Factors affecting corneal penetration of drugs

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While treating anterior segment of the eye in ophthalmological practice, topical medications are the most commonly prescribed medications. The current issue has three studies related to the efficacy or side effects of topical medications used in the management of various anterior and posterior segment diseases. The intraocular bioavailability is very low due to very rapid drainage of drug from the ocular surface and only few minutes are available for the drug to be absorbed. In most cases the topically administered ocular drugs do not reach the posterior segment of the eye like retina, vitreous and choroid and these can be treated by using intravenous or intra-vitreal routes of drug administration[1]. Only 1-7% of dose of the drug can reaches into the aqueous humor because corneal epithelium can effectively limit the drug delivery into the eye[2].

The penetration of drugs through cornea is very important clinically because it is the major determinant of the efficacy of drug topically applied to the eye. Ocular preparations in majority are formulated in an aqueous vehicle and the bioavailability of drugs from aqueous based products is mainly affected by the factors which are categorized in to the following three groups.

1- Physiological factors
2- Physicochemical factors
3- Formulation factors[3]

1- Physiological factors

Physiological factors include some pre-corneal factors and membrane factors.

Pre-corneal factors like tears secretions turn over, ocular drainage of the instilled drug, non-corneal absorption (Conjunctival absorption), protein binding and corneal absorption rate are the contributing factors in the net pre-corneal drug loss. These factors collectively lead to corneal contact time of the drug 2-4 minutes in human for an instilled solution. Normal tears volume is only 7 µl and tears wash out at the rate of 16% per minute. The pre-corneal area can hold approximately 30 µl including tears when eye is not blinking. When drug is instilled, the excess of volume is spilled out or drain through the nasolacrimal apparatus. Normally tears contain 0.7% of protein and this level increases during inflammation or infection. As tears are replaced quickly, so they remove both free and bound from of drug. Conjunctiva has 17 time greater surface area & higher permeability as compared to cornea. The absorption of drugs through the tissues other than cornea are considered as nonproductive absorption.

Thicknesses, porosity, tortuosity of the cornea, surface area available for absorption and lipophilicity / Hydrophilicity balance are the major membrane factors contributing in the ocular absorption of drugs. The lipophilic drugs have greater penetration through cornea as compared to hydrophilic drugs.

2- Physicochemical factors

Partition coefficient, solubility, ionization constant and molecular weight are the main physicochemical factors contributing in the ocular penetration of drugs[4]. Partition coefficient is the parameter used for the penetration of drugs through different biological membranes. The corneal permeability of any drug depends upon its lipophilic characters (Partition coefficient). The maximum penetration of a drug is the multiplicative factor of permeability coefficient and tears solubility. The concentration of poorly soluble drug in the pre-corneal tears film may be limited which can result in low corneal absorption. The ionization constant (pKa) of a drug is important factor for its corneal penetration. The extant of

ionization can influence the diffusion of drugs across the membranes. Most of the drugs are week acids or weeks bases and are partially ionized at physiological pH. The ionized form of drug is poorly lipid soluble (Limited corneal penetration) and if this proportion is high then it is difficult for a drug to achieve therapeutic concentration. Molecular weight is a less critical factor because ophthalmic preparations have very low and narrow molecular weight range. Drugs having molecular weight greater than 500 Da offer poor corneal penetration and vice versa.

3- Formulation factors

Concentration, particle size, shape & dissolution rate, pH & tonicity and viscosity are the formulation factors that can affect the corneal penetration of the drugs. By increasing the solution concentration, corneal penetration can be enhanced. Particle size & shape is mostly concerned with the use of ophthalmic suspensions. Drug particles can be deposited at the outer surface of the eye which can cause irritation & abrasion upon movement through eye lids while blinking. Increase in particle size can leads to poor corneal penetration. Irregular particles or edged particles can cause more irritation as compared to spherical particles. Concentration, size & shape of the particles together can determine the irritation potential of the suspended particles. The human tears pH ranges from 7.14-7.28 and possess relatively weak buffer capacity. The hypotonic solution can increase the corneal permeability while instillation of hypertonic solution can decrease the permeability of the corneal epithelium. The hypotonic solution can create an osmotic gradient between the tears film and surrounding tissues. The corneal epithelium has greater tolerability to large variations in the pH and tonicity. It is generally believed that by increasing the viscosity of the ophthalmic solution, corneal penetration can be increased because it can increase the contact time of the drug with corneal epithelium. The most commonly used viscolizing agents in ophthalmic preparations are hydroxy propyl methyl cellulose (HPMC) and Poly vinyl alcohol (PVA) etc. Penetration enhancers like actin cytoskeleton inhibitors (like Cytochalasin B) [5], Surfactants (like Benzalkonium Chloride, Sodium Lauryl Sulphate), Chelators (Like EDTA) and preservatives (like Benzalkonium chloride, organomercurials) etc. can be used in the ophthalmic preparations to enhance the corneal penetration by one or another mechanism.