The penetration of drugs in the eye after topical administration is one of the most interesting challenges the pharmaceutical science is facing. The objective of the scientist is to penetrate the protective barriers of the eye without damaging ocular structures.

In contrast with other epithelia, the epithelium of the ocular surface is not prepared for absorption which means that the time of permanence of a conventional formulation is under two minutes. To this we must add the losses generated by the systemic absorption of the drug through the conjunctival and the lachrymal conduit. It is estimated that the percentage of active substance reaching the anterior segment of the eye is in the range of 1-5% of the total dosage. For this reason, even though the drug is able to reach the aqueous humor, its dissemination to the posterior segment is insignificant in most cases.

When drugs are administered topically in the eye, the pathway of penetration is through the cornea (transcorneal pathway) or the conjunctiva and the sclera (conjunctival/scleral pathway). It is known that most of the active substances for topical absorption are absorbed through the transcorneal pathway. This explains why the conjunctiva was considered to be purely an elimination pathway. At present we know that there are substances which can penetrate the conjunctival and reach the posterior segment on some occasions (1).

In general, the corneal epithelium allows the passage of small-sized water repellent active substances through the epithelial cells by way of diffusion (trans-cellular pathway) and of hydrophilic substances between the spaces thereof in what has become known as the para-cellular pathway (2).

The conjunctival is a mucous membrane which covers approximately 8% of the ocular surface. It is made up of a bulbar portion which covers the anterior part of the globe (except the cornea) and two palpebral portions in the posterior faces of the upper and lower eyelids. The conjunctival epithelium comprises a number of stratified epithelial cells (between 5 and 15 layers) and is covered by microvellosities. The bulbar conjunctiva is covered by the lachrymal film and contributes to the formation thereof by the secretion of electrolytes, mucus and glycoproteins.

As with the cornea, the passage through the conjunctiva can be through the trans-cellular or para-cellular pathway (3). If we focus on the general properties of the active substances, the molecular size is the limiting factor in the para-cellular pathway, both for the cornea and the conjunctiva. The para-cellular pathways were described some years ago in rabbits utilizing polyethyleneglycol in different molecular weights (from 200 to 1000) (4). Said agents were selected because its characteristics are common for peptides and oligonucleotides (hydrophilia, the ability to form hydrogen bridges and molecular size). In this study, the conjunctiva was a lot more pervious and less restrictive than the cornea. The molecular size of the inter-cellular spaces in the conjunctiva is about double the size of...
the cornea spaces (5.5 nm) and the pore density is 16 times higher (1.9x10^8 pores/cm^2) (4). On the other hand, the epithelial cells of the conjunctiva exhibit the same intercellular junctions which characterize the corneal epithelium known as “tight junctions”, although the conjunctiva is more perivious to the passage of hydrophilic molecules. In addition, it is estimated that the paracellular space of the conjunctiva is over 200 times higher than that of the cornea.

Initially, the research on conjunctival absorption focused on enhancing the trans-cellular or paracellular pathway. To enhance the former, the option was to enhance the lypophylia of the drug utilizing pro-drugs or substances analogous to the active principle, whereas the paracellular pathway was enhanced by utilizing promoters which facilitate the opening of the intercellular junctions.

When it was demonstrated that the passage of substances through the conjunctiva can also utilize active transport through endocytosis or the sub-conjunctival space (by means of injections, implants or iontophoresis), new areas of research were opened in this field.

There is evidence of the existence of conjunctival active transport similar to that which occurred in the intestines, although in the first case it is more restrictive (3). One example of this type is the sodium monocarboxylate transporter which has been proposed for anionic drugs such as chromolin, flurbiprofene and dyclophenake utilized for treating different types of conjunctivitis. The active transport mechanisms of Cl-, Na+ and K+ ions contribute to the passage of liquid through the epithelium and can also be utilized for promoting the absorption of drugs through the conjunctiva. Thus, if the apical area of the conjunctiva is exposed to nutrients which induce the absorption of Na+ (such as amino acids) it is possible to enhance at the same time the absorption of liquid. If this physiological process is combined with the opening of the intercellular junctions through other mechanisms, it would enhance the absorption of hydrophilic solutions through the membrane.

The endocytosis process of the conjunctival epithelial cells is also an interesting alternative which has already been described for nanoparticles of 100 nm size prepared on the basis of polyactic-co-glycolic acid (PLAGA) (5). Even though this is still in research, there is a great deal of interest in this area.

The sub-conjunctival pathway has also been proposed as an alternative to intravitreous injections which are more aggressive for the patient. This pathway aims at increasing the intra-ocular concentration of the drug and reducing its frequency of administration. To this end, sub conjunctival implants have been developed (6) as well as nano and micro-particles (7). The latter gave rise to concentrations of active substance in the vitreous and in different areas of the retina.

Iontophoresis allows drugs to penetrate the membrane combined with ions through the application of an electrical current, which restricts this application to active substances which have the ability to become ionized. The electric current facilitates the passage of the drug through the cellular barrier. This technique comprises the ability to change the density of the current and its application time to achieve different effects. Iontophoresis can be applied in the cornea (trans-corneal iontophoresis) as well as in the conjunctiva and sclera (transconjunctival /scleral iontophoresis) (8) and it has allowed for increased concentrations of drugs in the vitreous and the retina.

Another interesting development is based on the role of the conjunctival as a pathway for the absorption of proteins or peptides whose passage through the cornea is limited. However, we must not forget that the enzymatic activity of this area can degrade the active substance significantly, as described for insulin and the P substance (9). This degradation can be redressed by adding protease-inhibitors to the formula, for example.

Nowadays the access pathways for the conjunctiva are under close study (paracellular, trans-cellular, active transport or endocytosis) and different strategies are being researched to enhance the penetration of active substances. Trans conjunctival iontophoresis is proposed as a non-invasive and safe technique that can improve the passage of substances to the vitreous and retinal tissues. However, the absorption mechanisms of the conjunctival are not as well described as those of the cornea. When this is accomplished, access through this pathway will be utilized in a more effective manner.

REFERENCES