* (**2004**) International Journal of Pharmaceutics 269: 1-14.
12. Karthika K *et al*, Int J Pharm Sci 2: 1-5.
13. Smedt SCD *et al* (**2017**) Advanced Drug Delivery Reviews.
14. Tao LL *et al* (**2017**) Advanced Drug Delivery Reviews 122:31-64.
15. Tekade RK *et al* (**2017**) Journal of Controlled Release 268: 19-39.
16. Pathak S, Chopra H (**2011**) International Journal of Pharmacy and Biological Sciences: 2230-7605.
17. Patel PB (**2010**) Systematic Reviews in Pharmacy 1.
18. Weisheng Guo *et al* (**2017**) Acta Pharmaceutica Sinica B 7: 281-291.
19. Yavuz B *et al* (**2012**) The Scientific World Journal.
20. Elisa JC, Antonio C, Joao M, António FA (**2017**) Nanomedicine: Nanotechnology, Biology, and Medicine 13: 2101-13.
21. Patel A *et al* (**2013**) World J Pharmacol 2: 47-64.
22. Madni A *et al* (**2017**) International Journal of Pharmaceutics 530: 326-45.
23. Costa VP, Marcelo LO, Freitas FR, Raul CM (**2012**) Pharmaceutics 2012 : 252-275.
24. Tekade RK *et al* (**2017**) Novel Journal of Controlled Release 268:19-39.
25. Khutoryanskiy VV *et al* (**2017**)

Colloids and Surfaces B: Biointerfaces 155: 538-43.

26. Vandamme TF (**2002**) Prog Retin Eye Res 21:15-34.

27. Liang H *et al* (**2008**) Mol Vis 14:204-16.

28. Lang, Roehrs J, Jani R, Remington R (2009) Ophthalmic preparations: 856.

29. Attama AA, Reichi S, Muller-Goymann (**2008**) Int J Pharm 355: 307-13.

30. Muller RH *et al* (**2008**) Eur J Pharm Biopharm 68:535-544.

31. Fialho SL, Da Silva-Cunha A (**2004**) Clin Exp Ophthalmol 32:626-32.

32. Garty N, Lusky M, Zalish M (**1994**) Invest Ophthalmol Vis Sci 35: 2175-86.

33. Civiale C *et al* (**2009**) Int J Pharm 378: 177-86.

34. Pignatello R, Bucolo C, Spedalieri G, Maltese A, Puglisi G (**2002**) Biomaterials 23 : 3247-55.

35. Aggarwal D, Garg A, Kaur LP (**2004**) J Pharm Pharmacol 56: 1509-17.

36. Loftsson T, Fririksdottir H, Thorsdottir S, Stefansson E (**1994**) Int J Pharm 104: 181-184.

37. Kristinsson JK *et al* (**1996**) Invest Ophthalmol Vis Sci 37:1119-1203.

38. Bochot A, Fattai E, Gullk A, Couyarraze G, Couvreur P (**1998**) Pharm Res 15 :1364-69.

39. Ahmed I, Patton TF (**1987**) Int J Pharm 38: 9-21.

40. Vandamme TF, Brobeck L (**2005**) J Control Release 102: 23-38.

41. Saettone MF, Perini G, Carafa M, Santucci E, Alhaique F (**1996**) STP Pharma Sci 6 : 94-98.

42. Anatomy of human eye february, 2018.

43. Eye anatomy retrieved from www.valleyeyecare.org. February, 2018.

44. Evans HE, Lahunta A (**2010**) Guide to the dissection of the dog, 7th edn Missouri: Saunders Elsevier.

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