OCULAR THERAPEUTICS AND DRUG DELIVERY

A MULTI-DISCIPLINARY APPROACH

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anilines [71]. There are some deviations from the parabolic relationship when drugs are of varied chemical structure and molecular weight [51]. This is mainly because various compounds have different transcellular pathways for penetration. Low molecular weight alcohols and ionized forms of drugs such as pilocarpine [72], cromolyn sodium [73] and sulfonamides [74] penetrate through less common paracellular pathways.

Enzymatic lability also influences the extent of penetration of prodrugs into the cornea. The penetration of aliphatic timolol esters across the cornea of rabbits shows enzymatic lability [70,75]. The rate of diffusion in the cornea increases with increase in the rate of hydrolysis of esters of prodrugs. Therefore, enzymatically susceptible straight chain alkyl esters penetrate more easily as compared to less susceptible branched chain alkyl esters of same lipophilicity. That is the reason why an esterase inhibitor decreases the corneal penetration of *O*-butyryltimolol, 1′-methylcyclopropanolytimolol and *O*-pivaloyltimolol by 30, 50 and 80% respectively [75]. When prodrug of pilocarpine is administered to the tear film, it is envisioned that the controlling factor for corneal penetration is the formation of pilocarpine in the epithelium instead of its absorption into the epithelium or its diffusion across the stroma to the endothelium.

MICELLAR SOLUBILIZATION

Solubilization in surfactant solutions above the critical micelle concentration (CMC) offers a very good method to formulate dosage forms of poorly soluble drugs in water. Because of their relatively nontoxic nature, nonionic surfactants have been used most frequently for drug solubilization. A new class of nonionic surface active polymers, polyoxy-ethylene-polyoxypropylene block copolymers, are also gaining a lot of attention due to their nontoxic nature. Different drugs behave differently when they are solubilized in a surfactant system. Some drugs get inactivated, whereas others show higher activity.

The properties such as solubility, diffusion coefficient, and lipid-water partitioning coefficient of drug-penetration enhancer complexes may differ significantly from the properties of individual components, i.e., the properties of the free drug or penetration enhancer. This is mainly due to the formation of mixed micelles. Mixed micelles of bile salt and insulin provide a high juxtamembrane concentration of soluble insulin which results in high flow rate of insulin monomers from the nares (nostrils) into the nasal membranes [76]. The effects of various lipid-bile salt mixed micelles on intestinal absorption of streptomycin were reported using *in situ* closed-loop method in rats [77]. While mixed micelles composed of monoolein or unsaturated fatty acids markedly enhanced the absorption of streptomycin, saturated fatty acids caused only a small enhancement of absorption, and

triolein, diolein, oleyl alcohol and methyl oleate had no enhancement effect on the absorption [77]. The difference in the enhancing effects of monoolein, unsaturated fatty acids and saturated fatty acids was not attributed to the interaction or the absorbability of lipids, but rather, to the alteration of the mucosal membrane permeability. No observation has been reported in literature relating mixed micelles of ocular drug and drug enhancer to the drug permeability. However, the mixed micelles of base and salt form of tetracaine (a local anesthetic agent) have been shown to be transported across mouse skin most effectively [78,79].

OSMOLALITY

The osmolality of the lacrimal fluid is dependent on the number of dissolved ions and crystalloids. Proteins make a very small contribution to the total osmotic pressure of tears because of their molecular weight and low concentration [80]. The osmolality varies from 302 $mOsm \cdot kg^{-1}$ to 318 $mOsm \cdot kg^{-1}$ in normal eye [81–83]. The osmolality of tears in the night during sleep varies from 280 to 293 $mOsm \cdot kg^{-1}$ [84]. The osmolality varies across the ocular surface. The osmolality in the fluid of the tear strip is less than the osmolality in the conjunctival sac [85]. The osmolality of tear films is increased in the case of ocular surface diseases like dry-eye and in contact lens wearers after forty years of age [83,86].

When hypertonic solution is applied to the eye, water flow passes from the aqueous layer through the cornea to the eye surface [87]; whereas, in the case of hypotonic solution, the permeability of the epithelium is increased considerably and water flows into the cornea [88].

The osmotic pressure of the mixture of tears and instilled solution depends upon the osmolality of the instilled solution. Ophthalmic solutions which produce osmolality lower than 266 $mOsm \cdot kg^{-1}$ or higher than 640 $mOsm \cdot kg^{-1}$ are irritating to the eye [89–92]. The original osmolality is achieved within 1 or 2 minutes after instillation of the nonisotonic solution depending on the drop size [93].

CONCLUSION

Although significant progress has been made in our understanding of ocular drug absorption and disposition over the last few years, ocular drug delivery by topical route is still considered to be primitive. This is because the physiological protective mechanisms of the eye in concert with the anatomical barrier, the cornea, prevent the free access of foreign substances including drugs to the inner eye.

The surface chemical considerations are very important in the formulation of efficient ocular dosage forms and delivery systems. Many interfacial

liquid. Viscosity of a liquid can then be determined from the following expression:

$$\eta_1/\eta_2 = \varrho_1 t_1/\varrho_2 t_2$$

where η_1, ϱ_1, and t_1 are viscosity, density, and the flow time of the solution and η_2, ϱ_2, and t_2 are the viscosity, density, and the flow time of the reference liquid.

SURFACTANTS

Surfactants may be added to an ophthalmic preparation to solubilize or disperse the drug effectively. Nonionic surfactants are the most commonly used in ophthalmic preparations because of their lower incidence of toxic effects. However, their interaction with other adjuvants and packaging components must be carefully evaluated. Surfactants have also been shown to improve corneal permeability. Nonionic surfactants have been shown to cause an appreciable increase in the penetration of fluorescein into the aqueous humor in man [74]. The presence of surfactants may affect the efficacy of preservatives used. For example, the preservative activity of methyl paraben is considerably reduced by the presence of polysorbate 80 [54]. Other preservatives such as chlorobutanol, phenyl ethanol and benzyl alcohol also interact with polysorbate 80, but to a considerably lesser extent than the parabens. The presence of an interaction between surfactants and preservatives does not necessarily mean that they cannot be used together. However, a knowledge of the extent and nature of such an interaction, and sufficient testing is necessary to develop an effective formulation. For potential toxicity reasons, the minimum possible quantity of surfactants must be used in ophthalmic formulations.

One of the most commonly used surface-active agents in ophthalmic formulations is benzalkonium chloride. It is the surfactant of choice because of its anti-microbial activity. Other surfactants used are benzethonium chloride, polysorbate 20, polyoxyl 40 stearate, alkyl aryl polyether alcohol, polyoxypropylene-polyoxyethylenediol, and dioctyl sodium sulfosuccinate.

STABILIZING AGENTS

If the drug molecule is susceptible to degradation by oxidation, stabilizers such as chelating agents or anti-oxidants are included in an ophthalmic formulation to improve the shelf-life of the product.