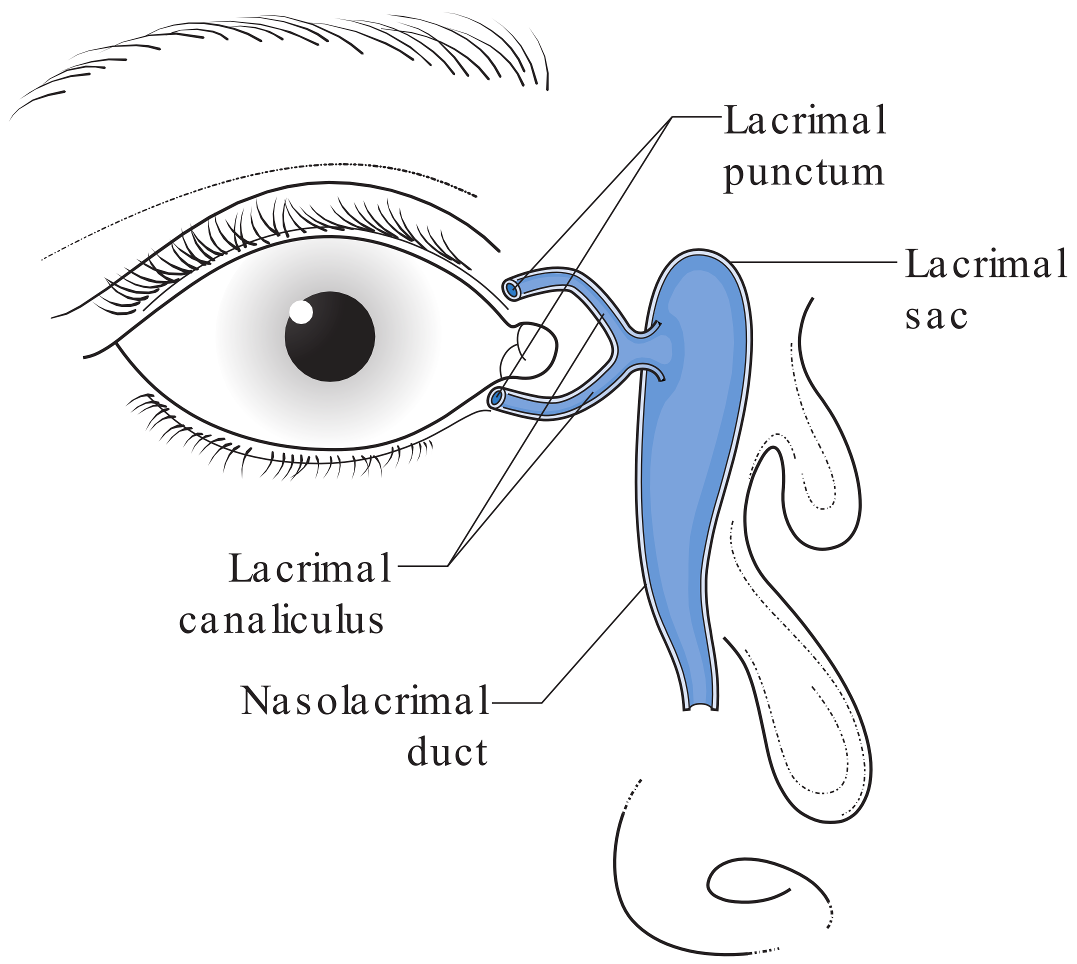

Fig. 41.2 • Illustration of nasolacrimal drainage.

reduce the elimination rate of administered eye drops, it is important that the topical preparations do not cause irritation. This can be achieved by designing their properties to be as close as possible to the lacrimal f uids covering the surface of the eye.

Formulating ophthalmic preparations

Osmolality

The concentration of salts in lacrimal f uids determines its osmolality. Predominant inorganic ions in tears are sodium, potassium, calcium, chloride and bicarbonate. These have an important function in controlling the osmotic pressure of the intercellular and extracellular f uids of the epithelial spaces of the cornea and conjunctiva. Osmolality in healthy, non-dry eyes has an average value of 302 mmol/kg during the daytime. Patients with dry eye syndrome have been found to present with tear film hyperosmolality which contributes to the symptoms of the disease.

When the eye is exposed to a hypotonic ophthalmic solution, the corneal epithelium becomes more permeable and water f ows into the cornea causing oedema. Hypertonic solutions have a dehydrating effect on the corneal epithelium. Hypotonic and hypertonic solutions are irritating to the eye and therefore induce an increased production rate of tears. The rate of tear production increases to several hundred microlitres per minute through ref ex tear secretion and ref ex blinks. This increased tear turnover rate reduces the retention half-life of a solution that has been applied to the eye.

Normal tear osmotic pressure is equivalent to 0.9% to 1.0% sodium chloride solution. Solutions of osmotic pressure equivalent to 0.6 to 1.3% sodium chloride appear to be well tolerated by the eye. Ophthalmic solutions can be made isotonic by the use of tonicity agents such as sodium chloride, potassium chloride, buffering salts, dextrose, mannitol and glycerol, as long as they are compatible with the other ingredients in the formulation.

Hydrogen ion concentration (pH)

The pH of tears is close to neutral and is controlled by various substances dissolved in the aqueous layer of tears: carbon dioxide, bicarbonate and proteins such as the basic lysozyme and an acidic tear prealbumin. The fatty acids produced by the Meibomian glands also mix with the aqueous phase of tears. The pH of tears is subject to diurnal variation and increases slowly from 6.9 to 7.5 during the waking hours of the day due to carbon dioxide evaporation. The buffer capacity of tear f uids is low but significant; it is predominantly controlled by the balance of bicarbonate and carbon dioxide, as well as proteins. Acidic or basic solutions instilled into the eye cannot be neutralized by the tears that are present and therefore ref ex tears are generated to dilute the administered drop and eliminate it. The recovery to the original pH of the tear film can vary from a few minutes up to 20 minutes. The duration of recovery is inf uenced by the pH, volume, and buffer capacity of the administered solution, as well as the age of the patient. Strongly acidic or basic solutions should not be administered to the eye as they can cause damage to the ocular tissue. The eye can generally tolerate topical ophthalmic preparations at a pH within the range of 3.5 to 9. However, it is preferable to formulate as close to physiological tear pH as possible to reduce discomfort and the associated increased lacrimation.

pH is important in drug ionization and product stability. Pilocarpine is a natural alkaloid used in the treatment of glaucoma. It undergoes pH-dependent hydrolytic degradation and one of the ways to maintain stability of pilocarpine aqueous solution is to maintain the pH at 4–5 through the use of a weak acidic buffer. Since the pH deviates from the physiological pH of the lacrimal f uids, the constituting buffer must be weak to allow the lacrimal f uids to be restored to their normal pH within a short period