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RECENT TREATMENT APPROACHES IN OCULAR DRUG DELIVERY SYSTEM: A REVIEW

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Abstract:
The bioavailability of the active drug substance is often the major drawback to overcome. The effective concentration of drug in the eye for sufficient period of time is a promising management for the eye ailments. The ocular dosage form, such as eye drops, are no longer sufficient to combat ocular diseases. Designing an effective therapy for ocular diseases, especially for the posterior segment, has been considered as a complicated task. Transporter targeted drug delivery has generated a great deal of interest in the field because of its potential to overcome many barriers associated with current therapy. Application of in-situ gel has been very promising in the treatment of an ocular diseases. In this review, we have briefly discussed several ocular drug delivery systems such as microemulsions, nanosuspensions, nanoparticles, liposomes, niosomes, implants, and in-situ gels.

Keywords: Permeation barrier, Drug transporters, Eye segments, Drug release method, Permeation enhancement.

抽象的：
活性药物物质的生物利用度通常是需要克服的主要缺点。药物在眼睛中的有效浓度足够长的时间是治疗眼病的有希望的方法。眼用剂型，例如滴眼剂，不再足以对抗眼部疾病。设计一种有效的眼部疾病治疗方法，尤其是后段疾病，一直被认为是一项复杂的任务。转运蛋白靶向药物递送在该领域引起了极大的兴趣，因为它有可能克服与当前治疗相关的许多障碍。原位凝胶在眼部疾病治疗中的应用前景广阔。在这篇综述中，我们简要讨论了几种眼部药物递送系统，例如微乳剂、纳米混悬剂、纳米颗粒、脂质体、niosomes、植入物和原位凝胶。

关键词：渗透屏障，药物转运蛋白，眼节，药物释放方法，渗透增强。

1. Introduction

Eye is the most bulkiest and sensitive phase of the human body. Now in the current times, many humans are struggling from the eye problems. The ocular drug delivery can be continued as one of the fascinating mission for the pharmaceutical researchers. The eye limits for the entrance of drug particles at the requisite

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site of movement because of its specific shape. Anterior and posterior are the two segments for the delivery of drug into the eye. The ocular disease can be treated for vision reassuring by the conventional system like eye drops, suspension and ointments [1] [2]. The Blood Retinal Barrier is the tight junction to restrict the passage of drug into posterior part of eye [3].

Now quite a few difficulties are more recent for pharmaceutical ocular preparations such as in-situ gel, nanoparticles, liposomes, nanosuspension, microemulsion, iontophoresis and ophthalmic inserts have been developed in closing 30 years to rise the bioavailability of a drug as a sustained and controlled way [4-11].

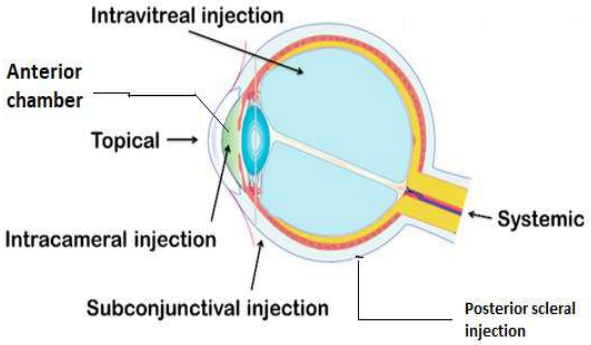

Fig. 1:- Structure of Eye [12]

Eye affecting diseases and its overview:-

The structure of eye can be divided into two subparts i.e. (i) anterior segment (ii) posterior segment. The anterior segment covered frontal one- third part of the eye like some parts of posterior segment and the other parts pupil, iris, cornea, ciliary body and aqueous humor covered the rear 2/3 part of the anterior segment to the eye like vitreous humor, choroid, optic nerve, retina and macula [13, 14].

Barriers to drug permeation:- The eye of the human are in the spherical shape and their diameter is 23mm. The ball of eye is divided into three layers based on their essential constituents is the outermost coat consists of the clear, transparent cornea, and the white, opaque sclera.

1. Ocular Surface Barriers:- The superficial layers of cornea and conjunctiva are the ocular surface form and it is contact with the tear film. This surface barriers are to be created the secured barrier beside penetration from undesired particles. The corneal surface consists of only 5% of the total ocular surface and the other 95% is filled with the conjunctiva [15]. The inner most layer of eye i.e. cornea is consist of five layers : (a) Epithelium, (b) Bowman's layer, (c) stroma, (d) Descemet's membrane,(e) Endothelium, but only the corneal squamous epithelial cell i.e. outermost layers form a intercellular drug penetration[16].

2. Tear:- It is the first protective layer of cornea and conjuctiva. They are made up of three layers i.e., a lipid layer (outermost layer), water layer (middle layer), and the lastly the mucous layer (innermost layer) [17] .The tear film is the precorneal barriers which decreases concentration of active drugs administered to the tear turnover by erosion (approx. 1µL/min), faster clearance, and the molecules of the drug binding to the tear proteins, pH and nutrient levels. The total volume of dose fixing is 25-50µL but the cul-de-sac size is 7-10µL. The extra tear volume is leaving via a nasolacrimal duct or rush on the skin of cheeks [18-20].

3. Conjuctiva:- The topical eye drops absorption route is mostly excludes the corneal route and the non-corneal route i.e. (conjuctival/scleral). This barrier is self-possessed from developed epithelial cells that travel from upper hand of the cornea to the centre and extent the bottom of the cornea. The limits of the drugs diffusion amid the cells that form the tight junctions in the topmost corneal epithelial cells [21]. Over the conjuctiva

and sclera, the drug may enters into the intraocular tissues in the non-keratin trails [17]. The conjuctival space is eradicated by the help of competent efflux system through the conjuctival lymphatics [22].

4. BRB (Blood Retinal Barrier):- The BRB inhibits the drug passes from blood into the retina. Blood Retinal Barrier is divided on the basis of endothelial cells of tight junction of RPE and retinal capillary, i.e. oBRB is used for the outer and iBRB is used for the inner [23]. The purpose of iBRB is maintained by astrocytes and Muller cells. The retinal endothelial cells of capillary are not have aperture and a scarcity of vesicles [24]. The outer blood retina barrier become estranged the retinal tissue fluid from choroidal tissue fluid extends by the help of RPE and Bruch's membrane. The purposes of RPE is to accumulation in active transport to the selective absorbency. The blood-eye-barrier contains the BAB and the BRB. The leading purpose is to switch the solute and the nutrients into the intraocular tissue [17].

Anterior segment of drug transport to the eye

1. Eye drops:- The eye drops are the topical administration of drugs which extend the withholding timing for anterior drug transport system and thus interacts among the API (excipients), the physiological environment of cornea and subconjuctiva.

Durasite DDS proposed on a polycarbophil aqueous solutions [25]. Polycarbophil is a cross-linked polyacrylic acid with divinyl glycol that creates hydrogen bonds with mucus, corneal and conjuctival epithelium that they all are not positively charged, so that's why they can prolongs the outcome of drugs to the several hours. For decrease the irritation or pain after the surgery of ocular, the drug is used Bromfenac in Durasite which is in Phase first or second [26].

2. Contact lenses:- The lenient contact lens are to be examined by some methodologies i.e., (i) absorption and soak of drug solutions [27], (ii) piggyback contact lenses joined with drug solutions or drug plate [28], (iii) to stop drugs on the layer of contact lenses by the surface-modification [29], (iv) the colloidal structure discrete in contact lenses by combination of drugs [30], (v) ion-ligand comprising the hydrogen of polymers [31], (vi) physiological science of stamping for drug [32,33].

The contact lenses which are hydrophobic in nature that can be worn to extend the ocular continuance time of the drugs. In humans, the Bionite lens prepared from hydrophobic polymers (2-hydroxy ethyl methacrylate) that can give a larger diffusion of fluorescein [34]. Contact lens that is discharge combined sodium cromoglicate for a day have been reported by two different companies like SEED Co., Ltd. (Tokyo, Japan) and Senju Pharmaceutical Co., Ltd. [35]. As likened to eye drops, contact lenses for drug transport delivery have some benefits that can better obedience, fewer complete absorption consequence, and allow high and constant resident drug stages on the ocular surface. Because of this, they permit eye to dissolve a higher percentage of the drug applied in the tear film [36].

3. Transdermal System:- It is a sort of controlled delivery film arrangements that apply restorative impacts through transdermal organization. This methodology keeps up with the convergence of the medication in the plasma and gives a proper level of medication. Transdermal frameworks can give something similar or higher medication bioavailability as effective instillation. Because of the consistent centralization of the medication can gave to treat ongoing [37].

4. Sub-conjunctival administration: - This administration function is effectively supply the drug to the uvea [38]. After injecting the injection into sub-conjuctival space, the medicine enters the sclera which is more permeable than the cornea. Distinct to the cornea and conjunctiva, scleral absorptivity is not reliant on drug lipophilicity, but primarily on the particle size [38].

A sub-conjuctival embed having (embedded Latanoprost SR) in Phase 1 clinical examination created by Pfizer, Inc. (New York, NY, U.S.) is made out of a poly (DL-lactide-co-glycolide) (PLGA) tube having a lantoprost-centre. The cylinder is covered with an impermeable polymer, silicone on one end and the opposite end is covered by a penetrable polymer, polyvinyl liquor [39].

Posterior segment of the drug transport to the eye.

1. Intravitreal administration:- This administration advantageous for more upfront accessible to vitreous and retina. It should be renowned, however that transfer from vitreous to the choroid is additional difficult due to prevention by the RPE barrier. Small particles are capable to spread out rapidly in the vitreous but the potency of huge particles, particularly positively charged is restricted [40]. The nanoparticle flexibility is extremely reliant on the structure. It plays a diffusive effort convection role [41].

Retisert an Intravitreal embed having fluocinolone acetonide [42-44], FDA has approved it for the treatment of non-irresistible back uveitis. The composition of embed medication discharge length is unique in relation to the previously mentioned Vitrasert®. The embed having a 0.59mg of FA and was intended to convey the medication for as long as 1000. The Retisert® embed is made out of a focal center comprising of FA compacted into a 1.5mm width tablet [45].

2. Periocular infusion:- Periocular infusion is applied to the space around the eye through the Tenon's back, subconjunctival, and pericyte pathways [37]. Among them subconjuctival infusion is read for the conveyance of quality medication [46]. Subconjunctival infusion isn't just about as compelling as IVT infusion, yet is less obtrusive. Looked at with skin organization, this strategy works on the bioavailability of medications in the retina and glassy [37]. Quality of medication can be suited at the infusion site and have less harmful incidental effects since they can't enter into other visual tissues or fundamental course because of their high molecular weight [46].

3. Choroid:- The choroid is an exceptionally vascularized boundary that lies between the RPE and the sclera. The level deliveries oxygen and supplements to the retina. It has a 200μm wideness and it is out-of-the-way into five level: The Bruch's film, the choriocapillaries layer, two vascular layer and the suprachoroidal layer [47]. As far as medication conveyance, it should be though about the choroid shows two distinct practises: (1) It goes about a static hindrance due to suprachoroid design and (2) it gives a dynamic hindrance as result of a choriocapillaries-layered blood stream. The two activities forestall the entry of carboxylic mixtures while emphatically charged hydrophobic medications can settle ties with the tissue, prompting slow-discharge warehouses. The atomic size of the medication additionally decides the diffusivity into the back portion [47, 48]

PROSPECTIVES OF OPHTHALMIC DRUG DELIVERY SYSTEM:-

Recent advances in local drug delivery had a making that expand ophthalmic remedy contact time and drug transport, including the enlargement of ointment, gels, liposomes preparations and some continuous and controlled-release substrates, such as the ocuserts, collagen shields and hydrogel lenses [49-51].

1. Liposomes:- The liposomes are phospholipid-lipid vesicles for pointing drugs to the definite-site in the body. It can be provided as controlled and discerning drug transfer and better-quality bioavailability and their probable in ophthalmic drug transfer appears superior for lipophilic than hydrophilic mixtures. They can essay about advantageous for fully recyclable and harmless but are a smaller amount constant than particulate polymeric drug delivery methods. They were originate to be a impending delivery system for administration of a number of drugs to the eye [52-53].

2. Nanoparticles:- In the field of 'nanomedicine' uses nanoscale skills (≤100 nm), normally for the research, treatment and/or a negotiable of diseases, and to realise a perceptive of the pathophysiology of a different types of disease, by the final object of refining value of life. There are several nanomedicine rewards which are compared to curable with drugs alone. These contains constant release of remedial agents, under attack delivery of drugs to particular cells or tissue, better delivery composed with water-insoluble drugs and big bimolecular drugs, and decrease the side effects[54].

In the present times, single chain polymer nanoparticles (SCNP's) directly transfer into the field of biomedical uses, with clearly developments in polymer sciences permitting the arrangement of bio-inspired nanosized architectures [60].

Table 1:- Formulations of drug nanoparticles by several eye diseases.

Drug Nanoparticles	Eye disease	Reference
Viral keratitis	Acyclovir	[55]
Post Cataract Treatment	Dexamethasone sodium phosphate	[56]
Dry Eye	Cyclosporine A	[57]
Glaucoma	Dorzolamide	[58]
	Brimonidine Tartrate and Timolol Maleate	[59]

3. In-situ gels:- In-situ gels are used as a solutions or suspension that are ability to form a rapid sol-to-gel. The preparation of in-situ gel have various factors like temperature modulation, pH change, UV irradiations that drug out in a continuous and controlled manner. In-situ gel are administered by the several routes like oral, ocular, injectable etc. and some advantages likely to sustained and comprehensive schedules to drug delivery systems[61]. Aqueous gels are formed by that polymers which are hydrophilic in nature i.e. hydrogels [62]. Middleton and Robinson formed a sol to gel system by mucoadhesive property to get transfer the steroid fluorometholone to the eye. The formulation gave superior relief of drug during a longer duration of time in the rabbit's eye as related to conventional eye drops [63].

4. Niosomes:- They are the two layered structural cavity made up of non-ionic surfactant that are knowledgeable for increasing every basophilic and hydrophilic components. Systemic drainage can be reduces by means of

the niosomes and refining the residing time and showcase the higher ophthalmic bioavailability. Niosomes are to be non-reusable and conflicting [64].

Vyas *et.al* reported that about 2.49 instances upward jostle the ocular bioavailability of timolol maleate condensed in niosomes equated to timolol maleate. [65].

5. Gels:- In few years, ophthalmic gel is more popular than ointment in ophthalmic treatment [66]. Precorneal residence time for the preparation may be improved by adding viscosity enhancer on the ophthalmic base. Viscosity enhancer form the viscous gel by increasing the concentration of water. Ocular gels have limited bioavailability due to its highly viscous in nature. Ocular gels cause a blur vision, matting of eyelids because of its highly viscous in nature that's why patient acceptance rate is low [67].

Methods Of drug release

There are several methods of drug release as per concept of the eye:-

(i) Diffusion

(ii) Bio-erosion

(iii) Osmosis

(i) Diffusion:- In this method[68,69], the release of drug is continuously by the way of tear fluid through membrane at a fixed rate. The solid non-erodible body is made up by the inserts with the help of minute openings and spread drug. The drug is released via diffusion by the help of minute opening. The true dissolution generally happens by the help of inflamed polymer in a soluble method. In swelling- controlled devices, the active agents is consistently mixed with glassy polymer and the glassy polymer is the drug-resistant and the diffusion can't take place with dry matrix. On the eye, insert is fixed then the tear fluid water start to permeate the matrix and after that selling and constant chain polymer relaxed and diffusion occurs. The swelling process followed him dissolution of matrix and thus hang on upon polymer structure: cross linked or partially crystalline polymers is so lesser dissolve than linear amorphous polymer.

(ii) Bio-erosion:- In this method of drug release[69,70], the results of interaction of the inserts with the tear fluid is that the controlled sustained release of the drug by bio-erosion of the matrix. It is supposed that additional controlled release than the drug may be distributed uniformly during the matrix is achieved, when the drug is quickly rigorous in the matrix.

In E-type devices, the polymer solubilization, and water soluble particles that takes forward the rate of drug discharge is organised by a chemical hydrolytic reaction. These polymers, as identified by Heller [71], may under taken the surface hydrolysis. Erodible inserts undertaking bulk hydrolysis can show the zero order kinetics.

(iii) Osmosis:- In this method[69], the insert consist of transverse impermeable elastic membrane and they are in-between the interior into a first compartment and a second compartment; the first compartment is made up of semi-permeable membrane and the impermeable elastic membrane, and the second compartment is made up of an impermeable material and elastic membrane. The drug release opening present in the impermeable wall of the inserts. The first compartment comprises a solute which can't permit through the semi permeable membrane and the second compartment gives a reservoir for the drug which are in liquid or gel form.

The drug is forced through the drug release orifice, when the insert is located in the aqueous atmosphere of the eye than eye disperses into the first compartment and elasticity the elastic

membrane to enlarge the first compartment and diminish the second compartment [69].

Ocular membrane permeability:-

Some chemical compounds of pharmacokinetics properties are to be cross the membrane of the eye that should be make difficulties and several opportunities in ocular drug delivery. The highly necessity of logP resulting 90% of epithelium absorbency for hydrophobic substances, but the almost sum up of macromolecules (radius of more than 10 A°). For the intraocular drug delivery, the epithelium is main restrictions. The particle of molecules (paracellular penetration route) and permeation which cross the coatings of endothelium that are lies on both logP and hydrophobic small molecules are considerably more impermeable in assessment to corneal stroma [72]. In recent times, the two models i.e. ex-vivo and in-vivo is used for determination of permeability and drug absorption in the cornea.

Agarwal and Rupenthal reported that [73], for revision of penetration, the cell based models are normally used. Some benefits of these models are normally differentiate the laboratory used animals in cheap budget with minimal number of animal studies. Out of these models, one is the closest model to the real cornea they rebuild the tissues cultures which is composed of different layers of cell that use in mimic and the three-layer structure like epithelium, endothelium and stroma Ex-vivo corneas of several animals like rabbit, porcine, bovine are normally use to evaluate the corneal permeability and absorption. The eyes of rabbit is normally used for ex vivo models, but in the rabbit eyes the Bowman's layer is not present to make the maximum penetration of substances that compare with the human cornea. Size of the eye-ball, corneal thickness, length ratio of the cornea to eye-globe diameter, including Bowman's membrane in porcine eye are nearest to the eye of human [73].

Permeation Enhancer:-

The corneal permeability is enhanced by using of permeation enhancers and this is scheme normally used to expand bioavailability of corneal epithelia upper on the surface instilled therapeutics targeting tissues. One theory proposed an increasing the permeability of cell membrane that it could be through effect on the P-glycoprotein [74,75].

In accumulation to direct enhancement of drug permeation, penetration enhancers can expand the bioavailability by other indirect mechanism. It can be advised that the raising to a liquid dosage form and shrinks the size of drop imparted by resulting reduction in non-productive and systemic dosage loss[76]. Some agents normally regulate the corneal and conjunctival surface and to enable onset drug penetration. Some ocular preservatives likes chelating agents, bile salts, and polyethylene glycol are several example permeation enhancers that increase drug bioavailability [77].

1. Amino-acid Transporters:- The amino acids transporters are liable for synthesis of protein by well-designed and physical reliability of retina/RPE and conjuctiva cares. Transferring the peptides from circulating blood to different organs are helped by this transporters. The existence of different amino acids transporter (LAT1, $ATB^{0+}$and ASCT1) into the cornea have been fixed by DNA and RNA. Thus dynamically present on passage of L-phenylalanine, L-arginine and L-alanine through cornea. The peptide transporter divided by their substrate specificity and sodium dependency [78]. Amino acid transporters are of two types of systems i.e. system L (large) and system y^+ (cationic) which goes to sodium independent transporters but

system X (anionic) [79]. The large neutral amino acids transporters is conveyed by two types of isoforms i.e. LAT1 and LAT2. LAT1 is normally elaborate the passage of large neutral amino acids, like Lue, Phe, Ile, Trp, His, Met and Tyr whereas LAT2 transports both bulky and slight neutral peptides [80, 81]. Blisse *et al.,* reported that the presence of B^{o+} peptide transporter and sodium-dependent with wide substrate specificity on human cornea and corneal of rabbit epithelium. Now neurotransmitter gene family are held by this transporters and established to have affinity's equivalent into the PEPT1 conveyance of moieties [82, 83].

2. Vitamin C transporter:- The cornea and the ocular tissues are to be protected by the help of antioxidant properties of vitamin C from UV radiation. Vitamin C is present in aqueous humour i.e. the higher concentration which is liable to the anticipation of cataracts. Sodium-dependent vitamin C transporter (SVCT1 and SVCT2), low capacity transporter, high-affinity, existing in the cornea's epithelium i.e. liable on behalf of moving for condensed form of Vitamin C (ascorbic acid), but GLUT, low affinity and high capacity effective hexose transporter, translocating to the oxidated form of Vitamin C (ascorbic acid) [84].

3. Glucose transporter:- Glucose is an important ingredient for metabolism [85], glucose is used in the retina to come across the energy for oxidative absorption. The stereo-specific facilitated diffusion are to be a crossed the blood retinal and the blood aqueous barriers by transporting the glucose. Glucose comes in seven different isoforms transporter (GLUT1-GLUT7), GLUT-1, 3 and 4 are the higher affinity glucose transporter, while the high-affinity fructose transporters is GLUT5, glucose transporter with a low affinity is GLUT2 [86]. The transporters like glucose transporters, nutrient transporter is the maximum effective transporters for the delivery of drug [87].

4. Peptide transporter:- The corneal epithelium is expressed as the amino acid transporters (PepT2, PepT1 and histidine/amino acid transporter- PHT1 and PHT2)[88]. Amino acid transporters are linked with the coupled of proton transporters for oligopeptide which comfort in the translocations of bi and tri-peptides and free steady that transversely the corneal epithelium [89]. Peptide transporter 1 and 2 (PepT1 and PepT2) suggest that important role in absorption of drug particles such as, β-lactum antibiotics and ACE inhibitors [90].

Viscosity enhancer:- When the formulation of viscosity is increases, than they extend the duration of precorneal residence time and bioavailability of ocular, which comes a superiority to a decreasing the frequency of dosing. The enhancers are mainly used in ophthalmic preparations to increase the ideal site of drug delivery. The several viscosity enhancers are used like polyacrylic acid (PAA), polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), carboxy methyl cellulose, hydroxy ethyl cellulose, carbopol and etc. [91-92]. Whereas, they make better for the ocular bioavailability, apart from they may effect such as blurring, tacky and uncomfortable to the eyes that may cause in patient compliance.

Table 2:- Viscosity enhancing for the formulations of ocular drug [93].

Viscosity agents	Activity	Applications
1. Carbomer 2.Sodium carboxymethylcellulose	+++ +++ ++	Cumulative bioavailability's of hydrocortisone in

3. Chitosan 4. Xanthum gum	+	laboratory animal (rabbit). Tropicamide uses for Mydriatic effect in laboratory animals (rabbits) Cumulative bioavailability of tobramycin in laboratory animals (rabbits). Pilocarpine formulation study in humans.

The capability of mucoadhesive viscosity enhancing is categorized as superb (+++), better (++), and low (+) .

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