Review Article

A Review on Mucoadhesive Polymers in Ophthalmics

Bhavani Boddeda, J Vijaya Ratna, Heera Battu
A.U.College of Pharmaceutical Sciences, Andhra University, Visakhapatnam, A.P., India.
*Corresponding author's E-mail: bhavani2008@gmail.com

ABSTRACT

In the present update on mucoadhesive polymers for ocular delivery dosage forms, the tremendous advances in the biochemistry of mucins, the development of new polymers, the use of drug complexes and other technological advances are discussed. This review focuses on recent literature regarding mucoadhesive polymers presently in use for ocular drug delivery. Gel-forming minitablets and inserts made of thiomers show an interesting potential for future applications in the treatment of ocular diseases.

Keywords: Mucoadhesive polymers, ophthalmics, mucin.

INTRODUCTION

Topical application of drugs to the eye is the most popular and well-accepted route of administration for the treatment of various eye disorders. The bioavailability of ophthalmic drugs is, however, very poor due to efficient protective mechanisms of the eye. Blinking, baseline and reflex lachrymation, and drainage remove rapidly foreign substances, including drugs, from the surface of the eye. Moreover, the anatomy, physiology and barrier function of the cornea compromise the rapid absorption of drugs.[1]

Frequent instillations of eye drops are necessary to maintain a therapeutic drug level in the tear film or at the site of action. But the frequent use of highly concentrated solutions may induce toxic side effects and cellular damage at the ocular surface.[2] To enhance the amount of active substance reaching the target tissue or exerting a local effect in the cul-de-sac, the residence time of the drug in the tear film should be lengthened. Moreover, once-a-day formulations should improve patient compliance. Numerous strategies were developed to increase the bioavailability of ophthalmic drugs by prolonging the contact time between the preparation, and the drug, and the corneal/conjunctival epithelium. The use of a water-soluble polymer to enhance the contact time and possibly also the penetration of the drug was first proposed by Swan.[3] Where very promising results and improved bioavailability were observed in animal studies; only a small increase in precorneal residence time was obtained in humans.[4] There is no reliable correlation between the performance of ophthalmic vehicles in rabbits and in humans, mainly due to differences in blinking frequency.[5-9] Viscous semi-solid preparations, such as gels and ointments, provide a sustained contact with the eye, but they cause a sticky sensation, blurred vision and induce reflex blinking due to discomfort or even irritation.[10,11]

An alternative approach has been the application of in situ gelling systems or phase transition systems, which are instilled in a liquid form and shift to a gel or solid phase in the cul-de-sac. The phase transition is triggered by the pH of the tears; the temperature at the eye surface or the electrolytes present in the tear film.[11] A further approach to optimize the ocular dosage form was the implementation of the mucoadhesive concept, which was successful in buccal and oral applications.[12,13] Interactions of suitable natural and synthetic polymers with mucin were evaluated. Due to interactions with the mucus layer or the eye tissues, an increase in the precorneal residence time of the preparation was observed. Some mucoadhesive polymers showed not only good potential to increase the bioavailability of the drug applied, but also protective and healing properties to epithelial cells.[8, 11-16]

ANATOMY AND PHYSIOLOGY

Only a brief discussion of the structures of the eye, which come in contact with drug delivery systems administered topically, is given.

Structure of the ocular globe

The eyeball has a wall consisting of three layers: the outer coat or the sclera and cornea, a middle layer or uveal coat and the inner coat or retina. The sclera is made of fibrous tissues shaped as segments of two spheres, the sclera and cornea.[9] The cornea is a clear, transparent, avascular tissue to which nutrients and oxygen are supplied by the lachrymal fluid and aqueous humour. It is composed of five layers: epithelium, Bowman's layer, stroma, Descemet's membrane and endothelium.[8, 9] The epithelium consists of 5 to 6 layers of cells. The cells of the basal layer are columnar. As they are squeezed forward by the new cells, they differentiate and exfoliate from the epithelial surface as flattened polygonal cells. Replacement of the epithelial cells occurs by mitotic division of the basal layer. The average life of a polygonal cell is about 4 to 8 days.[8, 9]

The basal cells are packed closely together like a pavement, forming not only an effective barrier to most microorganisms, but also for drug absorption. The low

permeability of the cornea suggests the presence of tight junctions between the cells [17] The tight junction complex includes two integral transmembrane proteins (claudin and occludin) and the membrane-associated protein ZO-1 [18] The squamous flattened cells have on their surface microvilli of different types and dimensions depending on the maturity of the cells. These microvilli enhance the cohesion and stability of the tear film. [19]

The conjunctiva is a thin transparent membrane, which lines the inner surface of the eyelids and is reflected onto the globe. At the corneal margin, it is structurally continuous with the corneal epithelium. The membrane is vascular and moistened by the tear film. [8,9] The conjunctiva is composed of an epithelium, a highly vascularised substantia propria, and a submucosa or episclera. The bulbar epithelium consists of 5 to 7 cell layers. The structure resembles a palisade and not a pavement when compared to the corneal epithelium. At the surface, epithelial cells are connected by tight junctions, which render the conjunctiva relatively impermeable. The conjunctival tissue is permeable to molecules up to 20,000 Da, whereas the cornea is impermeable to molecules larger than 5000 Da. [9,20]

The goblet cells are an important anatomical element of the conjunctiva. There are about 1.5 million goblet cells. The highest density is in the inferonasal quadrant (10 goblet cells/mm^2). The density is agedependent, with the highest density being in children and young adults, but important intersubject variations are noted. No differences between races seem to exist. [21] An abnormal decrease or absence of goblet cells is observed not only in several pathological conditions such as keratoconjunctivitis sicca, xerophthalmia and allergic conjunctivitis, but also chronic use of eye drops containing benzalkonium chloride. A significant increase in the number of goblet cells was reported in the case of vernal conjunctivitis and atopic keratoconjunctivitis [22-25] but a great variation in goblet cell density results only in a small difference in tear mucin concentration. [26] The vesicles contain neutral mucins, sialomucins and sulphomucins. [27,28] The role of these mucins is to anchor the goblet cell mucus to the surface of the eye. [27] Goblet cells synthesize secretory mucins (MUC 5AC) and TFF-peptides (formerly P-domain peptides) or trefoil factors (TFF1 and TFF3). The TFF-peptides contribute to the rheological properties of the tear film by specific non-convalent interactions with mucins forming an entangled network. The TFFpeptides can also influence corneal wound healing. [29]

A volume of about 2 to 3 µl of mucus is secreted daily. [9] The gel-forming properties are important in entrapping foreign particles and bacteria. During blinking, they are swept to the puncta, situated at the medial part of the eyelids, and then discharged to the drainage system. [22] A turnover of the mucus layer in approximately 15 to 20 h is reported, which is much slower than the tear turnover rate. It should be noted that the interaction of mucus with polymers and mucoadhesive dosage forms is still limiting, and therefore efforts should be devoted to the development of once-a-day medication. [13]

Tear film

The exposed part of the eye is covered by a thin fluid layer, the so-called precorneal tear film. The film thickness is reported to be about 3–10 µm depending on the measurement method used. The resident volume amounts to about 10 µl [8, 9, 30, 31]. According to the "three layers theory" the precorneal tear film consists of a superficial lipid layer, a central aqueous layer and inner mucus layer (Fig 1). [8,9]

The superficial lipid layer (a 100-nm-thick multimolecularfilm) is secreted during blinking by the meibomian glands embedded in the tarsal plate of the eyelids and the accessory sebaceous glands of Zeiss. The lipid layer spreads over the aqueous layer during eye opening. It consists mainly of sterol esters, triacylglycerols and phospholipids, free sterols and free fatty acids. The lipids play an important role in reducing the evaporation rate in a way that normal tear osmolality can be maintained, even when the tear flow is quite low. [32] The lachrymal gland and the accessory gland contribute to the formation of the aqueous layer, containing inorganic salts, glucose and urea as well as retinol, ascorbic acid, various proteins, lipocalins (previously known as tear-specific prealbumins), immunoglobulins, lysozyme, lactoferrin and glycoproteins. [30,33-35] Vitamin A and its derivatives are required for the normal growth and differentiation of the corneal/conjunctival epithelium. The osmolality of the tear film equals 310–350 mOsm/kg in normal eyes and is adjusted by the principal inorganic ions Na+, K+, Cl$^-$, HCO3$^-$, and proteins. The mean pH value of normal tears is about 7.4. Depending on age and diseases, values between 5.2 and 9.3 have been measured. Diurnal patterns of pH changes exist, with a general shift from acid to alkaline during the day. The buffer capacity of the tears is determined by bicarbonate ions, proteins, and mucins. [30, 33] Tears exhibit a non-Newtonian rheological behaviour. The viscosity is about 3 mPas. [8,36] The surface tension depends on the presence of soluble mucins, lipocalins and lipids. The mean surface tension value is about 44 mN/m. [34,35] The mucus layer, which is secreted onto the eye surface by the goblet cells, is intimately associated with the glycocalyx of the corneal/conjunctival epithelial cells. [37]

The mucus layer is very sensitive to hydration and forms a gel-layer with viscoelastic rheological properties. It protects the epithelia from damage and facilitates the movements of the eyelids. Mucins improve the spreading of the tear film and enhance its stability and cohesion. Mucus is wiped over the surface of the eye by the upper eyelid during blinking. The mucus gel entraps bacteria, cell debris, and foreign bodies, forming "mucous threads" consisting of thick fibers arranged in bundles. These 'threads' are transported during blinking to the inner canthus and expelled onto the skin. [8,9] The mucus layer can form a diffusion barrier to macromolecules

depending on the degree of network entanglement. On the other hand, mucus can bind cationic substances because of the negative charges of mucins.[1, 8]

Mucus consists of glycoproteins, proteins, lipids, electrolytes, enzymes, mucopolysacchrides and water.[8, 38] The primary component of mucus is mucin, a high-molecular-mass glycoprotein with subunits containing a protein core, approximately 800 amino acids long, of which about 200 are bearing polysaccharide side-chains. The protein core consists of tandem repeat regions, which are repeated sequences of mainly serine, threonine and proline. The polysaccharide side chains are linked to the protein core by an O-glycosidic bond between N-acetylgalactosamine on the sugar chain and the hydroxyl groups of the serine and threonine residues on the protein backbone.

As the polysaccharide side chains usually terminate in either fucose or sialic acid (N-acetylneuraminic acid pKa=2.6), the glycoprotein is negatively charged at physiological pH. In solution, large linear aggregates, which are formed by oligomerisation of several mucin glycoproteins, take the form of flexible rods with varying diameter. The aggregates are further stabilized by the entanglement of the flexible macromolecules and the formation of hydrogen bonds between adjacent carbohydrate residues.[39] Entanglement seems to be the preferred mode of molecular association in dilute solutions.[40] A combination of cross-linking via disulfide bridges and hydrophobic bonds, and also network formation through entanglement of randomly coiled macromolecules is often involved in the tertiary structure of mucin.[39]
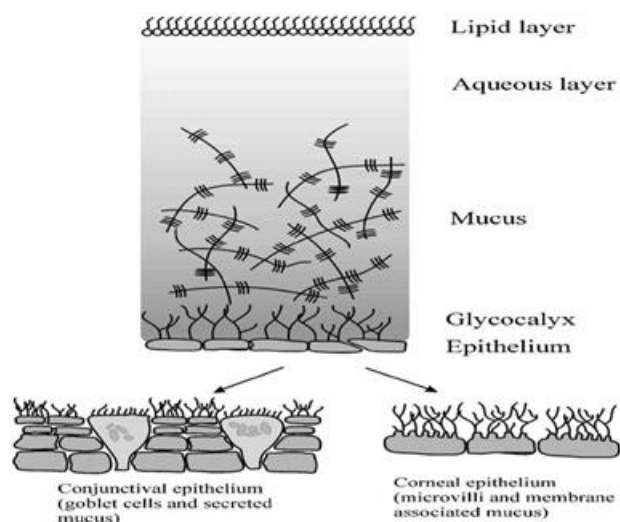

Figure 1: Schematic representation of the precorneal tear film.

Studies by Kuver et al. suggest that an increased intracellular calcium concentration (20 times the extracellular concentration) plays an important role in providing cationic shielding to keep negatively charged mucins condensed and tightly packed within the granules of goblet cells. Sudden calcium release unshields the negative charges of mucins, causing mutual repulsion of

polymer chains and network formation. The content of each granule swells rapidly, detaches slowly from the cell surface and forms large aggregates that diffuse onto the epithelial surface.[41] High calcium levels at the eye surface, as observed with dry eye patients, may contribute to changes in mucin secretion and mucus spreading at the ocular surface.[42] Lack of mucus coverage could result in less hydration, more dry spots and decreased tear film stability. Lack of mucus diffusivity leads to clumped mucus, and may be due to altered mucin intermolecular associations brought about by altered packaging.[43] The polymer chains must be mobile and flexible enough to interdiffuse into the mucus and penetrate to a sufficient depth in order to create a (strong entangled) network. They should interact with mucins by hydrogen bonding, electrostatic and hydrophobic interactions.[44-46]

These interactions depend on the ionic strength and pH of the vehicle, because changes in ionization of functional groups or shielding of charges influence electrostatic repulsion and expansion of the mucus network.[47] The presence of electrolytes in the vehicle can increase the fluid uptake by a polymer. This phenomenon can be an important factor in achieving a significant interaction with mucus. Decreasing the pH of the medium promotes mucoadhesion of polymers containing proton-donating carboxyl groups, because uncharged, rather than ionized carboxyl groups, react with mucin molecules, presumably through hydrogen bonds. Increasing the pH on the other hand promotes electrostatic repulsion of carboxylate anions, resulting in extension of the polymer chains. When the number of available charged groups increases, the swelling pressure across the polymer increases, which enlarges the free space within the polymer network. A decrease in density of the polymer chains will increase chain segment mobility, and enhance interdiffusion and physical entanglement. Depending on the pKa value of the functional groups of the polymer present in the drug delivery system, hydrogen bond formation or physical entanglement predominates.[44, 45, 47-49]

The tear film is only temporarily stable. The eyes cannot be kept open indefinitely. After 20–40 s, an unpleasant sensation compels humans to blink. In the short time interval between two blinks, rupture of the tear film occurs due to concentration gradients and dispersions forces on the mucus layer. The rupture causes dewetting of the cornea (dry spots formation), which irritate corneal nerve endings and induce blinking. During eyelid opening, a new tear film spreads over the external eye surface.[8, 50] The time of rupture of the mucus layer and the breakup time of the tear film depend on dispersion forces, the interfacial tension and viscous resistance of the mucus layer.[51-54] During development of mucoadhesive dosage forms and selection of soluble or insoluble polymers and additives, these factors should be taken into consideration.

Some topically applied drugs and vehicles influence the tear stability negatively or positively. Adverse effects of surfactants, benzalkonium chloride and topical

Int. J. Pharm. Sci. Rev. Res., 24(1), Jan – Feb 2014; n° 42, 237-245

ISSN 0976 – 044X

anaesthetics on the tear film stability are related to the decrease of the mucus–aqueous interfacial tension.[54-57]

A critical chain length is necessary to obtain interpenetration and molecular entanglement between the polymer and the mucus layer. The threshold required for successful mucoadhesion is a molecular weight of at least 100,000 Da. Excessive cross-linking in the polymer, however, decreases the chain length available for interfacial penetration. Also, excessive formation of interchain physical entanglement and hydrogen bonding within the polymer itself can lead to conformation hindering polymer diffusion into the mucus network.[11,47,49,50] As a result, chain flexibility is critical for interpenetration and entanglement with the mucus gel. The higher the mobility of the chain segment, the greater the interdiffusion and the interpenetration of the polymer within the mucus network .[46] Coiling of polymer chains, due to pH or osmolality of the medium, can result in the shielding of active groups necessary for the adhesion process.[11,46,49,50]

Many high molecular weight polymers with different functional groups (such as carboxyl, hydroxyl, amino, and sulfate) capable of forming hydrogen bonds, and not crossing biological membranes, have been screened as a possible excipient in ocular delivery systems. Unfortunately, in vivo studies in humans were not always performed. An overview of important

polymers investigated by several research groups is given in Table 1.[9, 38,17,44] The polymers are categorized according to mucoadhesive properties even if, due to various experimental approaches applied in the different studies, it is difficult to assign a mucoadhesive capacity to each polymer in order to allow comparison.

A general conclusion which can be drawn from Table 1 is that charged polymers both anionic and cationic demonstrate a better mucoadhesive capacity in comparison to non-ionic cellulose-ethers or polyvinyl alcohol (PVA). [58-61]

i) Cellulose derivatives

The first cellulose polymer, methylcellulose, was introduced over 50 years ago. Subsequently, a number of substituted cellulose-ethers have been employed for artificial tear solutions[62] and as viscosity-enhancing ophthalmic vehicles.[9] Methylcellulose also possesses wound healing properties and is a suitable tear substitute for dry eyes, especially for those with punctuate lesions.[63] All cellulose-ethers impart viscosity to the solution, have wetting properties and increase the contact time by virtue of film forming properties.[64]

Some cellulose-ethers (e.g. hydroxypropylmethylcellulose and hydroxypropylcellulose) also exhibit surface active properties, interact with components of the tear film and alter the physicochemical parameters governing the tear film stability.[64] Surface active viscosifying agents can influence the blinking rate, which in turn influences the elimination of the drug instilled. They cause irritation and

extensive lachrymation, provoking a rapid wash out of the ophthalmic solution and consequently a poor bioavailability.

Generally, less surface active hydroxyethylcellulose is better tolerated [6], but the mucoadhesive properties of non-ionic cellulose-ethers are rather poor. [58, 61] Sodium carboxymethylcellulose (NaCMC), however, exhibits a mucoadhesive capacity comparable to that of poly (acrylic acid) (PAA).[65]

ii) Acrylates

The first mucoadhesive polymers proposed were poly(acrylic acid) and carbomers (see Fig. 3) [18].[12] The mucoadhesive properties of poly(acrylic acid) are due mainly to hydrogen bonding, while hydrophobic interaction with mucin is not significant [131].[66] When anionic polymers interact with mucin, the maximum interactive adhesive force occurs at an acidic pH, suggesting that the mucoadhesive polymer in its protonated form is responsible for the mucoadhesion. The swollen polymer entangles with mucin on the eye surface, stabilizing a thick hydrogel structure .[9, 67]

In contrast, in the precorneal area, the neutral pH value of the tears and the shielding of the carboxyl groups by cations present in the tear fluid diminish the interaction of carbomer with the functional groups on mucin. A decrease in mucoadhesion is measured.[68]

Rheological studies performed with various kinds of carbopolR (974P NF, 980 NF, 1342 NF) demonstrated no significant differences in the interaction between these different carbomers and mucin. It was demonstrated that the interaction depends on the mucin concentration, which implies that this interaction is only possible close to the corneal/conjunctival epithelium.

The use of non-neutralized polycarbophil, in order to prolong the precorneal residence time due to in situ gel formation and mucoadhesion. [16] Polyanionic polymers such as polyacrylates or carbomers were proposed as long-lasting artificial tears for the relief of dry eye syndrome and traumatic injury. The use of these high molecular weight polymers is based on inherent mucus like and lubricating properties, shear thinning behaviour, and good retention on the ocular surface.[69-71] Concentration-dependent blurring of vision and uncomfortable feeling are sometimes reported.[72]

iii) Hyaluronan

Besides synthetic polymers, natural macromolecules such as hyaluronan (HA), present in the vitreous body of the eye, were proposed as viscosifying agents. Sodium hyaluronate molecules have physical properties and a composition comparable to tear glycoproteins, and easily coat the corneal epithelium. Polymers adsorbed at the mucin/aqueous interface extend into the adjacent aqueous phase, thereby stabilizing a thick layer of water. The non- Newtonian behaviour of sodium hyaluronate

combines the advantage of high viscosity at rest between blinks with those of lower viscosity during blinking.[9,12,73,74]

Diluted solutions of sodium hyaluronate have been employed successfully as tear substitutes in severe dry eye disorders. The beneficial effects are attributed to the viscoelasticity, biophysical properties similar to mucins, providing a long-lasting hydration and retention.

Moreover, good lubrication of the ocular surface is obtained .[9,12,75-79] Hyaluronic acid is an important constituent of the extracellular matrix and may play a role in inflammation and wound healing and may promote corneal epithelial cell proliferation.[80]

Gurny et al. confirmed the positive influence of hyaluronate vehicles on the bioavailability of pilocarpine.. High molecular weight of the polymer is an essential requirement for the prolonged precorneal residence time of the preparation.[68] Drug molecules not bound to the viscosifying agent can be squeezed out of the polymer network into the precorneal tear film during blinking.

Table 1: Viscosifying polymers and their mucoadhesive capacity for ocular delivery

Polymer	Charge	Mucoadhesive capacity
Poly(acrylic acid) (neutralized)Anionic	A	+++
Carbomer (neutralized)	A	+++
Poly (galacturonic acid)	A	++
Na alginate	A	++
Chitosan	C	++
Pectin	A	++
Xanthan gum	A	+
Scleroglucan	A	+
Poloxomer	NI	+
Hydroxypropylmethylcellulose	NI	+
Methylcellulose	NI	+
Poly (vinyl alcohol)	NI	+
poly (vinyl pyrrolidine)	NI	+

Charge: A:anionic; C: Cationic; NI non-ionic

Mucoadhesive capacity: +++: excellent; ++: good; +: poor/absent.

iv) Chitosan

As Lehr et al. suggested, cationic polymers were probably superior mucoadhesives due to an ability to develop molecular attraction forces by electrostatic interactions with the negative charges of the mucus, the polycationic chitosan was investigated as an ophthalmic vehicle.[81] The polymer is biodegradable, biocompatible and non-toxic. It possesses antimicrobial and wound-healing properties. Moreover, chitosan exhibits a pseudoplastic and viscoelastic behaviour.[9, 12, 17, 82-86]

The mucoadhesive properties of chitosan are determined by the formation of either secondary chemical bonds such as hydrogen bonds or ionic interactions between the positively charged amino groups of chitosan and the negatively charged sialic acid residues of mucins, depending on environmental pH. The mucoadhesive performance of chitosan is significantly higher at neutral or slightly alkaline pH as in the tear film.[81] Only in the presence of an excess of mucin, does a strengthening of the mucoadhesive interface occur.[85]

The rationale for choosing chitosan as a viscosifying agent in artificial tear formulations was based on its excellent tolerance after topical application, bioadhesive properties, hydrophilicity, and good spreading over the entire cornea.[87] The antibacterial activity of chitosan is an advantage, because in keratoconjunctivitis sicca, secondary infections due to the diminished tear secretion, which contains antibacterial lysozyme and lactoferrin, are frequently observed.

A 3-fold increase of the precorneal residence time of tobramycin was achieved when adding chitosan to the formulations, compared to the commercial solution of the drug. Only a minimal influence was observed from the concentration and molecular weight of chitosans employed, indicating a saturable bioadhesive mechanism based on ionic interactions of the cationic polymer with the negative charges of the ocular mucus.[84] Various chitosan derivatives were synthesized not only to improve the mucoadhesion, but also to enhance the penetration of drugs and peptides through the mucosa by opening the tight junctions between epithelial cells[85,86,88] or by intracellular routes.[89] However, in vitro studies showed that cell surface binding and absorption-enhancing effects were reduced in mucus covered cell lines .[90] The quaternized N-trimethyl chitosan and N-carboxymethylchitosan have proved to be potent intestinal penetration enhancers.[91] These polymers could be of interest in ocular formulations when high aqueous humour levels are required.

V) Polysaccharides

Besides chitosan, numerous polysaccharides were evaluated as mucoadhesive ophthalmic vehicles: polygalacturonic acid, xyloglucan, xanthan gum, gellan gum, pullulan, guar gum, scleroglucan and carrageenan.[9,12,48,58,92-95] Also, in the case of polysaccharides, the formation of macromolecular ionic complexes with drugs improved the bioavailability and lengthened the therapeutic effect when compared to drug solutions.[92,96]

Timolol, in association with xyloglucan, has a prolonged duration of action, and is suitable for ocular administration in cases of elevated intraocular pressure.[97]

Xanthan gum interacts moderately with mucin: a small viscoelastic synergistic effect can be observed, but the effect is due to physical entanglement of both components. Xanthan gum should exist as an ordered

double-stranded helix in the precorneal tear film, due to ions present in the lacrimal fluid. [98]

vi) Thiomers

In order to significantly improve mucoadhesion, The rationale of the concept is based on knowledge concerning the role of disulfide bridges in the three-dimensional mucin network formation.[39] Thiolated polymers, or socalled thiomers, are capable of forming covalent bonds with cysteine-rich subdomains of mucins whereas mucoadhesive polymers discussed so far formed non-covalent bonds (hydrogen bonds or ionic interactions) with mucus, or exhibited physical entanglements. [99]The extensive cross-linking process of the thiomers with mucins resulted in a tremendous increase in viscosity and mucoadhesion independent of pH or ionic strength of the medium.

Cohesive properties of thiomers are improved as a simple oxidation process in aqueous media leads to the formation of inter- and/or intrachain disulfide bonds within the network.[100,101] It has also been demonstrated that thiomers possess permeation enhancing properties for the paracellular uptake of drugs .[102,103] The mechanism is based on the opening of the tight junctions. The cysteine moieties of the thiomers are able to reduce oxidized glutathione

and, therefore, the concentration of reduced glutathione on the absorption membrane is increased. Glutathione inhibits the enzyme protein–tyrosine– phosphatase, which leads to the phosphorylation of the membrane protein occludin, resulting in the opening of the tight junctions .[103, 104]

As a consequence of the in situ gelling and mucoadhesive properties of thiomers, a prolonged residence of the formulation and subsequently a prolonged time period of drug absorption are achieved. The permeation enhancing properties will further improve bioavailability of incorporated drugs. When water-soluble polymers are cross-linked, the mobility of individual polymer chains decreases. The

effective length of the chain that penetrates into the mucus layer also decreases, which can reduce mucoadhesive strength.[44] Cross-linking or covalent attachment of large sized ligands leads to reduction in chain flexibility and results in a strong decrease in mucoadhesion.[105] Leitner et al. demonstrated that low molecular mass polymers with flexible chains favouring strong interpenetration are not cohesive enough for optimal mucoadhesion, whereas high molecular weight cross-linked polymers showing high cohesiveness do not display enough chain flexibility.[106] Thus, the right choice of the polymer during the development of ophthalmic delivery systems, taking into account the site of administration, will be essential.

Free radical formation and inflammation are involved in dry eye pathology .[107] Thiomers could be useful additives in artificial tear formulation due to antioxidative and

radical scavenging properties. Moreover, thiomers are similar to ocular mucins displaying numerous thiol groups. Thiomers could mimic the physiological process of the mucus layer such as tear film stabilization. The formation of disulfide bonds with mucins leads to strong mucoadhesion, prolonged residence time and protective effect for the corneal/conjunctival epithelium.

and prolonged therapeutic effect were observed, except when the drug had a high affinity for the polymer. The increased bioavailability was attributed to the bioadhesive properties of polyalkyl cyanoacrylates. The precorneal residence time of PACA nanoparticles could further be increased by incorporation into a poly(ethylene glycol) gel or by coating with poly(ethylene glycol).[108,109]

CONCLUSION

A good balance between excellent adherence, prolonged residence time, controlled drug release and low irritation potential, tolerability and acceptance by the patients must be achieved.

Mucoadhesion is based on entanglement or non-covalent bonds between polymers and mucus. Only thiomers form covalent disulfide bridges with mucins. Several studies demonstrated the need for high mucins concentrations which are probably not present in the tear film or at the surface of the eye. Thus, mucoadhesion as the sole factor responsible for an improvement in bioavailability is questionable. Interactions with corneal/conjunctival epithelium could play a role.

REFERENCES

1. Lee VHL, Robinson JR, Review: topical ocular drug delivery: recent developments and future challenges, J. Ocul. Pharmacol, 2, 1986, 67–108.

2. Salminen L, Review: systemic absorption of topically applied ocular drugs in humans, J. Ocul. Pharmacol. 6, 1990, 243– 249.

3. Swan K.C, The use of methyl cellulose in ophthalmology, Arch. Ophthalmol. 33,1945, 378–380.

4. 4 Ludwig A, Van Ooteghem M, Influence of viscolysers on the residence of ophthalmic solutions evaluated by slit lamp fluorophotometry, S.T.P. Pharma Sci. 2,1992, 81– 87,

5. Saettone MF, Giannaccini B, Teneggi A, Savigni P, Tellini N, Vehicle effects on ophthalmic bioavailability: the influence of different polymers on the activity of pilocarpine in rabbit and man, J. Pharm. Pharmacol, 34, 1982, 464– 466.

6. Saettone MF, Giannaccini B, Barattini F, Tellini N, The validity of rabbits for investigations on ophthalmic vehicles: a comparison of four different vehicles containing tropicamide in humans and rabbits, Pharm. Acta Helv, 57, 1982, 47– 55.

7. Zaki I, Fitzgerald P, Hardy JG, Wilson CG, A comparison of the effects of viscosity on the precorneal residence of solutions in rabbit and man, J. Pharm. Pharmacol 38 ,1986, 463–466.

8. Greaves JL, Wilson CG, Treatment of diseases of the eye with mucoadhesive delivery systems, Adv. Drug Deliv. Rev. 11, 1993, 349– 383.

9. Robinson JC, Ocular anatomy and physiology relevant to ocular drug delivery, in: Mitra AK (Ed.), Ophthalmic Drug Delivery Systems, Marcel Dekker, New York, 1993, 29– 57.

10. Dudinski O, Finnin BC, Reed BL, Acceptability of thickened eye drops to human subjects, Curr. Ther. Res, 33 ,1983, 322–337.

11. Robinson JR, Mlynek GM, Bioadhesive and phase-change polymers for ocular drug delivery, Adv. Drug Deliv. Rev, 16 ,1995, 45– 50.

12. Hui HW, Robinson JR, Ocular drug delivery of progesterone using a bioadhesive polymer, Int. J. Pharm, 26 ,1985, 203–213.

13. Vasir JK, Tambwekar K, Garg S, Bioadhesive microspheres as a controlled drug delivery system, Int. J. Pharm, 255 ,2003, 13– 32.

14. Robinson JR, Ocular drug delivery, Mechanism(s) of corneal transport and mucoadhesive delivery systems, S.T.P. Pharma, 5 ,1989, 839–846.

15. Le Bourlais CA, Treupel-Acar L, Rhodes CT, Sado PA, Leverge R, New ophthalmic drug delivery systems, Drug Dev. Ind. Pharm, 21 ,1995, 19– 59.

16. Calonge M, The treatment of dry eye, Surv. Ophthalmol, 45, Suppl. 2, 2001, S227–S239.

17. Kaur IP, Smitha R, Penetration enhancers and ocular bioadhesives: two new avenues for ophthalmic drug delivery, Drug Dev. Ind. Pharm, 28 , 2002, 353– 369.

18. Ban Y, Dota A, Cooper L J, Fullwood NJ, Nakamura T, Tsuzuki M, Mochida C, Kinoshita S, Tight junction-related protein expression and distribution in human corneal epithelium, Exp. Eye Res, 76, 2003, 663– 669.

19. Versura P, Bonvicini F, Caramazza R, Laschi R, Scanning electron microscopy of normal corneal epithelium obtained by scraping-off in vivo, Acta Ophthalmol. Copenh., 63, 1985, 361–365.

20. Huang AJW, Tseng SCG, Kenyon KR, Paracellular permeability of corneal and conjunctival epithelia, Invest. Ophthalmol. Visual Sci., 30, 1989, 684– 689.

21. Yeo ACH, Carkeet A, Carney LG, Yap MKH, Relationship between goblet cell density and tear function tests, Ophthalmic Physiol. Opt, 23, 2003, 87– 94.

22. Nichols BA, Chiappino ML, Dawson CR, Demonstration of the mucus layer of the tear film by electron microscopy, Invest. Ophthalmol. Visual Sci., 26, 1985, 464– 473.

23. Roat MI, Ohji M, Hunt LE, Thoft RA, Conjunctival epithelial cell hypermitosis, goblet cell hyperplasia in atopic keratoconjunctivitis, Am. J. Ophthalmol, 116, 1993, 456– 463.

24. Kunert KS, Keane-Myers AM, Spurr-Michaud S, Tisdale AS, Gipson IK, Alteration in goblet cell numbers and mucin gene expression in a mouse model of allergic conjunctivitis, Invest. Ophthalmol. Visual Sci., 42, 2001, 2483– 2489.

25. Pisella PJ, E. Lala E, Parier V, Brignole F, Baudouin C, Retentissement conjonctival des conservateurs: eˊtude compara ve de collyres beˆta-bloquants conserveˊs et non conserves chez des patients glaucomateux, J. Fr. Ophtalmol, 26, 2003, 675–679.

26. Kinoshita S, Kiorpes TC, Friend J, Thoft RA, Goblet cell density in ocular surface disease, A better indicator than tear mucin, Arch. Ophthalmol, 101, 1983, 1284– 1287.

27. Dilly PN, On the nature and the role of the subsurface vesicles in the outer epithelial cells of the conjunctiva, Br. J. Ophthalmol., 69, 1985, 477– 481.

28. Greiner JV, Weidman TA, Korb DR, Allansmith MR, Histochemical analysis of secretory vesicles in non-goblet conjunctival epithelial cells, Acta Ophthalmol. Copenh. 63, 1985, 89–92.

29. Langer G, Jagla W, W. Behrens-Baumann, S. Walter, W. Hoffmann, Secretory peptides TFF1 and TFF3 synthesized in human conjunctival goblet cells, Invest. Ophthalmol. Visual Sci., 40, 1999, 2220– 2224.

30. Bayens V, Gurny R, Chemical and physical parameters of tears relevant for the design of ocular drug delivery formulations, Pharm. Acta Helv. 72, 1997, 191–202.

31. King-Smith PE, Fink BA, Fogt N, Nichols KK, Hill RM, Wilson GS, The thickness of the human precorneal tear film: evidence from reflection spectra, Invest. Ophthalmol. Visual Sci, 41, 2000, 3348–3359.

32. Mathers WD, Lane JA, Sutphin JE, Zimmerman MB, Model for ocular tear film function, Cornea, 15 ,1996, 110 – 119.

33. Van Haeringen NJ, Clinical biochemistry of tears, Surv. Ophthalmol., 5, 1981, 84– 96.

34. Nagyova B, Tiffany JM, Components responsible for the surface tension of human tears, Curr. Eye Res., 19,1999, 4 – 11.

35. Tiffany JM, Tears in health and disease, Eye, 17, 2003, 1–4.

36. Pandit JC, Nagyova B, Bron AJ, Tiffany JM, Physical properties of stimulated and unstimulated tears, Exp. Eye Re,. 68, 1999, 247–253.

37. Gipson IK, Yankauckas M, Spurr-Michaud SJ, Tisdale AS, Rinehart W, Characteristics of a glycoprotein in the ocular surface glycocalyx, Invest. Ophthalmol. Visual Sci., 33, 1992, 218– 227.

38. Krisnamoorthy R, Mitra AK, Mucoadhesive polymers inocular drug delivery, in: A.K. Mitra (Ed.), Ophthalmic Drug Delivery Systems, Marcel Dekker, New York, 1993, pp. 199–221.

39. Khanvilkar K., Donovan MD, Flanagan DR, Drug transfer through mucus, Adv. Drug Deliv. Rev. 48,2001, 173–193.

40. McMaster TJ, Berry M, Corfield AP, Miles MJ, Atomic force microscopy of the submolecular architecture of hydrated ocular mucins, Biophys. J. 77, 1999, 533–541.

41. Kuver R, Klinkspoor JH, Osborne WR, Lee SP, Mucous granule excytosis and CFTR expression in gallbladder epithelium, Glycobiology, 10, 2000, 149– 157.

42. Gilbard JP, Human tear film electrolyte concentration in health and dry-eye disease, Int. Ophthalmol. Clin., 34, 1994, 27– 36.

43. Paz HB, Tisdale AS, Danjo Y, Spurr-Michaud SJ, Argu¨ eso P, Gipson IK, The role of calcium in mucin packaging within goblet cells, Exp. Eye Res., 77,2003, 69–75.

44. Lee JW, Park JH, Robinson JR, Bioadhesive-based dosage forms: the next generation, J. Pharm. Sci. 89, 2000, 850–866.

45. Mikos AG, Peppas NA, Systems for controlled drug delivery of drugs: V. Bioadhesive systems, S.T.P. Pharma Sci. 2, 1986, 705–716.

46. Imam ME, Hornof M, Valenta C, Reznicek G, Bernkop- Schnuerch A, Evidence for the interpenetration of mucoadhesive polymers into the mucous gel layer, S.T.P. Pharma Sci. 13, 2003, 171– 176.

47. Mortazavi SA, Smart JD, Factors influencing gel-strengthening at the mucoadhesive mucus interface, J. Pharm. Pharmacol. 46, 1993, 86– 90.

48. Madsen F, Eberth K, Smart JD, A rheological examination of the mucoadhesive/mucus interaction: the effect of mucoadhesive type and concentration, J. Control. Release 50, 1998, 167–178.

49. Madsen F, Eberth K, Smart JD, A rheological assessment of the nature of interactions between mucoadhesive polymers and homogenised mucus gel, Biomaterials, 19,1998, 1083–1092.

50. Holly FJ, Formation and rupture of the tear film, Exp. Eye Res. 15, 1973, 515– 525.

51. Sharma A, Ruckenstein E, Mechanism of tear film rupture and formation of dry spots on cornea, J. Colloid Interface Sci. 106, 1985, 12– 27.

52. Wong H, Fatt I, Radke CJ, Deposition and thinning of the human tear film, J. Colloid Interface Sci. 184, 1996, 44–51.

53. Gorla MSR, Gorla RSR, Nonlinear theory of tear film rupture, J. Biomec. Eng., Trans. ASME 122, 2000, 498–503.

54. Zhang YL, Matar OK, Craster RV, Analysis of tear film rupture: effect of non-Newtonian rheology, J. Colloid Interface Sci. 262, 2003, 130– 148.

55. Sharma A, Ruckenstein E, The role of lipid abnormalities, aqueous and mucus deficiencies in the tear film breakup, and implications for tear substitutes and contact lens tolerance, J. Colloid Interface Sci. 111, 1986, 8 –34.

56. Norn MS, Opauszki A, Effects of ophthalmic vehicles on the stability of the precorneal tear film, Acta Ophthalmol. (Copenh.) 55, 1977, 23– 34.

57. Greaves JL, Olejnik O, Wilson CG, Polymers and the precorneal tear film, S.T.P. Pharma Sci. 2,1992, 13– 33.

58. Meseguer G, Gurny R, Buri P, Rozier A, Plazonnet B, Gamma scintigraphic study of precorneal drainage and assessment of miotic response in rabbits of various ophthalmic formulations containing pilocarpine, Int. J. Pharm. 95, 1993, 229– 234.

59. Thermes F, Rozier v, Plazonnet B, Grove J, Bioadhesion: the effect of polyacrylic acid on the ocular bioavailability of timolol, Int. J. Pharm. 81, 1992, 59– 65.

60. Bron AJ, Mangat H, Quinlan M, Foley-Nolan A, Eustace P, Fsadni M, Sunder Raj P, Polyacrylic acid gel in patients with dry eyes: a randomized comparison with polyvinyl alcohol, Eur. J. Ophthalmol. 81, 1998, 81– 89.

61. Se´choy O, Tissie´ G, Se´bastian C, Maurin F, Driot JY, Trinquand C, A new long acting ophthalmic formulation of Carteolol containing alginic acid, Int. J. Pharm. 207, 2000, 109– 116.

62. Lin CP, Boehnke M, Influences of methylcellulose on corneal epithelial wound healing, J. Ocul. Pharmacol. Ther. 15, 1999, 59– 63.

63. Toda I, Shinozaki N, Tsubota K, Hydroxypropyl methylcellulose for the treatment of severe dry eye associated with Sjo¨ gren's syndrome, Cornea 15, 1996, 120– 128.

64. Benedetto DA, Shah DO, Kaufman HE, The instilled fluid dynamics and surface chemistry of polymers in the precorneal tear film, Invest. Ophthalmol. 14, 1975, 887–902.

65. Chen HB, Yamabayashi S, Ou B, Tanaka Y, Ohno S, Tsukahara S, Structure and composition of rat precorneal tear film. A study by an in vitro cryofixation, Invest. Ophthalmol. Visual Sci. 38, 1997, 381– 387.

66. Leung SS, Robinson JR, The contribution of anionic polymer structural features to mucoadhesion, J. Control. Release 5, 1988, 223–231.

67. Degim Z, Kellaway IW, An investigation of the interfacial interaction between poly(acrylic acid) and glycoprotein, Int. J. Pharm. 175, 1998, 9 –16.

68. Hartmann V, Keipert S, Physico-chemical, in vitro and in vivo characterisation of polymers for ocular use, Pharmazie 55, 2000, 440–443.

69. Brewitt H, Tra¨nenersatzmittel. Experimentelle und klinische Beobachtungen, Klin. Mon.Bl. Augenheilkd. 193, 1988, 275– 282.

70. Unlu N , Ludwig A, Van Ooteghem M, Hincal AA, A comparative rheological study on carbopol viscous solutions and, the evaluation of their suitability as the ophthalmic vehicles and artificial tears, Pharm. Acta Helv. 67, 1992, 5 –10.

71. Oescher M, Keipert S, Polyacrylic acid/polyvinylpyrrolidone biopolymeric systems: I. Rheological and mucoadhesive properties of formulations potentially useful for the treatment of dry-eye-syndrome, Eur. J. Pharm. Biopharm. 47, 1999, 113– 118.

72. Marner K, Moller PM, Dillon M, Rask-Pedersen E, Viscous carbomer eye drops in patients with dry eye, Acta Ophthalmol. Scand. 74, 1996, 249– 252.

73. Laurent TC, Biochemistry of hyaluronan, Acta Oto-Laryngol. (Stockh.), Suppl. 442, 1987, 7 –24.

74. Wysenbeek YS, Loya N, Ben Sira I, Ophir I, Ben Saul Y, The effect of sodium hyaluronate on the corneal epithelium. An ultrastructural study, Invest. Ophthalmol. Visual Sci. 29, 1988, 194–199.

75. Nelson JD, Farris L, Sodium hyaluronate and polyvinyl alcohol artificial tear preparation. A comparison in patients with keratoconjunctivitis sicca, Arch. Ophthalmol. 106, 1988, 484– 487.

76. Snibson GR, Greaves JL, Sope NDW, Tiffany JM, Wilson CG, Bron AJ, Ocular surface residence time of artificial tear solutions, Cornea 11, 1992, 288– 293.

77. Shimmura S, Ono M, Shinozaki K, Toda I, Takamura E, Mashima Y, Tsubota K, Sodiumhyaluronate eyedrops in the treatment of dry eyes, Br. J. Ophthalmol. 79 (1995) 1007–1011.

78. Solomon A, Merin S, The effect of a new tear substitute containing glycerol and hyaluronate on keratoconjunctivitis sicca, J. Ocul. Pharmacol. Ther. 14, 1998, 497–504.

79. Condon PI, McEwen CG, Wright M, Mackintosh G, Prescott RJ, McDonald C, Double blind, randomised, placebo controlled, crossover, multicenter study to determine the efficacy of a 0.1%(w/v) sodium hyaluronate solution (Fermavisc) in the treatment of dry eye syndrome, Br. J. Ophthalmol. 83, 1999, 1121–1124.

80. Aragona P, Papa V, Micali A, Santocono M, Milazzo G, Long term treatment of sodium-hyaluranate-containing artificial tears reduces ocular surface damage in patients with dry eye, Br. J. Ophthalmol. 86, 2002, 181– 184.

81. Lehr CM, Bouwstra JA, Schacht EH, Junginger HE, In vitro evaluation of mucoadhesive properties of chitosan and other natural polymers, Int. J. Pharm. 78, 1992, 43–48.

82. Hassan EE, Gallo JM, A simple rheological method for the in vitro assessment of mucin–polymer bioadhesive bond strength, Pharm. Res. 7, 1990, 491–495.

83. Felt O, Buri P, Gurny R, Chitosan: a unique polysaccharide for drug delivery, Drug Dev. Ind. Pharm. 24, 1998, 979–993.

84. Felt O, Furrer P,. Mayer JM, Plazonnet B, Buri P, Gurny R, Topical use of chitosan in ophthalmology: tolerance, assessment and evaluation of precorneal retention, Int. J. Pharm. 18, 1999, 185– 193.

85. Rossi S, Ferrari F, Bonferoni MC, Caramella C, Characterization of chitosan hydrochloride–mucin rheological interaction: influence of polymer concentration and polymer: mucin weight ratio, Eur. J. Pharm. Sci. 12, 2001, 479–485.

86. Alonso MJ, Sanchez A, The potential of chitosan in ocular drug delivery, J. Pharm. Pharmacol. 55, 2003, 1451– 1463.

87. Felt O, Carrel A, Baehni P, Buri P, Gurny R, Chitosan as tear substitute: a wetting agent endowed with antimicrobial efficacy, J. Ocul. Pharmacol. Ther. 16, 2000, 261– 270.

88. Artursson P, Lindmark T, Davis SS, Illum L, Effect of chitosan on the permeability of monolayers of intestinal epithelial cells (Caco-2), Pharm. Res. 11, 1994, 1358– 1361.

89. Dodane V, Khan MA, Mervin JR, Effect of chitosan on epithelial permeability and structure, Int. J. Pharm. 182, 1999, 21– 32.

90. Schipper NGM, Varum KM, Stenberg P, Ocklind G, Lennernas H, Artursson P, Chitosans as absorption enhancers of poorly absorbable drugs: 3. Influence of mucus on absorption enhancement, Eur. J. Pharm. Sci. 8,1999, 335– 343.

91. Thanou M, Nihot MT, Janssen M, M. Verhoef M, Junginger HE, Mono-N-carboxymethyl chitosan (MCC) a polyampholytic chitosan

derivative, enhances the intestinal absorption of low molecular weight heparin across intestinal epithelia in vitro and in vivo, J. Pharm. Sci. 90. 2001. 38–46.

92. Saettonen MF, Mont D, Torracca MT, Chetoni P, Mucoadhesive ophthalmic vehicles: evaluation of polymeric lowviscosity formulations, J. Ocul. Pharmacol. 10, 1994, 83–92.

93. Burgalassi S, Panichi P, Chetoni P, Saettone MF, Boldrini E, Development of a simple dry eye model in the albino rabbit and evaluation of some tear substitutes, Ophthalmic Res. 31, 1999, 229– 235.

94. Albasini M, Ludwig A, Evaluation of polysaccharides intended for ophthalmic use in ocular dosage forms, Farmaco 50, 1995, 633– 642.

95. Verschueren E, Van Santvliet L, Ludwig A, Evaluation of various carrageenans as ophthalmic viscolysers, S.T.P. Pharma Sci. 6, 1996, 203–210.

96. Saettone MF, Monti D, Giannaccini B, Salminen L, Huupponen R, Macromolecular ionic complexes of cyclopentolate for topical ocular administration. Preparation and preliminary evaluation in albino rabbits, S.T.P. Pharma Sci. 2, 1992, 68–75.

97. D'Amico M, Di Filippo C, Lampa E, Boldrin E, Rossi F, Ruggiero A, Filippelli A, Effects of timolol and timolol with tamarind seed polysaccharide on intraocular pressure in rabbits, Pharm. Pharmacol. Commun. 5, 1999, 361– 364.

98. Ceulemans J, Vinckier I, Ludwig A, The use of xanthan gum in an ophthalmic liquid dosage form: rheological characterization of the interaction with mucin, J. Pharm. Sci. 91, 2002, 1117– 1127.

99. Meseguer G, Buri P, Plazonnet B, Rozier A, Gurny R, Gamma scintigraphic comparison of eyedrops containing pilocarpine in healthy volunteers, J. Ocul. Pharmacol. Ther. 12, 1996, 481– 488.

100. Bernkop-Schnuerch A, Steininger S, Synthesis and characterization of mucoadhesive thiolated polymers, Int. J. Pharm. 194, 2000, 239– 247.

101. Bernkop-Schnuerch A, Scholler S, Biebel RG, Development of controlled release systems based on thiolated polymers, J. Control. Release 66, 2000, 39–48.

102. Clausen AE, Bernkop-Schnuerch A, In vitro evaluation of the permeation-enhancing effect of thiolated polycarbophil, J. Pharm. Sci. 89, 2000, 1253– 1261.

103. Bernkop-Schnuerch A, Kast CE, Guggi D, Permeation enhancing polymers in oral delivery of hydrophilic macromolecules: thiomer/GSH systems, J. Control. Release 93, 2003, 95–103

104. Clausen AE, Kast CE, Bernkop-Schnuerch A, The role of glutathione in the permeation enhancing effect of thiolated polymers, Pharm. Res. 19, 2002, 602– 608.

105. Bernkop-Schnuerch A, Mucoadhesive polymers, in: S. Dimitriu (Ed.), Polymeric Biomaterials, Marcel Dekker, Inc., New York, 2000, pp. 147–165.

106. Leitner VM, Marschu¨ tz MK, Bernkop-Schnuerch A, Mucoadhesive and cohesive properties of poly(acrylic acid)–cysteine conjugates with regard to their molecular mass, Eur. J. Pharm. 18, 2003, 89– 96.

107. Augustin AJ, Spitznas M, Kaviani N, Meller D, Koch F.H, Grus F, Gobbels M, Oxidative reactions in the tear film of patients suffering from dry eyes, Graefe Arch. Clin. Exp. Ophthalmol. 233, 1995, 694– 698.

108. Desai SD, Blanchard J, Pluronic F127-based ocular delivery systems containing biodegradable polyisobutylcyanoacrylate nanocapsules of pilocarpine, J. Drug. Deliv. Target. Ther. Agents 7, 2000, 201– 207.

109. Fresta M, Fontana G, Bucolo C, Cavallaro G, Giammona G, Puglisi G, Ocular tolerability and in vivo bioavailability of poly(ethylene glycol) (PEG)-coated polyethyl-2-cyanoacrylate nanospheres-encapsulated acyclovir, J. Pharm. Sci. 90, 2001, 288– 297.