It is a quaternary ammonium salt and causes epithelial toxicity on repeated administrations. Poor tolerance to treatment has been associated with preservatives and newer alternatives are being investigated.

Single dose units (SDUs) have been developed to circumvent the use of preservatives while maintaining stability. The manufacturing and packaging of these is however expensive and so they have not been embraced for all the marketed ophthalmic solutions. Several multi-dose bottles have been developed that maintain sterility without the use of a preservative; one of these is the ABAK patented filter system which uses a 0.2 μm nylon membrane to prevent bacteria from entering the bottle. It is known as Airless Antibacterial Dispensing System (AADS™, Pfizer) and works by preventing air, and therefore bacteria, from entering the container on dispensing. Furthermore, a silver coil is included in the bottle tip. Silver has antibacterial properties and therefore any bacteria contacting the tip do not contaminate the contents. This system guarantees three months of sterility.

Ocular drug pharmacokinetics

Drug half-life in the anterior chamber

Peak drug levels in the anterior chamber are reached 20–30 minutes after eye drop administration. These concentrations in the aqueous humour are typically, however, two-fold less than the administered concentration. From the aqueous humour the drug can diffuse to the iris and ciliary body where it may bind to melanin and form a reservoir allowing gradual drug release to the surrounding cells. Drug is eliminated from the aqueous humour by two main routes: aqueous turnover through the trabecular meshwork and Schlemm's canal (route 2, Fig. 41.1) and by the venous blood flow of the anterior uvea across the blood aqueous barrier (route 1, Fig. 41.1). Aqueous humour turnover is at a rate of 2.2 to 3.1 μL/minute during wakefulness. For an individual with an average anterior chamber volume of 185 μL, the half-life of anterior chamber fluid is 43 minutes. The other mechanism of drug elimination by the uveal blood flow is dependent on the drug's ability to permeate the endothelial cells of the blood vessels and is therefore more favourable for lipophilic drugs. The clearance of lipohilic drugs can be in the range of 10–30 μL/minute. Drug half-lives in the anterior chamber are typically short, about one hour. Drug distribution to the vitreous is extremely slow as the lens prohibits diffusion.

Active transporters of the cornea

Various uptake and efflux transporters have been shown to be present in the corneal epithelium. These transporters are also present in the epithelium of the intestine, blood-brain barrier and kidney tubuli. Efflux transporters protect cells from noxious stimuli and are also implicated in drug resistance. It is estimated that 25% of administered drugs are substrates for transporters. Since the cornea is in contact with the external environment it is not surprising that it expresses efflux transporters as part of a protective mechanism.

Efflux transporters that have been identified on the corneal epithelium include P-glycoprotein (P-gp, MDR1), breast cancer resistant protein (BCRP) and multi-drug resistant protein 5 (MRP 5). P-gp was found to be implicated in the transport of ciclosporin A (immunomodulator for treating dye eyes) in the cornea. The prostaglandin agonists used in the treatment of glaucoma; bimatoprost, latanoprost, travoprost, and their free acid forms, are substrates of the MRP 5 efflux pump on the cornea. Bimatoprost is also a substrate for P-gp. Co-administration of these prostaglandin agonists for the treatment of glaucoma has been proposed for overcoming efflux as well as achieving a synergistic pharmacological effect, since these molecules act at different receptors for reducing intraocular pressure.

One of the main uptake transporters in the cornea epithelium are the amino acid transporters. The corneal epithelium is a highly regenerative tissue with continuous protein synthesis, thus placing a demand on amino acid transport. The aqueous humour is the main source of nutrient provision for the corneal epithelium. Oligopeptide transporters have also been identified and shown to be involved in the transport of valaciclovir (L-valyl ester of aciclovir) through the cornea. They are also being utilized in prodrug delivery. Organic anion transporting polypeptide family (OATP) has substrates of mainly anionic, amphipathic nature. Their presence in the cornea may be implicated in the transport of the thyroid hormone, which has a role in the development and transparency of the cornea. Its involvement in drug transport has still not been determined.