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OCULAR DRUG DELIVERY: INSIGHTS TO BARRIERS AND STRATEGIC APPROACHES FOR ENHANCED THERAPEUTIC EFFICACY

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ABSTRACT: Ophthalmic drug delivery is a highly complicated task to actively target the internal structures of the eye. The eye being a very delicate organ is protected by multiple physiological barriers which include corneal epithelium, blood ocular -barriers, conjunctiva etc. which limits the transport of lipophilic and hydrophilic molecules across the various layers of the eye making it difficult to target the posterior areas of the eye. Although these regions can be accessed by interventional approaches like intravitreal injections and mechanical modifications like iontophoresis but are associated with physiological restrictions and patient discomfort. This review analyses all the barriers to ocular drug delivery along with different strategies to overcome these barriers including all the nanoparticulate strategies of drug delivery which aim to enhance permeation and bioavailability to ocular region. These methods accurately target the internal structures, practical to implement and are patient compliant. The review also gives a short information about the application of periocular route in drug delivery along with its significance in traditional medicine.

INTRODUCTION: The eye is one of the most advanced sensory organ of the human body, located in the anterior region of the skull into the orbital sockets which works to visualizing the environment surrounding the human without which no light can be detected and no object can be seen. The eye is divided into the anterior and the posterior chamber and each chamber can be associated with different types of ailments. The eye being an human organ is subjected to various illness due to multiple factors, refractive errors being the commonest of all [1-3].

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Anatomically the eye gets blood supply through the ophthalmic artery which is a branch of internal carotid artery but the limitation of this blood supply is that is restricted only to the vascular layers of the eye i.e. the retina, choroid and the ciliary body, the a vascular structures like the vitreous humor, aqueous humor and the corneal structures lack the blood supply.

Majorly most of the diseases are treated by the administration of suitable drugs either systematically or by topical administration but the eye being such a delicate and complex organ of which some of the internal components which lack a blood supply, the delivery of any drug becomes difficult. The drug can be neither topical administered (for ailments of inner ocular components) nor it can be given by blood routes which indicate the need of developing a separate

and targeted methodology to deliver drugs into the eye. The most easiest way to administer any drug to the eye is in form of ophthalmic solutions which are easy to commercially manufacture and are also patient compliant but the disadvantage is that the dose that can be administered is very low in a drop and also 40-60% of the drop gets drained through the lacrimal drainage thus further reducing the dose of the drug. Modifications like viscosity adjustments for prolonged ocular residence and, micronization of drug particles for faster uptake by ocular tissues can be attempted to bypass the disadvantages of simple eye drops but still the gap exists unattended to deliver the drug into the internal structures of the eye as superficially the corneal and the scleral histological structure blocks the penetration of drug molecules to the internal ocular components.

Ocular drug delivery not only focuses to deliver the drug to the superficial layers of the eye but also to the internal ocular structures hence understanding the barriers that restrict the delivery of drugs to the targeted components is of utmost necessary which will help in developing a suitable methodology that can effectively breach the barrier without damaging the vital layers of the organ also deliver the drug to the targeted component of the eye. The methodology should be accurate, should not be painful to implement and also must be patient complaint such that the patient can use the developed formulation with ease.

Anatomy of the Eye: The eye is located into the bilateral and medially divided orbit in the anterior region of the skull. The location of the eye into the orbit is oriented anterolaterally which facilitates binocular vision. The structure of the eye is further split into anterior and posterior region. The anterior region consists of cornea, conjunctiva, aqueous humor, iris, ciliary bodies and the lens which occupies roughly one third of the total eye volume. The remaining volume is captured by the posterior region comprising of the choroid, vitreous humor, retina and the optic nerve [4].

The human eyeball is organized into three preliminary layers, outer reinforcing layers consisting of cornea, sclera, and its invaginated zone; the limbus. The median uveal layer consists of centric perfused layer of the globe consisting of iris, ciliary body, and the choroid. The third layer is the inferior layer which is the retina consisting of retinal pigment epithelium and the neural retina [5].

The arterial-venous system consists of ophthalmic artery, which is an extension of internal carotid artery, symbolizing the primary arterial supply for the orbital cavity. The conjunctiva and other adjunct structures are the claimants of a binary vascular supply both from the limbs of extrinsic carotid and ophthalmic arteries [6].

Histology of Outer Layers of the Eye and its Influence on Drug Penetration: The outer layers of the eye; cornea and the sclera are the main biological barricades to the ocular drug delivery hence A histological understanding of the layers of the eye is necessary for diagnosing disease pathophysiology and also to grasp curative approaches. Comprehensively, from an anatomical perspective, the eye can be viewed as a range of superimposed layers of tissue but in terms of ocular drug delivery cornea and the sclera are a major concern which needs to be prevailed over to deliver drugs into the inner chambers of the eye [7].

Cornea: Cornea the outer transparent layer of the eye is a penta-layered tissue which protects as well as nourishes the eye. The cornea consists of corneal epithelium, the Bowmans Membrane, stroma, Descemet's Membrane and the corneal endothelium. The corneal epithelium functions as a protective barrier and contributes to transparent nature of the cornea and consist of non-keratinized stratified squamous epithelium cells. The cellular distribution begins with a single layer of columnar cells originating from the basal membrane, which also act as stem cells as they are mitotically active, further the wing cells which include bis or tris-layered polygonal cells, lastly the superficial squamous cells which are seen as a bis layered flat cells with microvilli on the surface covered by tear lacrimal fluid for optical lubrication The presence of tight junctions and the presence of lipids makes the layer lipophilic in nature which can be a major rate limiting barrier for the hydrophilic drugs which means that the histology favours lipophilic drugs (fat soluble drugs) like dexamethasone, timolol and latanoprost over hydrophilic drugs (water soluble drugs) [8-10].

The Bowmans membrane also known as the anterior limiting lamina is present below the epithelial basement membrane and histologically comprises of acellular layer composed of arbitrarily organised collagen fibrils incorporated in a grounded component. It functions as to provide mechanical robustness and a protective obstruct to trauma and infections. Due to the complex arrangement of collagen fibres it hinders drug diffusion and its permeability is very low almost impermeable for most of the drugs [11].

Substantia propria (Stroma) is the thickest layer present which acts as a secondary barrier and provides elasticity and transparency and preserves optical lucidity through homogeneous collagen distribution and precise hydration. The stroma is composed of corneal fibroblasts which are flattened cells that reside between lamellae and release collagen and proteoglycans. It also contains lamellae of collagen fibrils which are organized parallel within each lamella but perpendicular to adjacent lamellae, this arrangement ensures lucidity. Since, the composition of this layer is mostly aqueous and homogenously arranged collagen fibrils it favours hydrophilic drugs like gentamycin and acyclovir and restricts the movement of lipophilic drugs due to the aqueous surroundings.

The Descemet's Membrane is located at the foundation membrane of the endothelium works as a robust, elastic barricade that is resistant to trauma and infections. The membrane gets further subdivided into anterior branded zone and posterior non-banded zone and is composed of collagen types IV and VIII. In contrast with the stroma it offers minimal resistance towards movement of molecules due to the comparatively less homogenous dense organizations and offers moderate permeability of molecules [12]. The corneal endothelium is an individual layer of hexagonal cells which functions to maintain corneal hydration and lucidity by removing surplus fluid from the stroma into the anterior compartment. In contrast to the epithelium the presence of only single layer makes it significantly unsealed in nature. It allows the movement of both lipophilic (prednisolone acetate) and small hydrophilic drugs (ciprofloxacin) as the tight junctions areminimally developed. Since the removal of excess fluid from the stroma is facilitated by the sodium/potassium ion channels it actively supports paracellular diffusion and active ionic transport of suitable drugs as well [13-14].

Sclera: Sclera is the outermost layer of the eye depicted as the white visible area of the eye and functions by providing a boundary to the organ. The sclera holds the entire structure of the eye maintaining its definite shape. The sclera is composed of episcleral, scleral stroma and the Lamina Fusca. The episclera is located just beneath the conjunctiva and functions by providing a transition zone between the sclera and the conjunctiva [15]. The episclera is comprised of loose connective tissue containing collagen fibers and fibroblasts, it is highly vascular and helps enrich the superficial component of the sclera. The presence of loose connective tissue and high vascularity makes it relatively permeable and can also eliminate the drug expeditiously by absorption into systemic circulation which can significantly impact the drug residence time in the ocular region. The entire region is composed of collagen fibers making it an aqueous environment thus favouring moderate diffusion of hydrophilic drugs over lipophilic drugs [16].

The scleral stoma is the middle layer and functions by providing stress resistance and firmness to the eye structure. It comprises of tightly packed heterogeneously organized connective tissue mainly of type I collagen bundles, in contrast with cornea where in they are homogenously arranged. The fibroblasts are compressed and sandwiched between the collagen bundles. The scleral stroma is avascular unlike the episclera which is vascular. This layer is densely packed and with minimal hydration its restricts the movements of lipophilic molecules however small hydrophilic molecules can diffuse through the aqueous pores which lie between the collagen fibers. The deficit of tight junctions also favours passive diffusion but at a very slow rate [17-18]. The innermost layer is the Lamina Fusca and functions by binding sclera to the choroid and the melanin pigment present also helps in diminishing the light reflection within the eye. The Lamina Fusca comprises of loose connective tissue with pigmented melanocytes and tender elastic fibers. The collagen fibers are more loosely arranged than in stroma.

This loose arrangements of fibers facilitates transport of the drug molecules but the melanin binds to the foreign molecules thus trapping lipophilic and cationic drugs which prevents them from diffusing into deeper tissues [19-20].

Barriers to Ophthalmic Drug Delivery: The barriers which inhibit the easy approach of the drugs to internal ocular delicate tissues can be classified as follows **Fig. 1.**

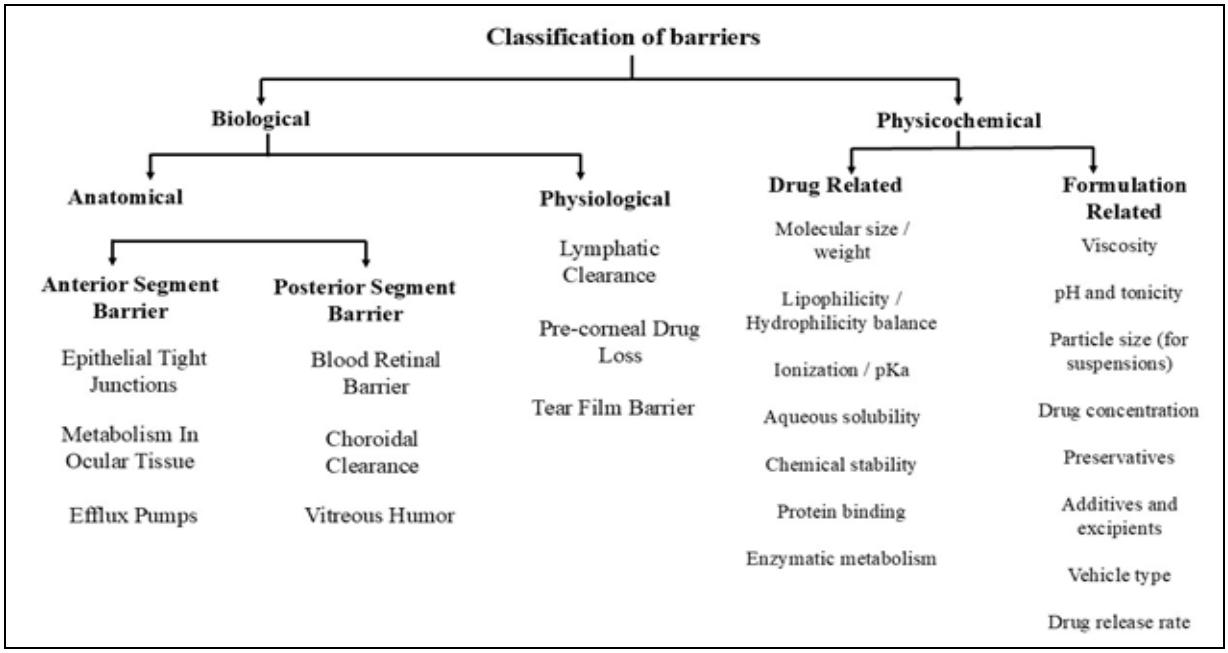

FIG. 1: CLASSIFICATION OF OCULAR DRUG DELIVERY BARRIERS

Anterior Segment Barriers:

Epithelial Tight Junctions: The eye is defended corneal epithelium by a robust barrier that isolates from the external environment. This axiom barrier is formed by the Zonula occludens or the tight junctions which are comprised of integral transmembrane proteins (claudins, occludin and membrane associated proteins ZO-1, ZO-2, ZO-3.) that circumscribe the cells inferiorly to the apical surface. This organization makes a perfect defensive shield against the passive movement of macromolecules and other substances. Apart from the 'shielding' function it also acts as a demarcating function. The tight junctions are a morphological analogue of a regional diffusion shield between the functionally split apical and basolateral domains [21].

Drug Metabolism in Ocular Tissue: The metabolic machinery is well constructed to inhibit the passage or amassing of foreign bodies from systemic circulation into the exquisite ocular tissues. The metabolic machinery consists of enzymes like esterases, aldehyde reductase, peptidases, which form a robust defensive-metabolic barrier which restricts the ocular entry of foreign bodies. A medley of esterases like acetyl, butyl, and carboxycholinisterases, have been evidenced to be expressed in ocular tissues. Cholinesterase is evidently found in iris, lens epithelium, cornea and ciliary bodies. It is also seen that CYP family enzymes (CYP450) are expressed in ocular tissues, these are of utmost pertinence to drug metabolism by N-oxidation, N-hydroxylation, sulfonation type of enzyme-catalase reactions. Various hydrolytic enzymes are also operative in the retina which includes aryl sulfatase, N-acetyl-β-glucosamide and acid phosphatase. These are broadly dispersed throughout the body with a wide range of substrate specificity [22-23].

Efflux Pumps: The efflux pumps show a wide substrate specificity and consist of 2 major efflux transporters P-glycoproteins and multidrug resistance associated proteins play a vital role in xenobiotics and inhibiting its ocular bioavailability. The *in-vivo* drug absorption in cornea is prevented by the P-glycoprotein by expelling large neutral or cationic compounds whereas the Multidrug resistance associated protein helps in eliminating anionic compounds [24].

Posterior Segment Barrier:

Choroidal Clearance: The transscleral drug delivery is restricted by another defensive mechanism known as the Choroidal Clerance, with this mechanism the drugs are rapidly up taken by the rapid blood flow and is expelled from the ocular tissue thus reducing the bioavailability and blocking the transport towards the retina. The choroid is regarded as a depot due to its high perfusion of blood where in the bioavailability is assumed to be zero during the pre-clinical studies [25].

Blood Retinal Barrier: The blood-retinal barrier is a protective barrier with a concept similar to blood -brain barrier that is essential to protect the delicate retina. The BRB is a compact and constraining physiologic fence that modulates the ions, proteins and water flux inflow and outflow from the retina.

The BRB is sub-organised into inner BRB consisting of tight junctions between retinal capillary endothelial cells and outer BRB consisting of tight junctions between retinal pigment epithelium cells. These tight junctions present in inner and outer BRB restrain the paracellular passage of fluids and macromolecules between the retina and blood and the endothelial cells deliberately modulate the influx and efflux movement [26].

Vitreous Humor: The vitreous humor mainly consisting of water (99%) along with hyaluronic acid and collagen fibers forms a limpid-jelly like structure that occupies the posterior chamber of the eye filling the area between retina and the lens, this forms an essential fence to the posterior segment drug delivery. Its compact and viscous matrix restrains the passive transport of dug molecules especially with a large molecular size, hydrophilic or cationic/anionic.

The collagen binding o drug further restricts the drugs bioavailability and decelerative their motion towards the retina and choroid. The movement within the vitreous is majorly passive diffusion which makes drug transport a very slow process. Metabolizing enzymes such as esterases and hyaluronidases also deteriorate the drug further reducing its therapeutic effectiveness. These attributes of the vitreous humor hinder dug delivery to the posterior segment of the eye [27-28].

Physiological Barriers:

Pre-Corneal Loss of the Drug: The typical precorneal volume ranges between 7-10µL however a commercial dropper can deliver up to 56 µL hence the remaining volume is lost either by nasolacrimal drainage or by reflex blinking.

Nasolacrimal drainage occurs through a tiny hole called as the lacrimal puncture that is present at the medial side of the eye towards the nose, where reflex blinking significantly means that when foreign substance enters the precorneal area, the blinking of eye lids begins as a reflex to eliminate the foreign substance, this process significantly reduces the overall drug bioavailability [29].

Lymphatic Clearance: The conjunctiva is tremendously rich in blood vessels along with the lymphatic vessels. Superficially applied drugs may be eliminated by the lymph dispersal system while crossing the conjunctiva which causes poor drug passage through the tissues. Additionally lymphatic systems may initiate immune responses which can further diminish the therapeutic efficacy of micro-particulate drug delivery systems [30].

Tear Film Barrier: The eye initial defensive strategies include dilution of external substances and subsequent outflow by excessive flow of the tears which is known as the tear film barrier. The tears or the lacrimal fluid is aqueous isotonic liquid which keeps the eye moist and lubricated.

Superficial application of any drugs leads to enhanced lacrimation thus diluting the formulation which in turn results in significant loss of therapeutic efficiency due to loss of drug. This process impacts on the ocular residence time which restricts the drugs absorption into the ocular tissues and ultimately impacts the therapeutic effect of the drug [31-32].

Physicochemical Barriers [33-36]: Physicochemical barriers are associated with the natural properties of the dug and the behavioural properties of the formulation hence physicochemical evaluation is conducted primarily in analysis of drug and in development of new dosage forms. The physiochemical parameters of drug **Table 1** and formulation **Table 2** are as stated below.

TABLE 1: DRUG PROPERTIES AS BARRIERS FOR OPHTHALMIC DRUG DELIVERY

Drug property	Effect on delivery	Justification
Molecular size/weight	Large molecules show poor permeability	Corneal epithelium allows mainly small molecules (<500Da) to pass through
Lipophillicity/ Hydrophillicity balance	Highly lipophilic drugs may get trapped in epithelium and highly hydrophilic drugs cannot cross lipid barrier	The cornea contains both hydrophilic (stroma) and lipophilic (epithelium) layers hence balance lipophilicity is ideal
Ionization/pKa	Degree of ionization affects absorption	Unionized forms penetrate lipid membranes better than ionized ones
Aqueous solubility	Restricted availability in tear film if the drug has low solubility	Insoluble drugs precipitate or form suspensions with poor diffusion
Chemical Stability	Susceptible to hydrolysis/oxidation in tears	Leads to drug deuteriation prior absorption
Protein Binding	Strong binding to tear proteins (lysozyme) reduces free drug concentration	Only the unbound fraction can penetrate ocular barriers

TABLE 2: FORMULATION PARAMETERS AS BARRIERS TO OPHTHALMIC DRUG DELIVERY

Formulation parameter	Effect on delivery	Justification
Viscosity	Low viscosity formulations are rapidly drained	Short precorneal residence time limits absorption
pH and Tonicity	Non-physiological values cause irritation, further causes reflex tearing and loss of drug	Ideal pH=7.4,isotonic with tears (0.9% sodium chloride)
Particle size (suspensions)	Large particles irritate and trigger tearing, too small may dissolve too rapidly	Ideal range 5-10 µm.
Drug concentration	Very high concentration doesn't proportionally increase absorption	Saturation of corneal transport and increased reflex tearing
Preservatives	Benzalkonium chloride and others can damage corneal epithelium	Disrupts barrier, causing unpredictable absorption and irritation
Additives and excipients	Surfactants or stabilizers has effects on drug partitioning	Can modify solubility or permeability
Vehicle type	Aqueous solutions, suspensions, ointments, gels, inserts, etc differ in retention time	Solutions are eliminated rapidly, viscous and lipidic systems have prolonged ocular residence
Drug release rate	Burst release or unregulated diffusion minimizes sustained availability	Essential in novel drug delivery systems.

Strategies to Bypass Ocular Barriers: The ocular barriers can be bypassed by the modification of formulation with respect to its physiochemical properties, delivery by novel drug delivery approaches, lipidic carrier systems, mechanical systems of enhancing permeation and many other methods as discussed below **Fig. 2.**

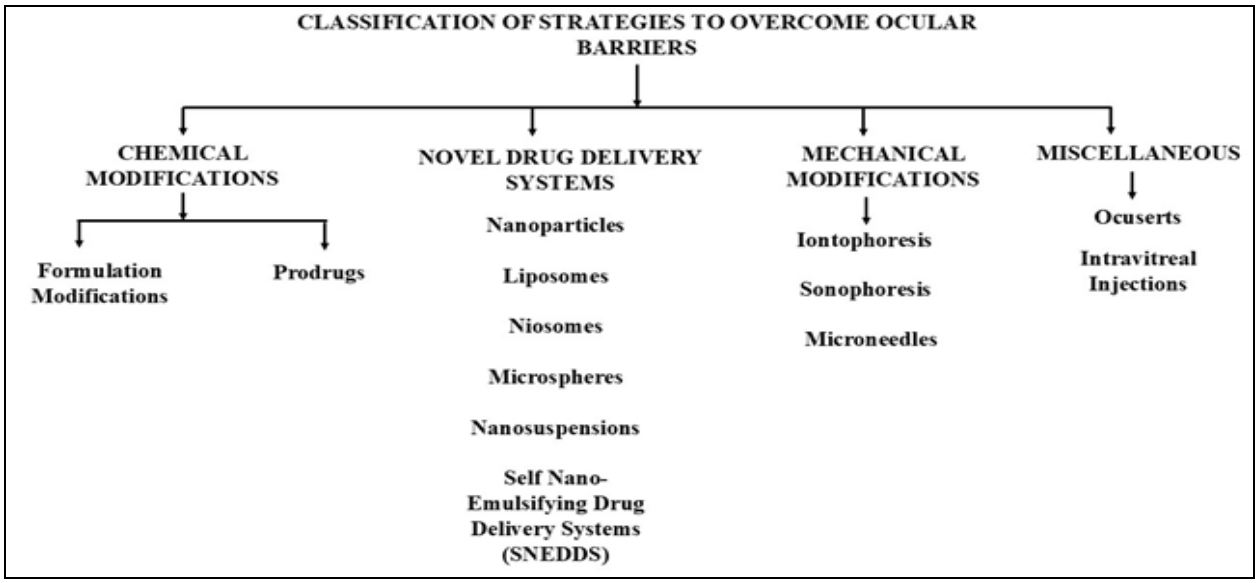

FIG. 2: CLASSIFICATION OF STRATEGIES TO OVERCOME OCULAR BARRIERS

Formulation Modification: The modification of viscosity is one of the rheological modifications which can affect the physical properties of the formulation. The increase in the viscosity means improvised ocular residence time, and reduced eliminated thus resulting in augmented absorption. Polymer derivatives such as methylcellulose, HPMC, hydroxyethyl cellulose and PVA can be employed to enhance viscosity. As per the studies conducted by Patton and Robinson the optimum viscosity ideal for ocular products (solutions) ranges from 12-15 cps, viscosity ranges higher than the optimal range is associated with ocular surface irritation, escalated blinking subsequently enhanced drainage. A highly viscous formulation may cause temporary blurring of vision as well [37].

Corneal absorption can be elevated by the modification of the structural novelty of the corneal epithelium by the use of permeation enhancers. Permeation enhancers increase corneal absorption by altering the originality of the corneal epithelium. Cationic surfactants (cetroidchloride, benzalkonium chloride), ionophores (razarosides), non-ionic surfactants (tween 60, tween 80) etc can be employed to enhance permeation [38-39].

The normal pH of tear fluid is 7.4 and osmolarity of around 300 mOsm/kg hence maintaining the pH and osmolarity formulation close to the normal values are the most significant formulation concepts to not only bypass ocular barriers but also to maintain patient comfort. Regulation of pH of formulation close to the physiologically accepted range reduces irritation, reflex blinking and ultimately improves ocular bioavailability. Regulation of pH also enhances the optimization of ionization state of the weakly anionic or cationic drugs thus enhancing corneal permeability [40-41].

Ocular bioavailability may also be improved by maintaining the isotonicity with the tear fluid. Isotonicity is the property of formulation to bear the same osmotic pressure as that of the physiological fluid hence maintaining isotonicity with tear fluid reduces lacrimation which can lead to loss of formulation by dilution thus leading to reduced bioavailability. Hypotonic solutions may elevate corneal hydration and diffusion of the drug, while hypertonic formulations find its importance in removal of fluid in cases of edema.

Thus, refined optimization of pH and tonicity helps maintain ocular comfort, reduce loss of drug from precorneal area and maintain ocular bioavailability of the drug [42].

Prodrugs: Prodrugs are pharmacologically quiescent analogues of drug molecules which requires a chemical or enzymatic modification to transform into pharmacologically active moiety within the physiologic compartment. The concept of prodrugs was launched about 15 years ago for ophthalmic purposes, which showed that the absorption of epinephrine was enhanced by its prodrug analogue dipivefrine.

Prodrug engineering is an chemical concept to dispatch parent drug to targeted site where is chemically converted to its active form to achieve maximum bioavailability in the targeted tissue. It is an highly efficient strategy to deliver those drugs which cannot bypass the physiologic and physicochemical barriers by itself [43-44].

An ideal prodrug should possess the functional group in its chemical structure which can be derivatized to convert in the active form by the enzymes present at the target tissue, further the parent drug, prodrug and the pro-moiety should be safe and non-toxic to the tissues with pro-moiety exhibiting fast exclusion from the tissues. Esterases and peptidases should be able to biologically convert the parent drug into the pharmacologically active species within the targeted region itself, the rate of conversion should be refined to avoid moiety severance and dumping of parent dug at non-specific target site [45].

Elementally, ocular prodrugs are can be organized according to their functional group refinement as ester, amide, oxime and carbamate prodrugs Ester prodrugs enhance corneal permeability by enhancing the lipophilicity, by esterification of hydroxyl or carboxyl group of the parent drug. For example, dipivefrin is ester prodrug of epinephrine utilized in glaucoma. Dorzolamide are stable derivatives of the amine prodrugs which endure retarded enzymatic hydrolysis offering sustained release of the drugs. Stability enhancement and membrane ingression is achieved by oxime prodrugs whereas carbamate prodrugs augment both solubility and enzymatic stimulation.

These adjustments potentiate the drug to permeate across the corneal epithelium, oppose precorneal metabolism and transform to its active form in ocular region thereby enhancing bioavailability and therapeutic efficacy of the drug [46-47].

Novel Drug Delivery Systems: The implementation of nano-technology derived drug delivery systems offers superior prospects for the dispatch of pharmaceutically active moiety when administered topically at the ocular premise. These platforms defend the encapsulated drug with supreme efficacy as well as expedite its penetration into the different ocular tissues.

Nanoparticles [48-54]: The ocular barriers can be bypassed by the usage of nanoparticles (10nm-100nm) which can significantly improve the permeability of large, poorly aqueous soluble molecules. Nanoparticles utilized in ocular drug delivery can be categorized as polymeric nanoparticles, quantum dots, hybridized nanoparticles and inorganic nanoparticles (silica nanoparticles, gold/silver nanoparticles, carbon nanotubes). Former investigations revealed the employment of cerium oxide nanoparticles **Table 3** for age -associated macular degeneration, gold nanoparticles for uveitis and silver nanoparticles for fungal keratitis.

The SLN are founded by bio-congruent lipids that are efficient substitute for ocular drug delivery systems as they can elevate corneal uptake of drugs and enhance ocular bioavailability of lipophilic and hydrophilic drugs Polymeric nanoparticles like SLN (Solid lipid nanoparticles) are organized as a rigid lipid matrix in nanometer range embedding the drug which is anchored by a layer of surfactants. Potential of controlled drug release, drug targeting, accelerated stability a significant drug loading, lack of biotoxicity are some of the merits of SLN in contrast over other colloidal carriers. Additionally, SLN can be sterilized by autoclaving which is an crucial element in formulation of ophthalmic products

TABLE 3: PRIOR INVESTIGATIONS SIGNIFYING THE USE OF INORGANIC NANOPARTICLES IN TREATMENT OF OCULAR AILMENTS

Type of inorganic nanoparticle	Composition	Loaded drug	Targeted ocular disease
Gold nanoparticles	Colloidal gold	Dexamethasone, Bevacizumab	Age-related macular degeneration, uveitis
Silver nanoparticles	Colloidal silver	Amphotericin B, Natamycin	Fungal Keratitis
Cerium oxide nanoparticles	Cerium oxide	Curcumin, Retinoic acid	Age-related macular degeneration , oxidative overload
Silica nanoparticles	Mesoporous silica	Cyclosporin A , Timolol	Glaucoma
Zinc nanoparticle	Zinc oxide	Ciprofloxacin, Ofloxacin	Blepharitis, Keratitis (anti-microbial)
Carbon nanotubes	Graphene oxide	Si-RNA, Tacrolimus	Diabetic retinopathy, Retinal vasculitis

Liposomes [55-56]: Liposomes are defined as orbicular vesicles of size ranging from 20nm up to 1000nm. These vesicles are composed of concentric lipid layer enclosing an aqueous core. The modulation of the phospholipid composition of the lipid membrane determines the physicochemical behaviour of the liposomes. Typically, only one type of phospholipid is employed in the formulation of the basic liposomal organization however using different combination of phospholipids have known to provide structural rigidity than using just one phospholipid. Soy phosphatidycholine, dioleoyphosphatidylglycerol have been used in ocular liposomal formulations due to their low biotoxicity, low immunoreactivity and benefit for corneal healing. For example, degrative ailments of the posterior region of the eye (diabetic retinopathy) have been successfully treated by the usage of lipid nano-systems in conjunction with si-RNA complexes. Previous study conducted by Smolin. *et al* exhibits the first employment of liposomes in ocular therapy which contrasts idoxuridine in solution with respect to liposomal form for the prophylaxis of acute and chronic herpetic keratitis in rabbits. It was evident that liposomal idoxuridine was more potent in healing the herpetic lesions rapidly than the solution. The later studies showed the enhanced effectiveness was due to amplified corneal

permeation attained through liposomal encapsulation.

Niosomes [57-58]: Niosomes are lipidic vesicles comprising of non-ionic surface active layers which serves as vector for the drug delivery to the targeted site. In contrast with the liposomes niosomes are composed of bilipid layers as compared to liposomes which have a single outer lipid layer. Niosomes are nano-sized lipid vectors which are formulated by a combination of non-ionic surfactant of the alkyl or dialklylpolyglycerol ether category and cholesterol with consequent hydration in aqueous media. The niosomes can be categorized as unilamllar or multilamellar and further sub organized into small unilamellar, large unilamellar vesicles. The size of small unilamellar vesicles is ranges between 10-100nm while large unilamellar vesicles range between 100-300nm, Multilamellar vesicles are bigger than 5 µm. Entrapment of both hydrophilic and lipophilic drugs, elevated transdermal / trans corneal penetration, Bio-compliant, non -immunogenicity and enhanced stability are some of the advantages of nisomal formulations.

Previous studies conducted has exhibited that there was significant decrease in intra-ocular pressure in contrast with marketed formulation of dorzolamide by the employment of bioadhesive sheathed nisomal formulation of acetazolamide synthesized from span 60, cholesterol, and stearylamine, also chitosan sheathed niosomal formulation of Timolol maleate (0.25%) showed a higher efficiency in reduction of intraocular pressure in comparison with the traditional marketed formulation.

Microspheres [59-61]: Microspheres and microcapsules are similar like tablets and capsules of the micron range Microspheres are homogenous particles comprising of a spongy or rigid polymer core on the contrary microcapsules comprises of a polymeric sheath enclosing a solid or liquid drug depo. Microspheres are attributably free flowing powder with particles ranging from 1-1000 microns. Polyethylene and polystyrene microspheres are the two widespread types of polymeric microspheres. The microspheres formulated using gelatin, albumin, poly (D,L lactic acid), polylactide, poly (glycolic acid) are generally employed in the prophylactic experimentation of vitreo-retinal degenerative ailments. Primarily the study conducted by Sieg and Tripplett showcased the obstacle of precorneal exclusion of particles by the utilization of 41 Ce-tagged polystyrene microspheres. Another study conducted by Beal *et al.* showed application of polypthalamide microcapsules containing enclosed technetium tagged albumin showed the enhanced residence of 60% instilled dose after 90 min in contrast with standard aqueous solution of albumin which showed 90% elimination within 10 min.

Nanosuspension [62-64]: Nanosuspensions can be defined as biphasic configuration of colloidal dispersion of nanonized drug particles that are reinforced by surfactants in an aqueous media. The decrease in particle size to nanometers results in increased surface area and saturation solubility which elevates the dissolution rate thereby showing enhanced absorption and subsequently higher bioavailability of the drug.

Top-down or bottom up methodologies can be implemented in the production of nanosuspensions. In high pressure homogenization nanoparticles are formed by cavitation and tangential stress when a gritty drug suspension is forced through a slim void under high pressure. In media milling method milling beads pulverise crystalline drugs into nano-sized particles. Further in precipitation methodology the drug is solubilized in a solvent and swiftly mixed with a non-solvent resulting in nano-crystal formation. Further supercritical carbon dioxide can be employed as an anti-solvent to precipitate minute drug particles.

Nanosuspension comprising of nanoparticles are advantageous over traditional dosage forms as they offer reduction in the amount of dose there by achieving the therapeutic outcome with minimal dose of the drug which further reduces the slightest possibilities of toxicity, sustained drug release for a prolonged time period thereby maintaining plasma drug concentrations to offer the therapeutic effect for a longer time period.

Self Nano-emulsifying Drug Delivery Systems (SNEDDS): Self-nano-emulsifying drug delivery systems (SNEDDS) are anhydrous preconcentrates of isotropic amalgam of surfactant, oil phase solubilizer and the therapeutic moiety.

Upon subtle mechanical stimulation in the targeted site these instantaneously form delicate oil in water nano emulsion with globules of size fewer than 200nm [65]. These small particles contribute by enhancing the drug dissolution and promote penetration across the conjunctival and corneal layers. The fine globules consist of the solubilized drug in the lipophilic constituent and facilitate elevated interfacial surface are for dispersion which facilitates movement across membranes by swaying the transport attributes. Transcellular and paracellular transport mechanisms are influenced by the lipidic constituents which enhance the drug uptake. The advantage of using SNEDDS is that the drugs from BCS class II (dexamethasone, cyclosporin A etc) and class IV (tacrolimus, amphotericin B etc) can be delivered by modifying the aqueous solubility of such drugs, also SNEDDS protects drugs from enzymatic metabolism and oxidative degradation [66].

Ionophoresis: Iontophoresis is a non-intrusive methodology used in intraocular drug instillation by enhancing permeation of ions thorough the ocular layers. In recent years the evolution of microprocessors, microcontroller technology and devices compliant for iontophoresis have significantly reduced in size and has become way too inexpensive due to low manufacturing costs. In iontophoresis a small amount of current is passed through the electrodes connected to the ocular tissues which delivers the drug of quantity equivalent to the applied current thus offering controlled drug delivery. The applied current is directly commensurate to the duration of current exposure and the surface area [67-68].

The mechanism of iontophoretic transport is mainly through electro repulsion and electro-osmosis. In electro repulsion there is organized motion of ions in electric field and in electro-osmosis there is liquid motion from the anode to the cathode due to the electric potential across a anionic membrane which helps in the penetration of high molecular weight drugs [69]. Trans corneal iontophoresis can be implemented in the prophylaxis of anterior segment ocular diseases (glaucoma, ulcers, inflammation) but doesn't find its potential in prophylaxis of posterior segment ocular diseases. Transscleral iontophoresis can be employed to bypass the lens-iris diaphragm barrier to deliver the drugs in posterior chamber of the eye that is to the vitreous and the retina. In this method an iontophoretic device is attached to the conjunctiva at the pars-plana position to dodge retinal detriment. This methodology proves to be an efficient technique over intravitreal injections in prophylaxis of ailments such as retinitis, uveitis, endophthalmitis and paediatric retinoblastoma [70-71].

Microneedles: Microneedles are micron sized (25-2000 μm) elongated particles with a pointed tip casted from a wide range of polymers. Generally casting of microneedles is done by using silicon, glass or metals, polymers are also used to fabricated rigid or hollow type of microneedles. Based on their organization and release methodologies they are classified into rigid microneedles which generates transitory pores for diffusion of the drug, sheathed microneedles have drug laminated on its surface which swiftly solubilizes after implantation [72].

Solubilizing microneedles are fabricated from biodegradable polymers that enclose the drug and upon implantation discharging the drug into the tissue. Hollow microneedles comprise of micro-ducts through which the liquid drug or the formulation is ejected [73]. Previous studies conducted by Thakur *et al.* exhibited fabrication of polyvinylpyrrolidine microneedles loaded with fluorescein sodium and fluorescein isothiocyanate-dextran for intraocular delivery. The *in-vitro* experimentation showed improved penetration of macromoleculs across the corneal and scleral tissues in contrast with conventional prophylaxis with aqueous formulation [74].

Microneedles offer the advantage of bypassing physiological barriers, targeted drug delivery (posterior segment ocular ailments), furthermore the solubilizing microneedles ae evident of functioning as micro-reservoirs in the targeted ocular tissues through which drugs can dissolve and discharged in a sustained approach [75-76].

Sonophoresis [77-79]: The technique of application of ultrasonic vibrations (20kHz to 1GHz is a minimally intrusive methodology of mechanically augmenting the drug delivery. The exact mechanism of sonophoresis is still not understood however cavitation which is inversely associated

with frequency is proposed to be a decent justification. Cavitation results in the evolution of inertial cavitation or a sluggish undulating movement of a bubble in ultrasound field which subsequently collapses to form minutes pores, also the sudden collapse of bubbles generates a shockwave modulating the tissues structural organization which functions as bypass systems for the penetration of drugs. Others than these mechanisms thermal effects and radiation load concepts are involved in the sonophoresis. Although the prior studies have affirmed the potential efficiency of ultrasound ocular drug deliver but the safety regarding cornea has to yet to be documented

Ocuserts: Ocuserts are drug embedded polymeric regulated-release formulations which are inserted as temporary or self-solubilizing implants in the eye's cul-de-sac, which was first formulated by Alza Corporation (USA) in 1975 [80]. Ocuserts are flat, resilient type sterile formulations wherein the drug depot is intercalated between two microporous films. The drug from ocuserts is released as the lachrymal fluid permeates through the membrane and the internal pressure influences the release of the therapeutic moiety from the drug depot. With the ocuserts placed in conjunction with the conjunctival tissue it slowly diffuses the drug over prolonged time period thus enhancing the overall residence period in ocular area and ultimately enhanced absorption [81]. Ocuserts exhibits multiple advantages over traditional dosage forms such as enhanced bioavailability due to increased ocular residence time, enhanced internal ocular targeting through periocular routes, increased self-life due to non-aqueous composition of the formulation, decreased systemic uptake and significantly lower chances of detrimental effects [82].

Intravitreal Injections [83-84]: Intravitreal injection is the invasive methodology of directly injecting the drug solution directly into the vitreous using a 30 gauge needle. The 30 gauge needle being thinner than conventional needles ensures prompt tissue penetration and also lesser pain is felt by the patient. Intravitreal injection is executed under superficial anaesthesia using aseptic methods employing povidone-iodine to minimize the conjunctival microbial load. Previous studies have shown the delivery of acyclovir, foscarnet, cephalexin, cefazolin into the vitreous by intravitreal injections to treat ailments such as retinitis and endophthalmitis. The injection position is at the inferotemporal zone to dodge accumulation of the drug anterior to visual axis. The pars plana is positioned 3-4mm posterior to the limbus. The injection should be done carefully to prevent jet formation or cystic flow hence the needle should be aimed obliquely at the mid-vitreous. The pharmacological agent is delivered using a single streamlined, persistent intervention; however, the volume of drug that can be injected is restricted to 0.1ml.

Periocular Route: The periocular route is the most efficient non-invasive route capable of delivering drugs to posterior segment of the eye. Periocular zone refers to the area surrounding the eye, anatomically periocular zone is composed of peribulbar, juxtasceral, retrobular and suntenon routes **Fig. 3** [85]. The periocular route is known for enhanced bioavailability of the drugs to the vitreo-retinal tissues in comparison with the traditional routes of ocular drug delivery due to the decreased precorneal loss. The previous studies have shown that the subconjunctival injections of dexamethasone or anti-VEGF agents have attained therapeutic concentrations in the retina and choroid in contrast with traditional drug solutions which impacts anterior tissues. Similarly periocular injection of triamcinolone acetone has exhibited elevated efficacy in the prophylaxis of posterior uveitis [86-87]. The periocular route of drug delivery is advantageous as this route targets proximate ocular area thus bypassing complications such as endophthalmitis, increased intraocular pressure, retinal detachment as seen in the cases of intravitreal injection [88].

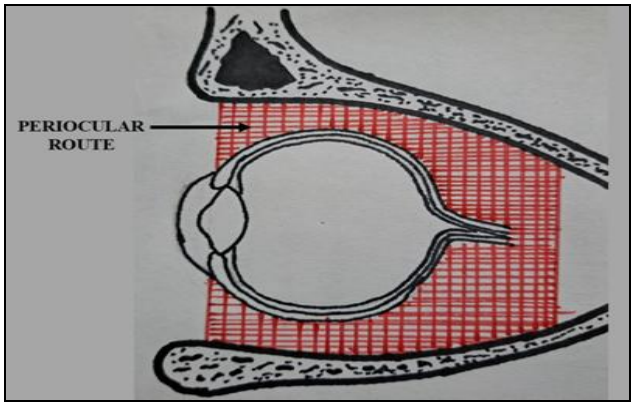

FIG. 3: PERIOCULAR ROUTE OF DRUG DELIVERY

Periocular route of ocular drug delivery is also evidently employed in traditional medicinal approach. According to *Shalakya Tantra,* (an Ayurvedic branch associated in treatment of eye nose and throat ailments) Trapana (retention of medicated ghee in eye), Putapaka (Instillation of heated therapeutic ghee in the eye), Seka (Pouring of medicated solutions in the eye), Aschyotana (application of medicated eye drops), Anjana (application of medicated pastes or collyrium in inner eye lid), and Parisheka (persistent spattering or washing of medicated liquids over the eyes) are some of the procedures involving periocular route of drug transport. Trpana and Putapaka are in close association with the periocular drug delivery method.

In Tarpana, a lentil based dough is applied over the face surrounding the eye where in the medicated ghee is poured over such that the eyes are submerged in the medicated ghee and the herbal therapeutic moiety is delivered to the posterior ocular region through the periocular route. Putapaka is a optimized upgrade of Tarpana where in freshly extracted herbal extracts combined with ghee is instilled in the eyes which gives a rejuvenating and anti-inflammatory response. These ancient methodologies are evident of supporting the principle of periocular drug delivery in modern ophthalmology by providing enhanced drug permeation, enhance ocular nourishment and sooth ocular lethargy [89-93].

CONCLUSION: The drug delivery to the ophthalmic region is restricted by multiple anatomical and physiological barriers however multiple attempts have been done to overcome these barriers by either modifying the formulation characteristics, by adapting interventional methodologies or by the means of mechanicals equipment's which physically modify the physiologic barriers to enhance permeation. This review involved a comprehensive analysis of various barriers to ocular drug delivery and the strategies to overcome; it can be concluded that with all the available strategies the efficiency of the drug delivery methods excels to anterior region only however some strategies show excellent results to deliver drugs to posterior chamber of the eye but are associated with certain anatomical risks and restrictions to approach delicate internal areas.

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