



A REVIEW ON: PENETRATION ENHANCERS FOR OCULAR DRUG DELIVERY

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INTRODUCTION

The eye is a unique organ, both anatomically and physiologically, containing several widely varied structures with independent physiological functions that render the organ highly impervious to foreign substances. Ophthalmic drug delivery is one of the most interesting and challenging endeavours faced by pharmaceutical scientist due to the presence of blood-retinal, blood-aqueous humour and blood-vitreous humour barriers. The most commonly used dosage form in treating ocular diseases is locally administered eye drops. Topical administration of drugs is beneficial for delivery to the anterior (cornea, conjunctiva, sclera, anterior chamber) as well as posterior (vitreous humor, retina, choroid) segments of the eye.^[1] Permeation of a compound via the conventional mode of ocular drug administration, the topical drop, is opposed by precorneal and corneal barriers. Pre-corneal barriers include formulation drainage; blinking; tear film; tear turn-over; and formulation-induced lacrimation. The corneal pathway is considered a major pathway for drug entry into the anterior and posterior segment of the eye.

The poor corneal penetration is attributed to the presence of tight junctions between juxtaposed corneal epithelial cells, which prevent drug molecules from moving between them.

The diversity of the corneal layer polarity further hampers the penetration of drug across the cornea. The corneal epithelial layer is lipophilic, preventing hydrophilic drugs from penetrating, while the stroma is hydrophilic, preventing lipophilic drugs from penetrating. As a result, to pass through the cornea, the drug molecule must have a certain degree of hydrophilic and lipophilic character. Owing to the physiological and anatomical barriers, only a small fraction of the applied dose is absorbed and reaches its target, i.e., anterior or posterior segments. Two key criteria for improving ocular bioavailability of topically applied formulation - the first, to increase the formulations corneal contact time, and the second, to use penetration enhancers to improve drug molecules corneal penetration.^[2] Ocular penetration enhancers are compounds that help to increase the permeability of active pharmaceutical ingredients across the ocular membranes including the cornea. Permeation enriching substances to be used in eye preparations must preferably be non-toxic yet non-irritating, efficient at a lower level, rapid action, as well as with reversible results.^[3]

Changing the balance of the tear film on the eye's layer

Altering corresponding epithelial cells' surface elements, like lipid bilayers Relaxing rigid epithelial joints

Different types of penetration enhancer and their mechanism for ocular drug delivery Permeation enhancers used in ocular formulations facilitate drug delivery via three main mechanisms.^[4-6] Although penetration enhancers cause a temporary structural alteration of the corneal epithelium, enhancers should be harmless, causing no long-term damage and initiate with a minor irritant effect. The classification of ocular penetration enhancers is as follows.^[7]

Listed below are the most commonly used ocular penetration enhancers.

Cyclodextrins: These are truncated cone-shaped cyclic oligosaccharides and have aqueous solubility.^[8] These form inclusion complexes with the hydrophilic or lipophilic drugs. Cyclodextrin molecules have lipophilic cavities- which enclose lipophilic drug molecules and the external surface has a hydroxyl functional group that helps to bind hydrophilic drug molecules. These molecules are unable to penetrate lipophilic membranes and the corneal epithelium, but they do allow drug interaction with the ocular epithelial surface. The enhanced ocular permeation of drug with cyclodextrin inclusion complex is attributed to the disruption of corneal the membrane, either by or by extracting some lipophilic components, such as cholesterol and phospholipids, from the membrane.^[9]

Crown ethers: These are a class of synthetic macrocyclic polyether molecules. They have a hydrophobic molecular ring structure with an electron-

rich hydrophilic cavity. Crown ethers can form complexes with metal ions, neutral as well as ionic organic molecules, yet these complexes can cross biological membranes.^[10,11]

Their unique structural feature imparts flexibility to crown ethers to structurally adapt itself to the surrounding biological environment. In an aqueous milieu, these can interact with water by exposing hydrophilic oxygen atom to external surrounding whereas in lipophilic medium crown ethers interact by exposing their ethylenic groups.^[12] The mechanism by which crown ethers work as a penetration enhancing agent is the same as cyclodextrin that is by modifying lipid bilayers.^[13]

Surfactants: Surfactants are amphiphilic molecules and serve the purpose of permeation enhancer for a drug by disrupting the epithelial layer that is by loosening tight junctions between the epithelial cells. There are four main types of surfactants- cationic surfactants, anionic surfactants, zwitterionic surfactants and non-ionic surfactants.

Non-ionic surface-active agents like tween-20, Brij-35 are the most commonly used surfaceactive agents as permeation enhancers in case of ocular drug delivery followed by cationic surfactants like benzalkonium chloride (BAC). Some plant-based surfactants like amphiphilic glycosides, e.g. saponins have also been tested and reported to be effective for improved ophthalmic delivery of a drug.^{[14],[7]} Sasaki et al. reported the use of penetration promoters for ocular beta-blockers with varying lipophilic features. The permeation enhancer taurocholic acid, saponin, EDTA and capric acid were compared for their permeation enhancing properties.

The study was also designed to compare corneal and conjunctival permeation in albino rabbits. The use of permeation enhancer markedly showed an increase in corneal permeability.^[15]

Transcutol® P is a topical solubilizer used as a permeation promoter for transdermal drug delivery systems. Liu et al. demonstrated that the use of Transcutol P in the concentration range of 0.005-0.03 % did not exert any irritation and showed slight irritation at a concentration of 0.05%.^[16]

Digitonin has some surface-active characteristics which seem to have the potential as penetration enhancer. Digitonin selectively solubilize cholesterol membranes and exfoliate the epithelial layer of cornea.^[9]

Labrasol® is a non-ionic surface-active agent, is a PEG derivative of a medium-chain fatty acid triglyceride of capric and caprylic acid and has the potential to be used as a corneal permeation promoter. Liu et al illustrated an increase in baicalin penetration through the cornea of the rabbit by 1.69, 3.14 and 2.23 folds at 1.5, 2.0 and 3.5%

Labrasol concentrations, respectively. Another potential corneal permeability enhancer is Azone™ (1-dodecylazacycloheptan) and amphiphilic surfactant, Gelucires.^[17]

Lysophospholipids are amphiphilic surface-active agents formed by the phospholipases in a naturally occurring manner. As an enhancer, their mode of action is not fully known. It is thought that phospholipases interact with intracellular proteins or even polar phospholipid groups in intercellular areas of corneal epithelium like other surfactants. This may favor the formation of channels that permit the water permeation and dissolved substances.^[6]

Bile Acids and Bile Salts: Bile acids /bile salt derivatives such as deoxycholate, glycocholate, and taurodeoxycholate naturally produced in the human digestive system. Bile salts alter the protective mucus barrier of ocular tissue by virtue of their mucolytic properties, thus allowing enhanced drug transit into ocular tissue.^[7]

Cell-Penetrating Peptides (CPPs): These are short sequences of amino acids joined via peptide bonds and derived from various combinations of amino acids. The possible mechanism of penetration enhancement is direct translocation and endocytosis.^[18] Liu et al. performed ex vivo permeation studies of a variety of fluorophore-labelled cellpenetrating peptides, including TAT, penetratin, poly (arginine), low molecular weight protamine, and poly (serine), using a rabbit model.^[19] Studies conducted by Pescina et al. centered on the functionalization of new CPPs for future use as permeation promoter for metabolically sensitive ocular drugs like aminoglycoside antibiotics, cysteamine and antiviral agents. The studies showed that CPPs can give a great amount of advantage in carrying these drugs across ocular barriers and has great potential to carry drugs to the anterior as well as the posterior segment of the eye.^[20]

Bioadhesion/Mucoadhesion – Maximize drug absorption by prolonging contact time with the eye, which can increase bioavailability, reduce dosing frequency, and subsequently improve patient compliance
Versatility – compatible with a wide variety of acidic, basic, and neutral APIs across a broad pH range while providing customizable rheology and viscosity for your product
Emulsification – ability to suspend oils in solution and suitable salt tolerance, which are important qualities for many topical products such as eye drops.

Bioadhesive Polymers

Polymers viz. Carbopol®, Pemulen™ and Noveon® are versatile and efficient in complex topical mucosal formulations. These monograph-compliant, mucoadhesive excipients are compatible with most active pharmaceutical ingredients (APIs) and offer several advantages for effective

Ocular formulation development, including

Non-irritating and non-toxic – enhances patient comfort and safety Sperminated pullulans: The charge density is a significant feature of cationic polymer for improved penetration. In the case of cationized polymers, spermine, a polyamine with four amino groups can be beneficial to enhance charge density. Pullulan has a number of hydroxylic groups that can react with spermine. Sperminated pullulans are modified form of pullulan to make the enhancer more powerful.

The impact of sperminated pullulans on corneal permeation was investigated on hydrophilic and lipophilic drugs. The findings indicate that sperminated pullulans greatly enhanced the transcorneal penetration of three hydrophilic drugs (Ofloxacin, Tobramycin as well as sodium fluorescein), however, the transcorneal penetration of a lipophilic drug was not greatly enhanced (dexamethasone). Drugs enter the cornea, either by flowing across or moving between the cells (transcellular) (paracellular).^[21]

Miscellaneous compounds: Fatty acids enhance ocular drug permeation by changing the properties of cell membranes and loosening tight junctions. Fatty acid-like caprylic acid and capric acid can form ion-pair complexes with cationic drugs. Capric acid disturbs both proteins and lipid components of cellular membranes, while caprylic acid interacts with proteins. Capric acid has been shown to improve ocular penetration of β -blockers, with mild improvements for hydrophilic β -blockers and only minor improvements for lipophilic β -blockers.^[17]

Borneol is a terpene derivative that can be used to improve ocular penetration. According to Yang et al, the ability of borneol to promote indomethacin and dexamethasone corneal permeability may be due to changes in the arrangement of lipid molecules in the cell membrane of corneal epitheliocytes, improving the orderliness of the molecular chains of lecithin.^[22] Colloidal carrier systems have been extensively investigated for ocular bioavailability improvement. The mechanism of enhancement is generally believed to be related to the ability of carriers to penetrate into the epithelial cells of the cornea without causing damage to the cell membrane.^[23]

These are some of the commercial products in which cyclodextrins are used as penetration enhancers: chloramphenicol (Clorocil ®: Edol), diclofenac (Voltaren Ophthalmic ®: Novartis), and indomethacin (Indocid ®: Merck Sharp & Dohme-Chibret).^[24]

CONCLUSION

Ocular topical delivery systems are popular due to the non-invasive nature of this route of administration along with ease of application. However, due to complexity in the chemical composition and structure of the eye, delivery of therapeutics is challenging for the formulator.

These challenges can be addressed with the help of ocular penetration enhancers. Though, a plethora of research is available in the field of ocular penetration enhancers, it is critical to identify the properties of the various novel excipients and understand how they help in increasing the drug penetration from the ocular drug delivery systems. This review is an attempt to summarize in brief the various advancements in the field of ocular penetration enhancers.

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