Chapter 10
Mucoadhesive Polymers and Ocular Lubricants

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Abstract Dry Eye Disease (DED) is defined as a multifactorial condition that results in discomfort, visual disturbance, tear film instability and damage to the ocular surface. It is characterized by the increased osmolarity of the tear film and inflammation of the ocular surface. Tear film stability is maintained by the coordinated functions of the outer lipid monolayer with its critical composition and the contents of aqueous interface. This chapter discusses the structure and function attributing to tear film integrity, mucoadhesive polymers used in tear substitutes/lubricants, tear secretagogues agents, anti-inflammatory immunosuppressants, and use of autologous serum, umbilical cord serum for the management of dry eye.

10.1 Introduction

The conditions of tear film formation and stability are governed by the surface chemical characteristics of the tear film system and proper functioning of the lacrimal apparatus. The tear film has to remain continuous between blinks in order to fulfill its function. Dry eye is a multifactorial disease of the tears and the ocular surface that manifests in a wide variety of signs and symptoms. It is prevalent in about 33 % of the population worldwide. The presence of an abnormal tear film results in dry eye states that can be detrimental to vision (Holly and Lemp 1977). Dry eye syndrome (DES) is a common ocular disorder affecting 5–6 % of population characterized by decreased production of tear or its increased evaporation. In Latin it is called as keratoconjunctivitis sicca (KCS), indicating the inflammation induced by dryness. Although it is a multifactorial disease, the end result of ocular surface damage is due to the lack of tear film stability in terms of its volume and

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composition. In either case corneal epithelial drying is accompanied by increased tear osmolarity due to water evaporation, causing hyperosmotic stress on epithelial cells. This osmotic effect is capable of dehydrating the corneal epithelium and precipitating foreign body sensation, itching, and irritation leading toward inflammation. Therefore, ultimately replenishing precorneal tear film, stimulating or improving tear secretion, and stabilizing the tear film are the current methods being adopted for its management.

Dry eye could be due to ocular surface disorders, surface surgeries (LASIK surgery), surface disturbances (contact lens usage), hormonal changes (postmenopausal and androgen deficiency), and secondary side effect of systemically administered drugs having anti-muscarnic activity (antihistaminics, antipsychotics, etc.). In most of the aforesaid cases, administration of tear substitutes have been found to be beneficial. Sjögren's syndrome is a chronic systemic autoimmune disease characterized by lymphocytic infiltration of exocrine glands causing poor lacrimal gland function. Sjögren's syndrome (SS) is the second most common autoimmune rheumatic disease. However, differential diagnosis remains confusing due to the high prevalence of vague symptoms of dryness, fatigue, and myalgias in the general population (Fox et al. 2000).

After overlapping "general" and "operational" definitions of dry eye, the definition and classification subcommittee of the International Dry Eye Workshop (2007) redefined it as, "Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface" (2007).

10.2   Structure and Functions Attributing to Tear Film Stability

Human tear film consists of a monolipid layer in the air-tears interface followed by soluble mucin-containing aqueous layer resting on the glycocalyx matrix on the corneal epithelium. The lipid layer is an essential component of the tear film, providing a smooth optical surface for the cornea and retarding evaporation from the eye (Fig. 10.1). The composition of meibomian lipids are well adapted for this purpose. They form a thin, smooth film containing lower amphiphilic phospholipids having their polar heads oriented toward aqueous film and hydrophobic tails giving interface for hydrophobic cholesteryl esters, wax esters, [O-acyl]-ω-hydroxy fatty acid, triglyceride, etc. (McCulley and Shine 2004). It has been reported that the thickness and composition of this layer influence the rate of evaporation (Bron et al. 2004). The protein and electrolyte composition of the aqueous part of the tears are derived from the lacrimal gland, as well as the accessory secretions of other glands and the conjunctiva.

Mucins are large, extracellular glycoproteins with molecular weights ranging from 0.5 to 20 MDa and belong to the family having O-linked carbohydrates. They
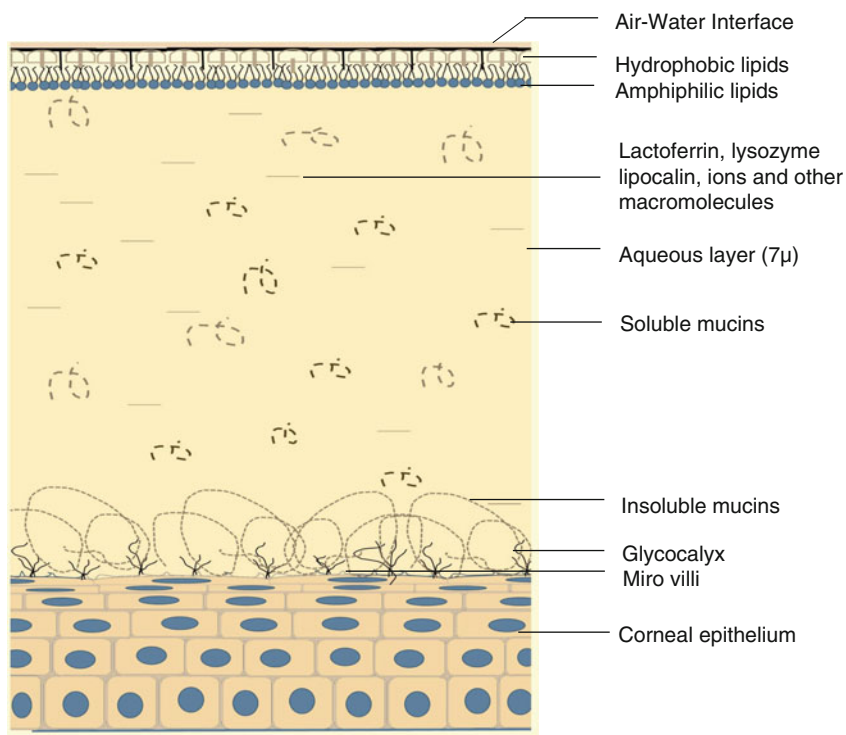
Fig 10.1 Human tear film comprise of the lipid layer followed by the aqueous layer resting on the glycocalyx matrix of mucin layer on the corneal epithelium

are classified as transmembrane or secretory mucins. Secreted mucins can be further subclassified as gel forming or soluble, based on their ability to form polymers. They are highly glycosylated, containing 80 % of carbohydrates, primarily N-acetylgalactosamine, N-acetylglucosamine, fucose, galactose, and sialic acid (N-acetylneuraminic acid), and traces of mannose and sulfate. Both secreted and membrane bound forms of mucins share many common features (Bansil and Turner 2006). Mucins that have been detected in the eye are MUC1, MUC2, MUC4, MUC5AC, MUC7, MUC13, MUC15, MUC16, and MUC17 (Johnson and Murphy 2004). Transmembrane mucins contain hydrophobic, membrane-spanning domains in their carboxyl-terminal region, which anchor them to the apical surface of conjunctival and corneal epithelial cells, facilitating formation of the ocular surface glycocalyx (Johnson and Murphy 2004; Tiffany 2008). MUC5AC, the major gel-forming mucin of tears, is secreted by conjunctival goblet cells. This complex macromolecule gives interface for holding moisture on the biological membrane due to various non-covalent interactions.

The primary function of tear film includes providing nutrition to the epithelium of the cornea, lubricating ocular surface, and removal of debris from the precorneal

area along with the factors for antimicrobial and immune functions. Tear film stability is achieved by the coordinated functions of lipid monolayer with its critical composition and the contents of aqueous interface. Tear instability causes dry eye due to various factors; any disturbance in the composition of the outer lipid layer can lead to the loss of primary defense of tear evaporation (Gipson and Argüeso 2003). Deficiency in mucin and aqueous volume (tear turnover rate) are the other factors responsible for destabilization of tear film integrity leading toward dryness.

10.3 Drugs Used in Dry Eye Condition

Mucoadhesive polymers in tear substitutes
Methyl cellulose, carboxymethyl cellulose, hydroxypropyl methyl cellulose, poloxomer, Hyaluronic acid
Ocular anti-inflammatory agents
Topical cyclosporine and tacrolimus
Secretagogue agents
Tear stimulants: Pilocarpine, cemeviline
Mucin and secretors: Rebamipide and diquafosol sodium
Miscellaneous
Topical sex steroids, androgens, estrogens, and phytoestrogens

10.3.1 Mucoadhesive Polymers for Ocular Surface

Conjunctival goblet cells in the eye secrete mucin which coats the epithelial cells to convert the hydrophobic epithelium to hold water against gravity which in turn maintains tear integrity. Goblet cells intercalated within the stratified epithelium of the conjunctiva secrete the large gel-forming mucin MUC5AC, and lacrimal gland epithelia secrete the small soluble mucin MUC7. Apical cells of the stratified epithelium of both corneal and conjunctival epithelium express at least three membrane-associated mucins (MUCs 1, 4, and 16), which extend from their apical surface to form the thick glycocalyx at the epithelium-tear film interface (Johnson and Murphy 2004). This interface is responsible for the conversion of the property of hydrophobic corneal epithelium into hydrophilic layer to hold tear of 7 μm thickness upon the cornea against gravity. In the inadequacy of the function of mucin, mechanical forces during blinking can result in inflammation of the ocular surface (Itakura et al.

2013). Therefore, efforts were made to constitute artificial tear solutions with muco-adhesive polymers, extracellular cations with a suitable pH and osmolarity for the management of dry eye syndrome.

Mucoadhesion is the property of some of the natural or synthetic macromole-cules which can adhere to a biological surface and retain their presence for a pro-longed duration. Polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), methyl cellulose, hydroxypropyl methyl cellulose (HPMC), carboxymethyl cellulose, hyal-uronic acid, polyethylene glycols, etc., are some of the polymers regularly used in most of the topical tear substitutes. However, mucoadhesive polymers such as thio-lated poly(acrylic acid), poloxamer, celluloseacetophthalate, methyl cellulose, hydroxy ethyl cellulose, poly(amidoamine) dendrimers, poly(dimethyl siloxane), and poly(vinyl pyrrolidone) are also used for increasing the precorneal drug resi-dence time in ocular drug delivery approaches (Wagh et al. 2008).

These bioadhesive polymers used in topical tear substitutes are known to have numerous hydroxyl or carboxyl functional groups having the capability of making hydrogen bond with water molecules in the precorneal area. In ophthalmic prod-ucts, bioadhesive pre-swollen polymers in water are used in a concentration to exhibit low viscosity. In the swollen state the interdistance between their chains leading to polymer flexibility causes uniform spreading upon the cornea and con-junctiva. Occurrence of polymer-mucin force of interaction has been reported when mucoadhesive polymers interact with corneal epithelium. Using in vitro and in vivo visometric data, mucoadhesive polymer interaction has been defined as polymer-cumin force of interaction in precorneal area. Depleting precorneal mucin by treat-ment with N-acetylcysteine reduced this interaction significantly (Saettone et al. 1994).

10.3.1.1 Tear Substitutes

Cellulose derivatives such as HPMC, methyl cellulose, and hyaluronic acid all share a common finding of having an –OH group to make hydrogen bonding and hydro-phobic methyl groups (Fig. 10.2). The amphiphilic nature of these polymers would be having required hydrophobicity to bind toward hydrophobic epithelium and get entangled in the glycocalyx matrix, thereby giving a required polyhydric hydroxyl groups, creating hydrogen bonding with water molecules. This function makes them as a substitute for mucin in artificial tears. Solutions of hydroxypropyl meth-ylcellulose (HPMC) and polyvinyl alcohol (PVA) are widely used as artificial tears. However, their usefulness is limited by the short duration of their effect. Dilute sodium hyaluronate solutions exhibit non-Newtonian rheology with high viscosities at low shear rates, which would be expected to enhance their ocular surface resi-dence time (Snibson et al. 1992). Although several combinations are available worldwide either with single or more than one polymer, so far they are not studied for their compositional variation to make it more suitable for its use in tear substitute.
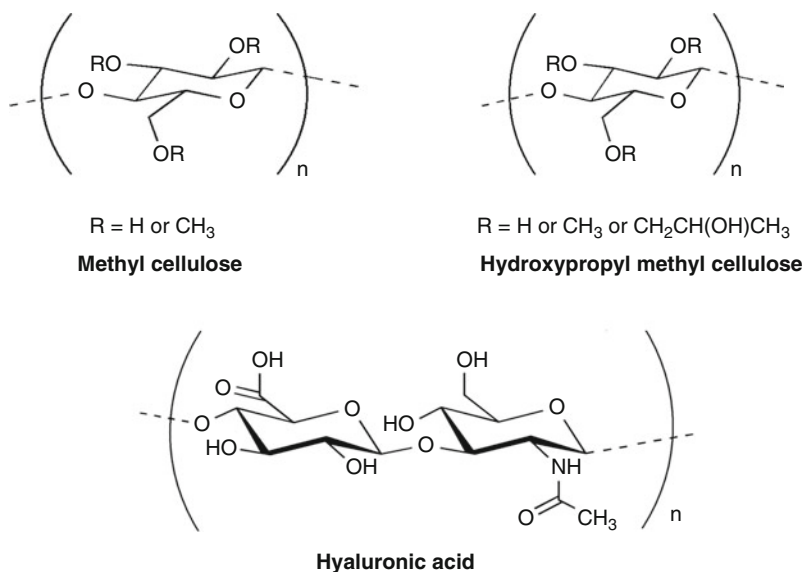
Fig 10.2 Tear Substitutes-Cellulose derivatives used in dry eye disease; HPMC, methyl cellulose, and hyaluronic acid

Throughout the world several compositions of artificial tear are being used and studied in different settings for dry eye. A meta-analysis reviewed 51 of such studies and reported that nearly all formulations of artificial tears provided significant benefit to patients with dysfunctional tear syndrome, but some proved superior to others (Moshirfar et al. 2014). This shows that artificial tear holds a prime position in the management of dry eye syndrome.

Although artificial tear solutions are mostly preferred for dry eye syndrome, at times ophthalmic ointments are used for prolonged management during ocular surgery or enabling nighttime applications. Changing refractive index between the tears and ointment causes blurring of vision and has been considered as one of the major disadvantages of ointments.

10.3.1.2 Other Ophthalmic Uses of Mucoadhesive Polymers

Mucoadhesive polymers are extensively used in ophthalmology during surgical procedures. Sodium hyaluronate (1 %) is very commonly used as one of the ophthalmic viscoelastic substance during capsulorhexis and intraocular lens (IOL) implantation in phacoemulsification surgery. Sodium hyaluronate, chondroitin, and hydroxypropyl methylcellulose are placed in the anterior chamber to prevent corneal endothelial damage during phacoemulsification and are removed after the completion of the procedure (Hutz et al. 1996). Intracameral injection of 2 % HPMC during

trabeculectomy has been reported to maintain anterior chamber depth and reduces incidence of complications related to shallow anterior chamber depth following trabeculectomy (Agarwal et al. 2005).

Extensively, mucoadhesive polymers were studied for their activity to enhance the contact time of drugs on the precorneal area (Bucolo et al. 2011); they are also reported to reduce the ocular irritation of drugs when applied topically.

The conditioning properties of the multipurpose contact lens solution with polymers such as HPMC showed improved wetting of lenses and enhanced lens wearing comfort. Moreover, it has also been suggested that binding of HPMC to the lens surface and subsequent time-release is the probable mechanism for these benefits (Simmons et al. 2001).

10.3.2   Secretagogue Agents (Tear Stimulants and Mucin Inducers)

10.3.2.1   Tear stimulants

Lacrimal glands having M3 muscarinic receptors are the prime targets for increasing the tear secretion rate. Pilocarpine and cevimeline are the muscarinic agents approved for the treatment of symptoms of xerostomia in Sjögren's syndrome.

Pilocarpine

Pilocarpine is a well-known muscarinic agonist used for decades for inducing lacrimation. It is an alkaloid isolated from the plant Pilocarpus jaborandi. Being a muscarinic agonist on all muscarinic receptors, its systemic side effects are bothersome. Administration of 5-mg pilocarpine tablets 4 times daily (20 mg/day) was well tolerated and produced significant improvement in symptoms of dry mouth and dry eyes and other xeroses in patients (Vivino et al. 1999).

Cevimeline

Cevimeline is a synthetic compound, chemically ((±)-cis-2-methylspiro [1,3- oxathiolane-5, 3′-quinuclidine]), available as monohydrochloride reported to be an agonist on M1 and M3 receptors. Cevimeline at a dosage of 30 mg 3 times daily resulted in substantive improvement by increasing the rate of saliva and tear flow in patients with Sjögren's syndrome, as well as improving subjective symptoms of dry mouth, dry eyes, and overall dryness (Petrone et al. 2002). Frequently reported adverse events included headache, increased sweating, abdominal pain, and nausea. Increasing the dose to 60 mg TID increased higher gastrointestinal side effects.

However, at the dose of 20 mg three times daily, it has showed significant improvements in the subjective symptoms, tear dynamics, condition of the corneoconjunctival epithelium, and global improvement rating with lesser side effects (Ono et al. 2004)

10.3.2.2 Mucin inducers

Conjunctival epithelial and goblet cell P2Y2 nucleotide receptors regulate ion transport and glycoprotein release onto the ocular surface to promote tear and mucin secretion via elevated intracellular Ca^{2+} concentrations. Diquafosol tetrasodium (INS-365), a second-generation uridine nucleotide analog reported to act through P2Y2 receptor, induces the secretion of aqueous tear components from conjunctival epithelial cells and secretion of mucin from conjunctival goblet cells, thereby improving corneal epithelial integrity and stabilizing the tear film (Terakado et al. 2014). Diquafosol ophthalmic solution (3 %) is currently approved in Japan and South Korea for the treatment of dry eye.

In patients with dry eye, topical therapy with diquafosol significantly improved fluorescein and rose bengal staining scores as compared with placebo. Topical solution of 3 %, one drop, four times a day, was reported as noninferior to sodium hyaluronate ophthalmic solution 0.1 % (Keating 2015). Based on the published randomized clinical trial data on the use of diquafosol (3 % topical) in the management of dry eye, it has been suggested that topical therapy consistently improved tear film volume and stability (Lau et al. 2014). Whereas it was not accompanied with major improvement in symptoms related to dry eye disease. This could be due to the complex nature of dry eye disease having multiple etiologies. In most of the cases, the treatment period required was also long (6 months) to get subjective and objective improvement in aqueous-deficient dry eye, whereas topical diquafosol therapy was effective for patients with obstructive meibomian gland dysfunction (Arita et al. 2013). Diquafosol ophthalmic solution 3 % was generally well tolerated in patients with dry eye, with eye irritation the most commonly reported adverse event (Keating 2015).

10.3.2.3 Rebamipide

Rebamipide is initially developed as a gastroprotective compound capable of inducing mucin secretion through prostaglandin generation in the gastric mucosa. This compound has been selected from over 500 amino acid analogs of 2(1H)-quinolinone tested for gastroprotective action and for efficacy to heal experimental gastric ulcers (Arakawa et al. 1998) and nonsteroidal anti-inflammatory drug-induced gastric ulcers. MUC5AC has been identified as a major secretory mucin of conjunctival goblet cells and precorneal tear film. It has been found to decrease significantly in patients suffering from dry eye (Zhao et al. 2001). In vitro

studies showed that rebamipide stimulated proliferation of conjunctival goblet cells in primary culture (Rios et al. 2006). Oral administration of rebamipide represents a new therapeutic modality in the treatment of Sjogren syndrome (Kohashi et al. 2008). It has been reported to stimulate EGF receptor (EGFR) and p44/p42 mitogen-activated protein kinase (MAPK) to cause mucin secretion from conjunctival goblet cells (Ríos et al. 2008). Rebamipide promoted glycol conjugate, which has a property as a mucin-like glycoprotein, in human corneal epithelial cells. The increased production was mediated by MUC1 and MUC4 gene expression (Takeji et al. 2012).

Being a suspension, it has been reported to affect optical quality by ocular higher-order aberrations and forward light scatter upon its use in patients (Koh et al. 2013)

Clinically, rebamipide ophthalmic suspensions were tested and reported to be effective in restoring tear stability in patients with dry eye. Topical rebamipide has also been shown to be effective in treating other ocular surface disorders such as lagophthalmos, lid wiper epitheliopathy, and persistent corneal erosion Kashima et al. (2015). Oral rebamipide administration for the period of 3 months showed significant levels of rebamipide in the tear film, indicating potential value in management of mucin-deficient tear film dysfunction (Tandon et al. 2012).

10.3.3   Anti-inflammatories and Immunosuppressants

10.3.3.1   Topical Cyclosporine

Cyclosporine-A (CsA) is a lipophilic cyclic undecapeptide, produced by the fungus *Beauveria nivea*. CsA suppresses humoral immunity and T-cell-dependent immune mechanisms which are responsible for transplant rejection and forms autoimmunity. Systemically administered CsA is metabolized by CYP3A4 and showed severe systemic toxicity such as renal dysfunction, tremor, hirsutism, hypertension, hyperlipidemia, and gum hyperplasia.

The mechanism involved in chronic immune inflammation during dry eye disease has been defined as a sequence of primary insult of various etiologies. An acute corneal inflammation caused by the irritation of the ocular surface (viral, bacterial, and environmental) leads to rapid vascular endothelial selectin expression and diapedesis of non-primed (non-targeted) T cells into the conjunctiva. When this condition gets into chronic phase, its challenge to the ocular surface (over time) leads to activation and drainage of antigen-presenting (including dendritic) cells to lymphoid organs permitting T cells to be primed and capable of targeting the ocular surface. These symptoms correlate primarily with corneal epithelial damage, thought to be due to cumulative damage mediated by cytotoxic effects of inflammatory and pro-apoptotic stimuli and hyperosmolarity. This cascade proceeded on to

epithelial loss/devitalization is the stimulation for corneal nociceptive nerve endings (McDermott et al. 2005)

Although topical cyclosporine in vegetable oils (olive and arachis oil) at higher concentrations (1–2 %) was attempted for immunosuppression in corneal graft survival, its anti-inflammatory role, predominately T cells, made it to be used in ocular surface inflammation. For this purpose it was approved at the concentration of 0.05 % in keratoconjunctivitis sicca. Lack of systemic toxicity upon topical administration of CsA due to its low/undetectable levels in the blood paved the way for its safer use in dry eye (Pfau et al. 1995). A recent meta-analysis included 12 randomized clinical trials comparing topical CSA with placebo involving 3034 eyes of 1660 participants with dry eye syndrome. This study showed that statistically significant improvements on scores of breakup time (Zhou and Wei 2014).

10.3.3.2 Tacrolimus

Tacrolimus, formerly known as FK506, is a macrolide antibiotic with immunosuppressive properties. It belongs to the class of immunosuppressants but structurally unrelated to cyclosporine A (CsA); it principally acts through the impairment of gene expression in target cells. Tacrolimus bonds to an immunophilin, FK506-binding protein (FKBP). This complex inhibits calcineurin phosphatase. The drug inhibits calcium-dependent events, such as interleukin-2 gene transcription, nitric oxide synthase activation, cell degranulation, and apoptosis (Thomson et al. 1995). Recently, a double-blind randomized study showed that topical 0.03 % tacrolimus eye drop (vegetable oil based) instilled one drop every 12 hours has been reported to improve tear stability and ocular surface status in cases of inflammatory or Sjögren-related dry eye (Moscovici et al. 2015).

10.3.4 *Autologous Serum and Umbilical Cord Serum Eye Drops for Dry Eye*

Autologous serum is usually prepared from the patients and diluted to 20 % by saline. The detailed protocol to prepare autologous serum is given in the chapter of extemporaneous formulations (Chapter 15). The use of blood derivatives represents an alternative therapeutic approach that is gaining interest in regenerative medicine due to its potential to stimulate and accelerate tissue healing (Anitua et al. 2015). Autologous serum is rich in several plasma-driven growth factors which are reported to increase the tissue repair and rejuvenation of cells.

Epitheliotropic effect of serum eye drops is attributed to the number of bioactive factors such as fibronectin, EGF, TGF beta-1, HGF, vitamin A, and antiproteases.

As this formulation is expected to contain approximately 1 % albumin, it serves as a natural polymer; with this it improves the signs and symptoms of dry eye. Umbilical cord serum eye drops were more effective in decreasing symptoms and keratoepitheliopathy in severe dry eye syndrome and increasing goblet cell density in Sjögren's syndrome compared with autologous serum eye drops (Yoon et al. 2007).

Autologous serum eye drops are safe if they are compounded in sterile form and used with proper care of not contaminating it. Moreover, such eye drops must be stored in frozen or refrigerated conditions to improve the shelf life. Autologous serum is used in the conditions like keratoconjunctivitis sicca, superior limbal keratoconjunctivitis, recurrent erosion syndrome, persistent epithelial defects, etc. However, it may not be useful in secondary Sjögren's syndrome due to the elevation of proinflammatory cytokine levels in the serum.

10.3.5   Miscellaneous Agents

In Sjögren's syndrome, oral prednisone or hydroxychloroquine showed limited benefits in a few clinical trials. However their benefits are not clearly elucidated (Ramos-Casals et al. 2010). Gefarnate, a water-insoluble terpene fatty acid, has been reported to contribute to restoring mucins on the ocular surface. Similarly, the mucolytic drug bromhexine has also been reported to induce mucin production in the tears. There are studies attempted to evaluate the role of male/female sex (Piwkumsribonruang et al. 2010) hormones, their combination (Scott et al. 2005), metabolic precursor (dehydroepiandrostenedione), and phytoestrogens (Scuderi et al. 2012) for postmenopausal dry eye. However, their therapeutic role still remains uncertain.

10.4   Treatment for Dry Eye

As there is no definitive diagnostic test, it is often difficult to segregate patients to rationalize drug treatment. Therefore, treatment strategies are decided based on the severity of the symptoms. Mild intermittent bouts of symptoms can be solely managed by ophthalmic lubricants. If symptoms remain unresolved on lubricant therapy and ocular irritation persists, one can opt for topical anti-inflammatory therapy including short-term corticosteroids, topical cyclosporine A emulsion, oral tetracycline therapy, oral omega-3 fatty acid supplements, and autologous serum eye drops. In case of moderate conditions, topical secretagogue agents such as rebamipide or diquafosol can be attempted.

Physical measures (punctal plugs, moisture-retaining eye wear) are implemented for those with moderate-to-severe symptoms. Autologous serum tears, scleral con-

tact lenses, and surgery are reserved for patients with severe symptoms who have an unsatisfactory response to anti-inflammatory medications.

Sjögren's syndrome is a systemic autoimmune disease characterized by dry eyes and dry mouth. In primary disease, Sjogren's syndrome is a solitary process, whereas in secondary cases it accompanies another autoimmune disease, most often rheumatoid arthritis. The recommended treatments include topical lubricants, topical anti-inflammatory therapy, and tear-conserving strategies and orally administered secretagogues; however, they seem to be of greater value in the treatment of oral dryness than ocular dryness (Akpek et al. 2011). Surprisingly, systemic TNF-alpha antagonists did not show any significant use in this condition.
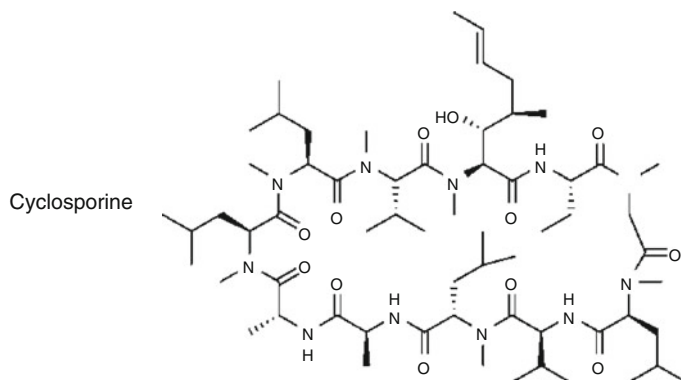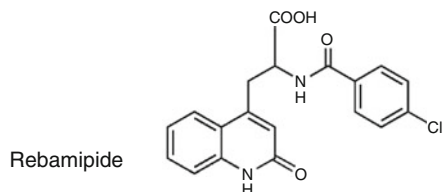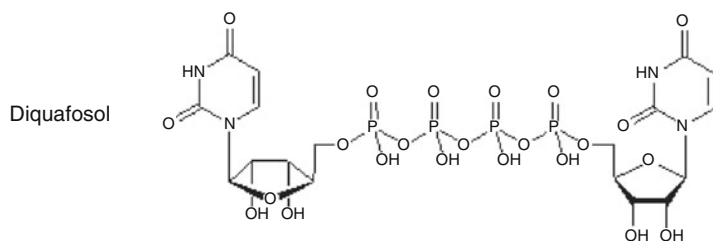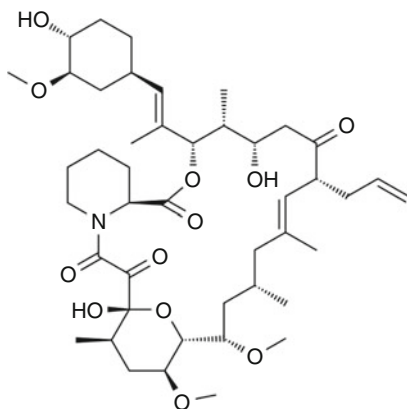
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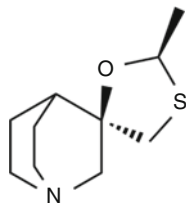
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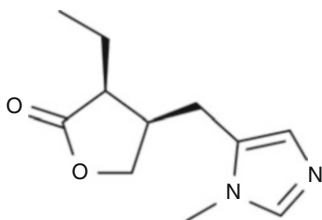
Tacrolimus

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