Francesco Puoci *Editor*

Advanced Polymers in Medicine

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Preface

Life is a perfect equilibrium between mind and body. It is a whole of different variables that, during our life we have to set up. In this challenge the safe maintenance of the human body represents one of our most important goal. In this sense, science and technology play a key role in the extended life expectancy. In the last century and especially in the last years, the medical area, in order to afford the new challenge in health care, was subject to necessary and deep changes (improvements), thanks also to a cross-fertilization of several disciplines.

Surgery, for example, has developed with a wide range of innovative techniques and new devices (implants and surgical instruments) resulting in a reduction of morbidity and mortality.

The use of drug delivery systems to improve the efficacy of bioactive molecules remains an important strategy for achieving progress against the disease and progress in this field has been remarkable. Over the past 20 years, the number of novel therapeutic approaches has expanded from traditional small chemical medicinals to a wide variety of biomolecules, including peptide/protein- and nucleic acid-based therapeutics. All of these therapies require the administration of stable dosage forms in adequate concentrations and exposure periods with the aim to realize their potential.

At the same time new medical categories are widely expanded: tissue engineering has made great strides in the replacement of worn out organs and tissues due to disease, injury, etc. in order to have real efficiency and efficacy, medical therapy needs efficient and effective biomaterials both for intra and extracorporeal treatments.

Biomaterials and in particular polymeric ones are the focus of this scientific revolution and represent one of the major researches around the world.

One of the reasons for the great popularity in the use of polymers in medicine is that their properties can be tailored to meet specific needs by varying the "atomic composition" of the repeat structure, molecular weight, or performing chemical modifications of natural polymers.

The rationale of this contributed book stems from the premise to have an important instrument that can be a knowledge bridge between teaching experience and scientific research.

This idea represents a true answer to the natural question: What is the novelty in *Advanced Polymers in Medicine*? The first part of the book reviews the relevant background information on polymer chemistry and the physicochemical characterization and represents the scientific support for the following chapters. The second part is devoted to a complete overview of "Medically" oriented polymers and every chapter is dedicated to a medical specialty. In my opinion, this type of approach will provide a better overview of polymers and medical applications and allows an effective use both for teaching that scientific reference book. Therefore, this book is intended for students and researchers who work in the area of biomaterials. I am conscious that a successful book is a product of several integrated expertises; in this contributed volume, many of these were given by contributing authors, all of which are listed in the bibliography. Thank you!

Francesco Puoci

Contents

Chapter 6
Polymers in Ophthalmology

Javier Adrián Calles, José Bermúdez, Enrique Vallés, Daniel Allemandi and Santiago Palma

Abstract Ophthalmological sciences are disciplines focused in the health of the eyes and related structures, as well as vision, visual systems, and vision information processing in humans; dealing with the anatomy, physiology and diseases of the eye. Along time a wide variety of materials, including metals, ceramics and polymers, have been developed and used in different ophthalmic applications. Although, modern ophthalmic devices and drug platforms are made with polymeric materials. Applications of polymers in ophthalmology include vitreous replacement fluids, contact lenses, intraocular lenses, artificial orbital walls, artificial corneas, artificial lacrimal ducts, glaucoma drainage devices, viscoelastic replacements, drug delivery systems, sclera buckles, retinal tacks and adhesives, and ocular endotamponades. Both synthetic and natural polymeric biomaterials are used in ophthalmological applications, although in the lasts years most efforts were focused in natural and biocompatible materials, such as gelatin, hyaluronan, chitosan, gums, etc.; developing, tablets, films, suspensions, nanosystems, inserts, etc. This chapter attempts to offers an insight into the importance of polymers in the design and development of pharmaceuticals platforms used in ocular therapeutics.

Keywords Ophthalmology · Polymers · Inserts · Hydrogels · Microparticles · Nanoparticles · Drug delivery

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Abbreviations

MC	Methylcellulose
HEC	Hydroxyethylcellulose
HPC	Hydroxypropycellulose
HPMC	Hydroxypropylmethylcellulose
CMC Na	Sodium carboxymethylcellulose
PVA	Poly(vinyl alcohol)
SH	Sodium hyaluronate
AUC	Area under the curve
HEMA	Hydroxy ethyl metacrylate
PVP	Polyvinyl pyrrolidone
EGDM	Ethylene glycol dimethacrylic acid
DDS	Drug delivery system
PLA	Polylactic acid
PGA	Polyglycolic acid
PLGA	Copolymer polylactic-co-glycolic acid
NEs	Nanoemulsions
PEO	Polyethylene oxide
PPO	Polypropylene oxide

Introduction

Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientist. Over the past decade, the understanding of ocular physiopathology and pharmacokinetic and pharmacodynamic parameters of ophthalmic drugs has increased markedly and resulted in the development of new drugs and drug delivery systems for the human eye. The move from traditional ophthalmic dosage forms toward more sophisticated drug delivery systems has been slow. This is due to the fact that certain prerequisites are necessary for ophthalmic formulations which impose certain limitations to the formulator. These include sterility, absence of local toxicity, tolerance, ease of dispensing, antimicrobial preservation for multidose formulations, and iso-osmolarity for aqueous-based formulations. On the other hand, the development of drug treatments for diseases of the retina and posterior tissues of the eye have been slow. Among the principal causes for this, the technical difficulty in delivering drugs to the back of the eye seems to be the most important. Most of the drugs used in ophthalmology had initially been developed for other applications and subsequently found to be useful in ophthalmology. All these factors have limited the access to the market of innovative ophthalmic modified-release formulations. One potential reason for this is economics. Even worse, many potentially effective drugs languish on the laboratory shelves of pharmaceutical companies for lack of safe and efficacious formulations. This problem is critical in the eye due to the great differences and variety of

tissues that need to be targeted according to the involved therapy and the significant barriers for penetration of foreign or exogenous compounds through ocular mucosa. After topical instillation of an eye drop, the drug is subject to a number of very efficient elimination mechanisms such as drainage, binding to proteins, normal tear turnover, induced tear production, and nonproductive absorption via the conjunctiva. Typically, the effective period of time for drug absorption is about 90s due to the rapid removal of drug from the precorneal area. Besides, the cornea is poorly permeable to both hydrophilic and hydrophobic compounds. As a result, only approximately 10 % or less of the topically applied dose can be absorbed into the anterior segment of the eye. Basically, the two major barriers found in ocular drug delivery are (a) short residence time in the precorneal area and (b) poor permeability of the cornea. For example, various efforts have been made to prolong the drug solution residence time via vehicle modification [1, 2], bioadhesives [3], inserts [4]. A successful design of a drug delivery system, therefore, requires an integrated knowledge of the drug molecule properties and effective formulation strategies in order to overcome the constraints offered by the ocular route of administration.

There is a clear need for ophthalmic products able to offer more therapeutic benefits than those derived from simple solutions/suspensions. Another important aspect of drug delivery is "targeting." To maximize efficacy and safety, drugs need to be directed as best as possible to a specific tissue or cell type once ocular penetration has been achieved. In certain circumstances, the drug delivery systems can be designed in order to achieve this goal. The development of the nanotechnology oriented to the design of drug delivery systems offers new possibilities for the improvement of the treatment of ocular diseases. Particularly, the potential use of nanoparticles became one the most attractive alternative for this objective.

The final goal of drug delivery system is to achieve and maintain therapeutic concentrations of the drug at the site of action along sufficient time to produce a beneficial effect. A secondary aim is to avoid exposing eye's tissues to high enough drug concentrations able to cause unacceptable side effects. In the design of a drug delivery system intended for ophthalmic administration an equilibrium must be kept among the limitations imposed by the physicochemical properties of the drugs, the limitations imposed by the anatomy and disease state of the eye, and the dosing requirements of the drug for that particular disease.

A significant challenge to the formulator is to circumvent the protective barriers of the eye without causing permanent tissue damage. Development of more sensitive diagnostic techniques as well as novel therapeutic agents leads to the design of ocular delivery systems with higher therapeutic efficacy. Although being useful formulations several decades ago, conventional ophthalmic dosages forms such as solution, suspension, and ointment no longer constitute an optimal therapy for these indications. Therefore, nowadays a lot of attention is paid to the development of the pharmaceutical system in addition to efficiency of the drug itself.

Although many drugs can be safely delivered by mean of eye drops, the efficiency of the treatment depends on patient compliance. Non-compliance is a major problem, especially in poorly educated patients and patients who are required to

apply drops frequently. Lack of compliance frequently results in suboptimal therapeutics, which may lead to blindness depending on the pathology.

The dosing of patients suffering chronic conditions or motor problems is very complicated since an adequate schedule of administration of eye drops is very hard to complete.

However, the next decade promises great strides in therapy for many poorly treated or untreatable ocular diseases with any drug treatment. For new medications to be used effectively, and for those now available to provide maximal benefit, improvements in ocular drug delivery are essential.

This new type of ophthalmic formulations has to possess well defined properties in order to meet biopharmaceutical requirements such as be capable of delivering the effective ocular drug concentrations along an extended period of time (without inducing systemic side effects), user friendly, and exempt of side effects such as blurring, irritation, or foreign-body sensation.

Many attempts have been made to develop practical approaches to the modified delivery of drugs. The reason for the high demand for developing novel options for delivery of drugs to the eye is based on the need to progress from drug delivery concerns discovered in earlier research on topically administered drugs.

The unique anatomy and physiology of the eye offer many challenges to develope effective ophthalmic drug delivery systems, but the knowledge in this field is rapidly expanding. Systems range from simple solutions to novel delivery systems such as biodegradable polymeric systems, corneal collagen shields, iontophoresis, and viral and non viral gene delivery systems, to name a few. An increase in our understanding of ocular drug absorption and disposition mechanisms has led to the development of many of these new systems.

The aim of this Chapter is to describe the various polymeric systems used to achieve prolonged contact time of drugs with the cornea and increase their bioavailability. Advantages and shortcomings of the different systems are discussed, as well as their characteristics and their in vivo applications.

Anatomophysiological Aspects in Ocular Drug Therapy

The eye is the organ of vision; it receives and encodes external light stimuli that are then sent through the optic nerve to the occipital lobe of the brain where images are processed. To achieve this, the eye requires some independence and protection from the external environment, in order to maintain their structures unchanged. However, this feature makes it an organ difficult to reach for certain types of drugs.

The eyeball (Fig. 6.1) is composed of three compartments, front to back: (i) anterior chamber, (ii) posterior chamber and (iii) vitreous chamber. It also has three concentric layers from outside to inside they are: (i) outer fibrous tunic, (ii) vascular tunic and (iii) retina.

The fibrous layer is composed of a rear opaque part, the sclera, and anterior and transparent, the cornea. The cornea is the transparent frontal window of the

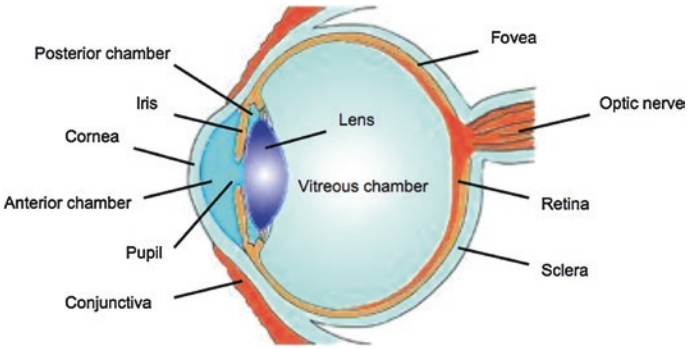

Fig. 6.1 Eyeball anatomy

eye, is formed by several layers: an outer hydrophobic epithelium of about 50 μm thick delimited by the Bowman's layer, followed by the hydrophilic stromal layer and finally, the thin Descemet's membrane and the endothelium. The intact corneal epithelium permeability is very low, due to its polylaminated non-keratinized structure with zonulaocludens joints (tight junctions) between the cells of the outer layer. This structure has a protective function and exclude any movement of solutes (resulting consequently in exclusion of hydrophilic drugs with low lipophilicity or large molecular sizes) except those that occur through the apical and basal plasma membranes of surface epithelial cells [5]. The vascular tunic is formed, from back to front, by the choroid, ciliar body and iris, which form a continuous structure. The ciliary body, has several important functions, including the active secretion of aqueous humor. Much of the volume secreted goes through the trabecular meshwork to Schlemm's canal, leaving the eye through the episcleral veins [6]. Here there is a blood-aqueous barrier formed by tight junctions between epithelial cells of the non-pigmented ciliary processes along with not fenestrated vessels of the iris, limiting the systemic all access of drugs. Finally, the retinal pigment epithelium also forms a blood-retinal barrier to accessing components that may come from systemic circulation.

Whereas the dosage form most widely used in topical ocular treatment are the eye drops (conjunctivitis, dry eye syndrome, glaucoma, iritis (anterior uveitis), keratitis); there are other parameters of ocular surface that affect pharmacotherapy, including: lower conjunctival sac capacity, blinking, tear secretion and tear drainage.

When the lower eyelid is carried forward gently with your fingers the lower conjunctival sac forms a funnel-shaped reservoir that can accommodate the instilled formulation, but the conjunctival surface cannot accommodate a larger volume than 25 μL if added quickly. When the eyelid returns to its normal position conjunctival sac capacity is reduced to less than 10 μL.

Blinking is one me the most important defense mechanisms of the eye. The blink reflex is usually fast enough to anticipate a strange body approaching at high speed to the eye. Flicker is also essential in the reformation of the tear film and

activates the pump mechanism by which the tears drain. Blink rate in humans is 15–20 per minute.

Under normal baseline, the total volume required to cover the eye surface is approximately 6–8 μL, the tear secretion rate is about 1.2 μL/min and the rate of lacrimal turnover per minute is 16 % of total tear volume. However in stimulus conditions, by irritation of the conjunctiva or cornea reflects, tearing occurs. The volume of the tear film grows to about 16 ml, with a range between 5 and 6 μL [7]. Thus reflex tearing stimulated for any reason, including many parameters of eye drop formulation to enhance solubility and stability of the dosage form, cause an accelerated drop instilled washing.

The tear leaves the surface of the eye and eyelids before going to the lacrimal sac before draining to the nasolacrimal duct. In addition much of the tear film is removed by evaporation or absorption at lacrimal sac level. When blinking is prevented, tear accumulation occur, leading to spill to the skin of the eyelids and cheeks [8]. Some studies have shown that the drainage of the instilled solution is the main cause of the loss of drug in the precorneal area [9].

In response to this problem a growing interest in research related to pharmaceutical technology has been generated. A lot of work has been done on solving inherent problems of drug release, administered dose and site of action in order to design new drug delivery platforms. The design of this new group of pharmaceutical forms has focused primarily on the use of polymers as base material.

Systems for Ocular Controlled Drug Delivery Currently Investigated

Hydrogels

Hydrogels are water-swollen, cross-linked polymeric structures produced by the simple polymerization reaction of one or more monomers or by association of bonds such as hydrogen bonds and strong van der Waals interactions between chains. These systems exist in a state between rigid solids and liquid and this feature sets them apart from other forms of matter. Presently, a huge number of synthetic hydrogels is known. Hydrogels and viscous solutions, based upon the addition of hydrocolloids to simpler aqueous solutions, are the most common formulations. There is no clear cut frontier between very viscous solutions and gels in terms of biopharmaceutical results. According to Plazonnet et al. [10], aqueous gels are at the upper limit of viscous preparations, and they are formed when high molecular weight polymers or high polymer concentrations are incorporated in the formulations.

Currently, two groups of hydrogels are distinguished, namely preformed and in situ forming gels. The preformed gels can be defined mainly as hydrogels which do not undergo further modification after administration, whereas in situ gelling systems can be described as viscous liquids or suspensions that, upon exposure

to physiological eye conditions (ionic strength, temperature or pH), will shift to a gel phase. Preformed gels are administered in the same way as an ointment, which is less convenient for the patient than the instillation of a viscous drop. The most common polymers used in viscous solutions are cellulose derivatives, carbomers, polysaccharides, and, recently, hyaluronic acid. The advantage offered by this last product depends upon the active ingredient and the formulation environment [11]. Polyvinyl alcohol and polyvinyl pyrolidone are also used in ophthalmic drugs. Gels permit longer residence time in the precorneal area than viscous solutions. This has encouraged researchers to work on formulations that would be (viscous) solutions in the drug vials but would gel in the conjunctival cul-de-sac. The polymers chosen to prepare ophthalmic hydrogels should meet some specific rheological characteristics. It is generally well accepted that the instillation of a formulation should influence tear behavior as little as possible. Because tears have a pseudoplastic behavior, pseudoplastic vehicles would be more suitable than Newtonian formulations, which have a constant viscosity independent of the shear rate. Pseudoplastic solutions exhibit decreased viscosity with increasing shear rate, thereby offering lowered viscosity during blinking and stability of the tear film during fixation.

A large amount of today's research is focused on the so-called 'smart' or 'intelligent' hydrogels. A representative of this interesting class of hydrogels is a polymer system with a defined phase transition capable of abruptly swelling to many times its original size or collapsing into a compact mass when stimulated externally [12]. Smart hydrogels react in response to an external stimulus in a manner similar to many living organisms rather than to non-living organic matter [13].

The improvement in residence time of ophthalmic semisolid hydrogels is primarily based on an increase in ocular residence time as a result of a reduction in drainage rate through enhanced viscosity and mucoadhesive properties.

Preformed Hydrogels

Preformed hydrogels for topical administration in the eye can be based on natural, synthetic, or semisynthetic polymers.

Cellulose Derivatives. The pioneering group of polymers used as components of ophthalmic preformed hydrogels is the family of cellulosic derivatives. Because pure cellulose is not water soluble due to its relatively high crystallinity, cellulosic derivatives have been used for a long time as viscosifiers in collyria. Methylcellulose (MC) (Fig. 6.2) was first introduced in ophthalmic formulations in the 1940s as a mean of decreasing their fluidity [14]. Since then, cellulosic polymers have been extensively studied in human, [15–17] as well as in veterinary medicine [16, 18–20], for ocular administration. The cellulosic derivatives most commonly used in ophthalmology are: (1) Methylcellulose, (2) Hydroxyethylcellulose (HEC), (3) Hydroxypropycellulose (HPC), (4) Hydroxypropylmethylcellulose (HPMC) and (5) Sodium carboxymethylcellulose (CMC Na).

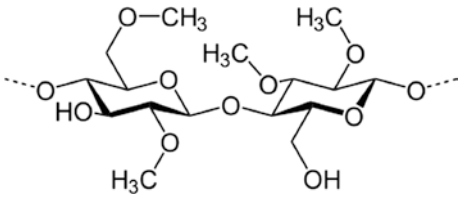

Fig. 6.2 Methylcellulose monomer

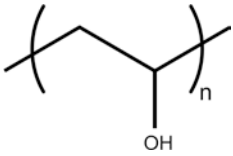

Fig. 6.3 Poly(vinyl alcohol) monomer

The boundary between viscous solutions and gels for cellulosic derivatives is particularly difficult to define, because data regarding the hydrocolloid concentration or the viscosity of the final formulation are not always available. These cellulosic polymers appear in several currently available commercial preparations such as Adsorbotear® (Alcon, Fort Worth, Texas), Lacril® (AUergan, Irvine, California) and Celluvisc® (AUergan, Irvine, California).

Subsequent advances in the polymers field with respect to ocular drug delivery have led to the use of poly(vinyl alcohol) (PVA); sodium hyaluronate, and carbomer, which often give better results [21–24] than celluloses. On the other hand cellulose-based hydrogels are still in focus for ophthalmical applications as ocular bandage [25].

Poly(vinyl alcohol). Scientific interest has been directed toward using other viscosifying agents. Poly(vinyl alcohol) (PVA) is a synthetic polymer commercially obtained by polymerization of vinylacetate to poly(vinyl acetate) (Fig. 6.3) and subsequent hydrolysis to PVA [26]. Polyvinyl alcohol was introduced in the early 1960's as a mean to increase solution viscosity and, hence, prolong precorneal residence time. The presence of PVA in ophthalmic preparations has been shown to significantly delay precorneal drainage of topically applied formulations and to increase drug bioavailability as well as pharmacological effects such as miotic response to pilocarpine exposure when compared with conventional saline [27]. Some commercial products, particularly for the treatment of dry eye, are based on PVA, including HypoTearse® (IOLAB Corp., Claremont, California) and Liquifilm® (Allergan, Irvine, California).

Sodium Hyaluronate. The actual trend in ocular delivery is to use sodium salt of hyaluronic acid (SH). The SH is a high molecular weight biological polymer composed of repeating disaccharide units of glucuronic acid and n-acetylglucosamine (Fig. 6.4), a specific ultrapure fraction being patented as Healon (Kabi Pharmacia, Sweden) by Balazs [28] in 1979. The HS is a natural polysaccharide found in skin, connective tissues, umbilical cord, vitreous body and aqueous humor. The main advantages of SH are its excellent biocompatibility, mucoadhesiveness as well as its pseudoplastic and viscoelastic behavior. Its use

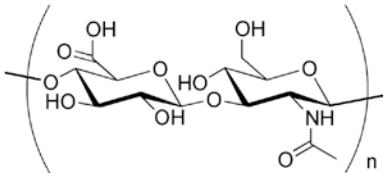

Fig. 6.4 Hyaluronic acid monomer

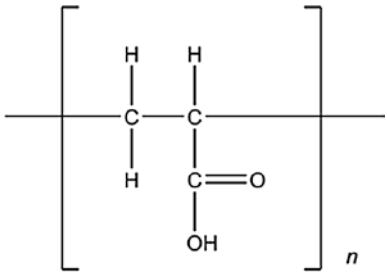

Fig. 6.5 Poly(acrylic acid) monomer

as a vehicle in ocular drug delivery has been extensively reviewed by Bernatchez et al. [29]. This polysaccharide is frequently proposed as a vehicle of choice in tear substitutes since it has been reported to possess a desirable protective effect against damage caused by benzalkonium chloride, a compound commonly added as a preservative in multiple dosage forms [30]. An extended residence time is one of the factors used to select artificial tears for the therapy of KCS (Keratoconjunctivitissicca), being effective in reducing common symptoms such as blurring vision, pain and photophobia. A further advantage of SH in this application is its pseudoplastic behavior. The ability of SH to prolong drug release by increasing precorneal drug residence time has been studied (mostly in animals) for several ophthalmic compounds such as pilocarpine [31–33] or, more recently, gentamicin [34]. Some commercial products containing SH are currently available being mostly indicated (for example Healon® and Viscoat®) for use as surgical aids in anterior segment procedures such as cataract extraction or intraocular lens implantation rather than for topical administration.

New efforts were directed to use this material in novel ophthalmic drug delivery platforms; recent reports in scientific literature propose the SH as solid bioadhesivedrug delivery system. Crosslinked SH films loaded with timolol maleate were successfully used to reduce intra ocular pressure in normotensive rabbits, prolonging the hypotensive effect for longer than commercial timolol maleate eye drops [35].

Carbomer. Cross-linked poly (acrylic acid) (Fig. 6.5) of high molecular weight, commercially available as Carbopol® (B.F. Goodrich Chemical Company, Cleveland, Ohio), is widely used in ophthalmology to enhance precorneal retention to the eye. The superiority of Carbopol over simple saline and suspensions in enhancing precorneal residence time [36] and drug bioavailability [37, 38] has been demonstrated by several authors. Preparation of Carbopol hydrogels is simply based on the dispersion of the polymer in water at room temperature, followed by

a neutralization process with agents such as sodium hydroxide, triethanolamine, or directly with active basic compounds. The maximal viscosity is obtained at neutral pH. Carbopol offers the advantage of exhibiting excellent mucoadhesive properties when compared with others polymers (e.g., cellulose derivatives, PVA and SH). The efficacy of Carbopol in enhancing precorneal residence time has been extensively studied by incorporating tracers such as sodium fluorescein [39] or active compounds such as pilocarpine or prednisolone [24, 38, 40]. A large number of commercial ophthalmic preparations contain Carbopol, including tear substitutes such as Lacrigel® (Europhta, Monaco), Lacrinorm® (Chauvin, Montpellier, France) or formulations containing active compounds such as Iduviran® (Chauvin, Montpellier, France) and Pilopine® (Alcon, Fort Worth, Texas).

Other polymers. Other natural or synthetic polymers have also been evaluated as potential vehicles to prolong the residence time of drugs at the surface of the eye but are currently being further investigated, such as xanthan gum or chitosan are currently under investigation for topical administration. An important difference between the two polymers is the anionic character of xanthan gum, whereas chitosan exhibits positive charges. Xanthan gum has been proposed as a material for artificial tears preparations [41] as well as vehicle for drug delivery [42, 43]. Evaluating transcorneal delivery of pilocarpine from several ophthalmic formulations, Saettone et al. [44] demonstrated that the presence of 1.5 % of xanthan gum induced a significant improvement of the pharmacokinetic parameters of the drug such as area under the curve (AUC), half-life time of elimination and the mean residence time in aqueous humor. Chitosan is emerging as a polymer of interest for ophthalmic use [45–47]. Formulations based on the concept of mucoadhesion (Fig. 6.6) have been investigated to overcome the rapid elimination of instilled ophthalmic solutions. They appear less viscous than those based on traditional viscolizers. The possible advantage of chitosan over xanthan gum lies in the presence of positive charges at physiological pH on the sugar backbone of chitosan, which are supposed to interact with the negative charges of the mucus, thereby conferring a bioadhesive property to this polysaccharide. Therefore, chitosan has attracted attention for topical ophthalmic applications, for example, promising results have been obtained demonstrating

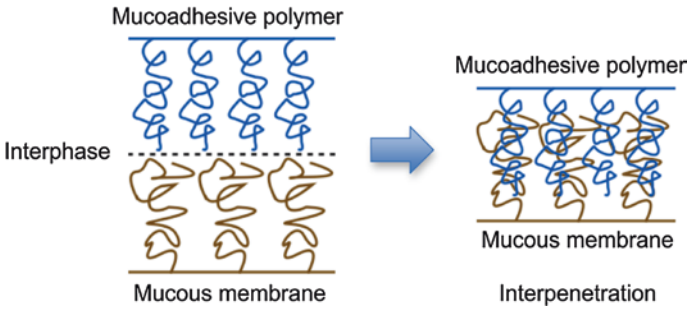

Fig. 6.6 Polymer-mucous membrane chains interpenetration in mucoadhesion phenomena

that chitosan formulations remained significantly longer on the corneal surface when compared with a conventional commercial solution [48].

In Situ Forming Gels

The use of preformed hydrogels still has drawbacks that can limit their interest for ophthalmic drug delivery or as tear substitutes. They do not allow accurate and reproducible administration of quantities of drugs and, after administration, they often produce blurred vision, crusting of eyelids, and lachrymation. A new approach is to try to combine advantages of both, solutions and gels, such as accuracy and facility of administration of the former and prolonged residence time of the latter. Thus, in situ hydrogels can be instilled as eye drops and undergo an immediate gelation when in contact with the eye.

"Smart" hydrogels or stimuli-sensitive hydrogels or in situ forming (Fig. 6.7), are very different from inert hydrogels in that they can "sense" changes in environmental properties such as pH and temperature and respond by increasing or decreasing their degree of swelling. These sensing capabilities are attractive in many biomedical applications. The volume-changing behavior of "smart" hydrogels is particularly useful in drug-delivery applications as drug release can be desirably triggered upon environmental changes [49–51]. Temperature responsiveness is particularly useful for in situ formation of drug-delivery devices since it allows handling of the formulation in the sol-phase at room temperature and solidification of the carrier upon injection [52]. Stimuli-responsive hydrogels, especially those sensitive to temperature and pH, are attractive because these factors are variables that change in typical physiological, biological and chemical systems. Product(s) using the gellan gum technology [53], and with polymer associations like those published by the University of Nebraska researchers [54, 55], and Smart Gel® technology [56] are examples of technologies that use this approach. This field of intricately entangled polymers seems promising since new "patentable" entities might be obtained through in-depth studies of associations of well-established products.

In situ forming gels influenced by ionic strength. Ionic-strength-responsive polymers undergo their phase transitions, resulting from the different concentration of salts (e.g., ionic strength). Gellan gum is an anionic polysaccharide

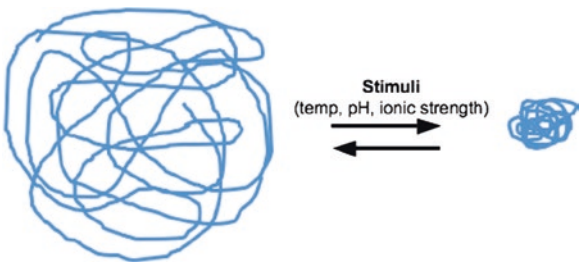

Fig. 6.7 Stimuli-sensitive hydrogels

produced by the bacterium Pseudomonas elodea [57] which, when dispersed in aqueous solutions, undergoes a liquid-gel transition under the influence of an increase in ionic strength [58]. The acetylated form is commercially available as Gelrite® (Kelco Division of Merck and Co, USA). The sol-gel transition process is induced by the presence of monovalent or divalent ions such as Na^+ and Ca^{2+}. Some other parameters influence the phase transition, e.g., the concentration of polysaccharide, the temperature of the preparation, and the nature and the concentration of cations. Exceptional rheological properties of gellan gum such as thixotropy, pseudoplasticity, and thermoplasticity [59] are further advantages for its use in ophthalmology: the fluidity of the solution can be increased simply by shaking or slightly warming the preparation. The gellation increases proportionally to the amount of either monovalent or divalent cations present in the lacrimal fluid and in vitro experiments have demonstrated that divalent cations are more efficient in promoting sol-gel transition than monovalent ions. However, the in vivo conditions (i.e. the concentration of sodium in tears) is sufficient to induce the gellation process. Recently two other natural polymers believed to be able to form in situ gels by interacting with the lachrymal fluid have been evaluated as potential adjuvants in ophthalmic formulations [60, 61]. Carrageenans, a group of water soluble sulphated galactans extracted from red seaweed, showed similar features to gellan gum regarding their rheological behavior, gelling properties [62], and tolerance. This suggested that they could be interesting polymers for prolonging the residence time of topical ocular formulations [60]. Furthermore, the authors suggested that since these compounds are strong polyelectrolytes, they will have an identical gelling mechanism to gellan gum. Some alginates, rich in guluronic acid residues, have been demonstrated to exhibit reversible liquid-gel transition after administration and to be efficient in reducing intraocular pressure when carrying pilocarpine [61]. Also, alginate-pectine combinations and thiolated pectines were studied. Thiolation of pectin was observed to result in an increase in the gelling behavior, viscosity, and bioadhesive strength; combination of pectin and sodium alginate demonstrated good in vitro release characteristics [63].

In situ forming gels influenced by temperature. The volume-changing behavior of "smart" hydrogels is particularly useful in drug-delivery applications as drug release can be desirably triggered upon environmental changes [49–51]. Temperature responsiveness is particularly useful for in situ formation of drug-delivery devices since it allows handling of the formulation in the sol-phase at room temperature and solidification of the carrier upon injection [52]. These hydrogels are liquid at room temperature (20–25 °C) and undergo gelation when in contact with body fluids (35–37 °C), due to an increase in temperature. Different thermal setting gels have been described in the literature, including for example acrylic acid copolymers [43, 64] and N-isopropylacrylamide derivatives [65]. However, specific requirements inherent to ophthalmic administration such as tolerance have limited the choice of such polymers. Poloxamers, commercially available as Pluronic® (BASF-Wyandotte, USA), are the most commonly used thermal setting polymers in ophthalmology owing to their low toxicity, mucomimetic properties and optical clarity. They are formed by a central hydrophobic part

(polyoxypropylene) surrounded by hydrophilic part (ethylene oxide). Their concentration is chosen in accordance with the desired liquid-gel transition [66]. At concentrations above 20 % w/w, poloxamers exhibit the phenomenon of reverse thermal gellation, that is, gelling upon warming up from ambient to body temperature [67]. Interestingly, the temperature of transition of poloxamers can be modulated by adding solutes or polymers such as poly(ethylene glycols) [68] or cellulosic derivatives such as MC or HPMC to the formulation. The mucomimetic property of poloxamers is supposed to be due to their hydrophobic and hydrophilic sequences simulating mucin action by adsorption of the aqueous layer of tears on the hydrophobic epithelium. However, the disadvantage of poloxamers as compared to Gelrite® lies in their mechanism of gellation. In fact, since sol-gel transition takes place as the temperature increases, accidental gellation during conservation may occur. A new attractive thermal sensitive hydrogel, Smart Hydrogel® composed of a polymeric network of poly (acrylic acid) and poloxamer, has been described by Gilchrist et al. [69]. Owing to their protective and mucomimetic action, poloxamers have also been evaluated for the treatment of dry eye [70]. Poloxamers have also been widely investigated as ocular drug delivery systems. Miller and Donovan [71] reported enhanced activity of pilocarpine in poloxamers 407 gels when compared with a simple solution, whereas Dumortier et al. [72] have shown that a thermoreversible gel does not improve the kinetic profile of morphine over a reference solution. Despite all the promising results obtained with thermoreversible gels, it remains an important drawback associated with the use of these hydrogels; the risk of gelling before administration by an increase in the ambient temperature during packaging or storage.

In situ forming gels influenced by pH. All the pH-sensitive polymers contain pendant acidic or basic groups either accept or release protons in response to changes in environmental pH. The polymers with a large number of ionisable groups are known as polyelectrolytes. Swelling of the hydrogel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decreases if the polymer contains weakly basic (cationic) groups [73].

pH-sensitive hydrogels are composed of polymer chain networks crosslinked to each other and surrounded by a salt solution. A change in the pH of the solution surrounding the gel will initiate a physical process of either gel swelling or deswelling. The physical process, in general, is not instantaneous, and modelling the gel swelling/deswelling rate helps us to have a thorough understanding of the gel dynamics. This is particularly important when hydrogels are used in controlled drug-delivery devices, where the drug is released during the swelling process.

Pseudo-latexes have been defined by El-Aasser [74] as artificial latices obtained by the dispersion of a pre-existing polymer in an aqueous medium. Such systems correspond to low viscosity aqueous dispersions, which can undergo spontaneous coagulation in the conjunctival cul-de-sac owing to an increase of the local pH. The massive swelling of the particles is due to the neutralization of the acid groups contained in the polymer chain. The increase in viscosity is by several orders of magnitude [75]. In situ gelling pseudo-latexes can be prepared by two manufacturing processes; the solvent evaporation process [76] and the salting out process [77].

The uses of new technologies were recently combined to developnovel pH triggered polymeric nanoparticulate in situ gel for ophthalmic delivery of acetazolamide to enhance conjunctival permeation and precorneal residence time of the formulation. Nanoparticles were developed by nanoprecipitation method and exhibited significantly higher ex vivo transcorneal ACZ permeation than eye drops and ACZ suspension [78]. Similar findings were also described for a fluconazole pH triggered nanoemulsified in situ ophthalmic gel [79].

Inserts

This section is devoted to solid devices delivering drugs to the anterior segment of the eye that are denoted by the general name insert, originating from the Latin *inserere*, to introduce. Ophthalmic inserts are defined as preparations with a solid or semisolid consistency, whose size and shape are especially designed for ophthalmic application (i.e. rods or shields) [80]. These inserts are placed in the lower fornix and, less frequently, in the upper fornix, or on the cornea. They are usually composed of a polymeric vehicle containing the drug and are mainly used for topical therapy.

Ophthalmic inserts have been, and continue to be, in fashion in research and development laboratories, which is testified by abundant literature [81, 82]. The insert is probably the oldest ophthalmic formulation. Historically, the first solid medication precursors of the present insoluble inserts, were described in the 19th century. They consisted of squares of dry filter paper, previously impregnated with drug solutions (e.g., atropine sulfate, pilocarpine hydrochloride) [83], small sections were cut and applied under the eyelid. However, although the British Pharmacopoeia 1948 described an atropine in gelatin "wafer", and notwithstanding all the formulation possibilities as well as the modulation of biopharmaceutical properties that inserts permit, the insert market never took off. This was apparently caused by incompatibility between the product-insert and the user-patient, particularly in the elderly; difficulty of insertion by the patient and foreign-body sensation. Besides the initial discomfort upon administration, other potential disadvantages arising from their solid state are, possible movement around the eye, occasional inadvertent loss during sleep or while rubbing the eyes, interference with vision and difficult placement (and removal for insoluble devices) [84]. Most of the ongoing research is therefore dedicated to improving ocular retention and to ensure an easy placement, while reducing the foreign body sensation in the eye. Two products, AlzaOcusert® [85] and Merck Lacrisert® [86], have been marketed, although Ocusert is no longer sold. Ocusert was an insoluble delicate sandwich technology filled with sufficient pilocarpine for 1 week's use, whereas Lacrisert is a soluble minirod of hydroxypropyl cellulose, nonmedicated and dissolving within 24 h to treat dry-eye syndromes [86]. Other inserts are more like implants to be placed in the eye tissues by surgery and are not within the present scope of this Chapter.

Ophthalmic inserts are generally classified according to their solubility behavior and their possible biodegradability.

Soluble Inserts

Soluble inserts are the most frequently investigated class of ophthalmic inserts. Their main advantage relies on their complete solubility compared with their insoluble counterparts, so that they do not need to be removed from the eye after deposition. The major problems of these soluble inserts are the rapid penetration of the lacrimal fluid into the device, the blurred vision caused by the solubilization of insert components and the glassy constitution of the insert increasing the risk of expulsion. They are usually divided into two categories according to their polymer composition. The first type is based on natural polymers whereas the second is derived from synthetic or semisynthetic polymers.

Natural polymers. Natural polymers include collagen, which was the first ophthalmic insert excipient described in the literature. Inserts containing collagen were first developed by Fyodorov [87, 88] as corneal bandages following surgical operations and eye disease. Later, collagen shields as drug carriers were suggested by Bloomfield et al. [89]. As described for contact lenses, the therapeutic agents are generally absorbed by soaking the collagen shield in a solution containing the drug and, once placed in the eye, the drug is gradually released from the interstices between the collagen molecules, as the collagen dissolves. Accordingly, the residence time of drugs [90] such as antibacterials, [91, 92] anti-inflammatory agents [93, 94] antivirals [95] or combination drugs [96] was increased when compared to traditional eye drops. However, as observed for contact lenses, most drugs are released quite rapidly by a diffusion process, whereas dissolution requires a much longer time.

Solid Precorneal Inserts (Collagen Shields). Collagen shields were first introduced by Fyodorov in 1984 for use as a bandage contact lens following radial keratotomy and photorefractive surgery [97]. Collagen shields are manufactured from porcine scleral tissue and commercially available (Bio-Cor, Bausch & Lomb) with three dissolution times of 12, 24, and 72 h, depending on the level of collagen cross-linking induced during the manufacture process. Bloomfield et al. [89] were the first to suggest that collagen might provide a suitable carrier for sustained ocular drug delivery. They showed that wafer shaped collagen inserts impregnated with gentamicin produced higher levels of drug in the tear film and tissue in the rabbit eye compared to drops, ointment, or subconjunctival injection. They appeared useful as a delivery system for anti-infective agents and might possibly be of interest for some other drugs. Hydrophilic drugs are entrapped within the collagen matrix when the dry shield is soaked in aqueous solution of the drug whereas water-insoluble drugs are incorporated into the shield during the manufacturing process. When compared with intensive topical treatment, collagen shields have been found superior with regard to the delivery of different antibiotics and antifungal agents in the rabbit model [91, 98, 99]. In experimental bacterial

keratitis in animal models, the enhanced drug delivery ability of collagen shield was translated to enhanced bacterial eradication [92, 100–102]. Improved results were reported also for the delivery of anti-inflammatory agents by collagen shields [93, 94, 103].

The main advantages of collagen shields over contact lenses is their solubility. For this reason they do not need to be removed. However, collagen may cause an inflammatory response in the ocular tissues. Also, if shields are not used in association with antibacterials, a secondary infection may occur [95]. Nowadays, these devices have the further disadvantage of not being well accepted by the authorities, because of possible prion-based infection. Furthermore, the complexity of the manufacturing process and the resulting blurred vision are serious drawbacks that have curbed the enthusiasm raised during the development of corneal shields. Corneal shield self-administration is also difficult for the average user and their positioning should be monitored since they can be easily dislocated.

Another interesting approach is Gelfoam©, which is made of absorbable gelatin sponge USP. It can be inserted in the conjunctival pouch in the form of small disks (e.g., 4 mm in diameter and 0.5 mm thick) impregnated with drug solutions. They have been shown to improve the management of pupillary dilation in humans as well as the delivery of pilocarpine [104–106].

Synthetic and semisynthetic polymers. Ophthalmic inserts containing synthetic, i.e. PVA [107, 108] and semisynthetic, i.e. cellulose based [108–110] polymers, are extensively described in the literature. This stems in part from their advantage of being based in products well adapted for ophthalmic use and their ease of manufacture by conventional methods, including extrusion [110], compression [111] and compression molding [112]. Ethylcellulose, a hydrophobic polymer, can be incorporated in the formulation to decrease insert deformation, and therefore prevent blurred vision [113]. Regarding the risk of expulsion, several authors have incorporated carbomer, which, at low concentrations, is strong, but well-tolerated bioadhesive polymer.

Lacrisert® is a soluble insert that was successfully commercialized by Merck Sharp and Dohme in 1981 [87]. The device weighs 5 mg, measures 1.27 mm in diameter with a length of 3.5 mm, and is composed of HPC and is useful in the treatment of dry eye syndrome.

Insoluble Inserts

Insoluble inserts can be classified into two categories: reservoir and matrix systems.

Reservoir inserts. Reservoir inserts consist of a central reservoir of drug enclosed in a specially designed semipermeable or microporous membranes which allow the drug to diffuse from the reservoir at a precisely determined rate in a zero order release fashion. Reservoir controlled release systems may be manufactured in a wide range of geometries including conventional tablets/pellets, laminated films and other defined shapes, (e.g., hemispheres, cylinders, rods). Similarly there

are a number of methods by which these systems may be produced. For example pellets, spheres and tablets may be coated with an insoluble polymeric coating using conventional spray/film coating techniques, e.g., pan coating, air suspension coating. Alternatively, planar (laminated) drug delivery systems, e.g., transdermal patches, are manufactured using extrusion or film casting techniques. All reservoir systems share a common design, namely the drug core is housed within a polymeric barrier. The choice of the composition of the polymeric membrane is performed according to the physicochemical properties of the drug, particularly the ability of the therapeutic agent to diffuse through the polymer coating at the appropriate rate, the chosen manufacture method and the proposed route of administration to the patient. Reservoir inserts based on an osmotic release mechanism of the drug are mostly described in the patent literature, however in vivo tests on such technologies are rarely reported [80]. These types of ocular delivery systems are generally made up of a unique central reservoir surrounded by a peripheral component [114]. The peripheral part of these osmotic inserts comprises in all cases of a covering film made of an insoluble semipermeable polymer.

Ocusert® (developed by Alza Corporation, Palo Alto, California) is undoubtedly the most extensively described insoluble insert in the literature [115, 116]. The delivery of therapeutic agents to the eye for the treatment of disorders of the eye, (e.g., glaucoma), using conventional drug delivery systems, e.g., drops, ointments, is an inefficient process. This is primarily due to the rapid clearance of drugs from the surface of the eye due to blinking and tear flow. One method by which the efficiency of ocular drug delivery may be improved is through the use of polymeric implants that are implanted under the lower cul-de-sac of the eye [117]. The Ocusert represents one such example that has been designed to release either 20 $\mu g\ h^{-1}$ or 40 $\mu g\ h^{-1}$ of a therapeutic agent (pilocarpine) for a seven day period following implantation. In design terms the Ocusert is flat, flexible elliptical device which consists of a pilocarpine reservoir comprising alginic acid, which is surrounded on both sides by a membrane of ethylene-vinyl acetate copolymer. These layers act as the rate controlling membranes. The device is encircled by a retaining ring impregnated with titanium dioxide. Drug release from this delivery system occurs by diffusion. Initially lachrymal (tear) fluid diffuses through the rate controlling membranes and enters into the inner (alginate) matrix at which stage dissolution of pilocarpine occurs. Now in the molecular state, pilocarpine diffuses from the region of high concentration (the drug-containing matrix) to the lachrymal fluid through the rate controlling membrane. Recent clinical studies were done to compare the efficacy and safety of a new ocular insert versus conventional mydriasis in cataract surgery. Mydriasert® (Laboratories Théa, Clermont-Ferrand) is a tropicamide and phenylephrine insert, formulated with ammonio methacrylate copolymer, polyacrylate dispersion and ethylcellulose as excipients. The researchers concluded that the effect of the Mydriasert insert was similar to conventional mydriatic agents. Pupil size was restored to normal faster when using the Mydriasert insert compared with conventional mydriatic agents for pupil dilation. Another advantage of the insert is that this method requires only two simple maneuvers, one to insert and one to withdraw the device, thus reducing patients'

discomfort and saving time for the nursing staff, compared to having to administer drops to patients every 15 min [118].

Matrix inserts. The matrix insoluble inserts are typically represented by the contact lenses. The initial use of contact lenses was for vision correction. Its use has been extended to drug delivery devices by presoaking them in drug solutions. The main advantage of this system is the possibility of correcting vision and releasing drug simultaneously. Contact lenses are composed of a hydrophilic polymer which swells by absorbing water. The swelling, caused by the osmotic pressure of the polymer segments, is opposed by the elastic restoring forces arising along the chains as they are stretched until a final swelling (equilibrium) is reached. Refojo [119] has proposed classifying contact lenses according to five groups, namely rigid, semi-rigid, elastomeric, soft hydrophilic and biopolymeric. Soft hydrophilic contact lenses were developed for prolonged release of drugs such as pilocarpine [120], chloramphenicol and tetracycline [121], and prednisolone sodium phosphate [122]. This type contact lenses are better tolerated on ocular surface than collagen shields. The most commonly used polymer in the composition of these types of lenses is hydroxy ethyl metacrylate (HEMA) copolymerized with polyvinyl pyrrolidone (PVP) or ethylene glycol dimethacrylic acid (EGDM). PVP is used to increase water retention, while EGDM is used to decrease the water of hydration.

The main drawback of a contact lens as a therapeutic lens is their high cost of manufacture, and the low drug-loading capacity, which is not sufficient to build up a therapeutic concentration in the eye for most drugs [123]. Besides, these devices are insoluble, hence they need to be removed from the eye after treatment. For hydrophilic contact lenses, evidence has shown that the drug-loading capacity can deliver a drug amount, which is equivalent to only a small fraction of the dose that can be delivered by topical drug instillation [124]. Indeed, this Drug Delivery System (DDS) is barely represented in the modern array of ocular DDS [125]. Disposable contact lenses have been commercially available for many years, and the continued progress made in polymer chemistry should facilitate the development of this type of ocular insert.

Actually new concepts in drug loaded contact lenses is investigated. Diverse polymers properties discussed in this chapter were combined in temperature sensitive contact lenses. Authors focuses on dispersing timolol encapsulating highly crosslinked nanoparticles in contact lenses to increase the duration of drug release to about 2–4 weeks. The highly crosslinked particles were prepared from monomers with multivinyl functionalities such as ethylene glycol dimethacrylate and propoxylatedglyceryltriacylate. In vitro release studies exhibited drug release profiles compatible with a first order reaction model with a temperature dependent rate constant [126].

Biodegradable Inserts

In recent years, systems that control and prolong the action of therapeutic agents have grown in importance with the development of biodegradable polymers. There are stringent requirements, the drug delivery for the ocular route should

be sterile, isotonic, and nonirritant. There are no available marketable sterile ophthalmic products based on these systems. Biodegradable polymers are the polymers of choice for retinal drug delivery. The drug release from biodegradable polymeric devices depends on several factors: the molecular weight of the polymers, the monomer composition, and drug loading [127]. These polymers provide the advantage of being degraded and eliminated from the body thus avoiding the risk of toxic accumulation or the need for intervention to eliminate them. Lactic acid and glycolic acids are biodegradable, and they are produced and eliminated by the body. These polymers decompose into carbon dioxide and water. Polylactic acid (PLA) and polyglycolic acid (PGA) and their copolymer polylactic-co-glycolic acid (PLGA) are among the most widely used biodegradable polymers. They are approved for human use by worldwide health authorities and are degraded to nontoxic compounds (lactic acid and glycolic acid, respectively) following hydrolysis and enzymatic cleavage. These polymers undergo bulk erosion and drug diffusion may change according to the erosion rate of the polymer matrix. The great advantage of these inserts is the possibility of modulating their erosion rate by modifying their final structure during synthesis, and by addition of anionic or cationic surfactants. Thus, drug burst phenomena are likely to occur depending on the MW and chemical structure of the polymers. PGA for example is not an appropriate candidate for prolonged controlled DDS as it is highly sensitive to hydrolysis. However, erodible systems can have significantly variable erosion rates based on individual patient physiology and lachrymation patterns. In some cases, the degradation products or residual solvents used during the polymer preparation can cause inflammatory reaction. In conclusion, the majority of therapeutic agents can be delivered using inserts which are a promising alternative administration route, because of their various advantages compared with classical dosage forms. In contrast, other biodegradable polymers like polyorthoester and polyanhydride undergo surface erosion, and subsequently the drug release from such systems depends on the extent of the surface area. However, only few of these compounds have been commercialized. This can be attributed to the reluctance of ophthalmologists and patients to replace the traditional ophthalmic solutions as well as the cost and the need to train both the prescribers and the patients to place the inserts correctly in the eyes. In the future, the use of ophthalmic inserts will certainly increase because of the development of new polymers, the emergence of new drugs having short biological half-lives or systemic side effects, and the need to improve the efficacy of ophthalmic treatments by ensuring an effective drug concentration in the eye for several days.

In another interesting approaches, a composite collagen hydrogel containing protein-encapsulated alginate microspheres was developed for ocular applications using bovine serum albumin. Sustained release of bovine serum albumin was achieved during an 11 day period in neutral phosphate buffer [128]. Also, micro- and nanostructured poly(caprolactone) films were studied in terms of ocular tolerance and structural integrity while residing in rabbit's eye, exhibiting acceptable results [129].

Dispersed Systems

Dispersed systems based on liposomes, nanoparticles, or nanocapsules have been extensively studied for potential ophthalmic use [130–132]. The development of marketable products based on these nanoproducts has been challenging but a definitive technology has not yet been established. The major issues for this type of delivery system include: percentage of dispersed phase/entrapment coefficient problem (i.e. how much of the active ingredient will be present in a drop of the final product), stability and shelf life, antimicrobial preservation, tolerance of the used surfactants, and, last but not least, large-scale manufacture of sterile preparations. Beyond the problem of the entrapment percentage of the active pharmaceutical ingredient, the retention of these particles in the conjunctival pouch is a key consideration. This retention must be effective in providing an extended source of active drug and to allow the drug to leak out from the dispersed phase before the instilled formulation is drained away from the precorneal area.

Liposomes

While these systems exceed the chapter topic, a brief description of them will be done because of their relevance in scientific literature related to ocular treatment.

Liposomes (Fig. 6.8) are microscopic vesicles composed of alternating aqueous compartments and lipid bilayers (mainly phospholipids and cholesterol). The efficacy of liposomes in ophthalmic therapy depends on several parameters, including (1) the drug encapsulation efficiency, (2) the size and the charge of the vesicles, (3) the distribution of the drug in the liposomes, (4) the stability of the liposomes after instillation, (5) the residence time of the liposomes in the conjunctival sac, and finally, (6) the affinity of the liposomes with the cornea [131]. Of these, a major factor affecting ocular drug bioavailability is the unstability of liposomes to the proteins in the conjunctival sac. Liposomes and other types of colloidal drug

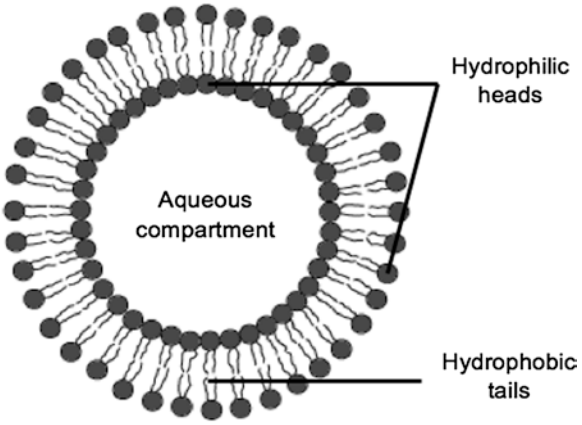

Fig. 6.8 Liposome

carriers offer at least some potential in relation to ocular drug delivery, since they can be used to generate a sustained release, and also a prolonged retention of the drug in intraocular cell populations. The use of liposomes as ocular delivery systems was first reported by Smolin et al. [133] and Schaeffer and Krohn [134]. A central strategy of the use of liposomes in ocular drug delivery based on liposomes has been to improve the adhesion between the liposomes and the cornea. This can be achieved in different ways, including: (1) Ganglioside-containing liposomes together with wheat ger agglutinin, a lectin binding to both the cornea and gangliosides, (2) Liposomes coated with antibodies to components in the corneal surface, and (3) Liposomes coated with mucoadhesive polymers.

One of the major constraints of the ocular route of delivery is the very low residence time of a drug in the ocular cavity, leading to a subsequent reduction in the bioavailability of therapeutic moieties. Charge and vesicular size are important parameters that affect the biodistribution of liposomes. Law et al. [135] reported a higher corneal uptake of positively charged liposomal acyclovir. Also Seyfoddin and Al-Kassas found faster permeation through excised cornea indicating potential enhanced corneal penetration properties for acyclovir nanostructured lipid carriers [136].

New formulations of polymeric and lipid nanoparticles are currently in development. The non-biodegradable positively-charged polymer Eudragit® RS 100 and semi-solid lipid excipient Gelucire® 44/14 were used as a vehicle, the cationic lipid octadecylamine was used as a cationic agent; obtaining successfully a pilocarpine HCl system for ocular application [137].

Microparticles and Nanoparticles

Microparticles and nanoparticles are colloidal drug carriers in the micrometer and submicrometer range, which have been evaluated for ophthalmic drug delivery purposes over the past 15 years. Micro- or nanoparticles are divided in two groups, micro- or nanospheres and micro- or nanocapsules. Microspheres are monolithic particles possessing a porous or solid polymer matrix, whereas microcapsules consist of a polymeric membrane surrounding a solid or a liquid drug reservoir [138]. Practically, the term nanoparticles is applied to nanospheres and nanocapsules because it is often difficult to determine if they are real capsules or matrix-type particles. The active compound can be dissolved, trapped, encapsulated, adsorbed or linked to these colloidal systems [138]. Nanocapsules can be used to increase the accessibility of drugs to the receptors localized in specific areas. They can serve as vehicles for use in the treatment of ophthalmic pathologies, because increased corneal penetration and prolonged therapeutic response have been achieved for some drugs [139]. Another drug used as eyedrops, pilocarpine, was encapsulated in polyisobutylcyanoacrylate nanocapsules incorporated in a Pluronic F127 gel [140]. The formulation increased the contact time of the drug with the absorbing tissue in the eye and improved ocular bioavailability. The principal materials used so far to prepare colloidal systems for ophthalmic drug delivery have been synthetic biodegradable polymers belonging to the group of

poly(alkyl cyanoacrylate). These polymers can be degraded following two concomitant metabolization pathways, which are the erosion of the polymer backbone leading to the formation of formaldehyde [141] or the cleavage of the ester inducing the formation of a water-soluble polymer backbone and the corresponding alcohol [142]. The potential of microparticulate formulations has been described but, as of today, they are not frequently employed as part of ophthalmic vehicles [143, 144].

Indomethacin in vitro corneal penetration was evaluated using nanocapsules as drug carriers [145]. The transcorneal flux of the drug through isolated rabbit cornea showed a considerable increase of 4–5 times the penetration rate of the nanoencapsulated drug compared to commercial eyedrops. In addition, PCL nanocapsules containing indomethacin were coated with chitosan, poly(l-lysine), or both in order to combine the features of nanocapsules with the advantages of a cationic mucoadhesivecoating [146]. Chitosan-coated nanocapsules provided an optimal corneal penetration of indomethacin and displayed good ocular tolerance. Promising findings were also reported for optimized celecoxib loaded bioadhesive cationic chitosan or anionic alginate nanoparticles. All formulations possessed pH and viscosity values compatible with the eye and uniform drug contents. In vitro release data showed a sustained release without any burst effect then followed by Higuchi non-Fickian diffusion mechanism. The results of in vitro cell toxicity revealed that all prepared formulations were non-toxic, with percentage cell viability ranging from 89.9 to 97.7 % [147].

Microemulsions and Nanoemulsions

Microemulsions might be systems of future interest, with the basic caveats concerning sterile manufacturing, long-term stability, patient tolerance vis-a`-vis any surfactant, and the difficulty to adequately preserve a biphasic system. The O/W Nanoemulsions (NEs) can also be used for ocular delivery to improve corneal penetration or sustain the pharmacological effect of drugs [148, 149]. These emulsions could be advantageous because they are supposed to diminish vision-blurring effects [150]. These NEs can prolong the release of the drug and sustain the pharmacological effect of drugs in the eye following ocular application [151]. Muchtar et al. [148] and Navech et al. [149] showed the application of NEs to prolong the response of antiglaucomatous drugs applied to rabbits.

Micelles

In micellar systems, nonpolar molecules are solubilized within the internal micelle hydrophobic core, polar molecules are adsorbed on the micelle surface and substances with intermediate polarity are distributed along surfactant molecules in intermediate positions. Micellar ocular DDS should be based on nontoxic and non-irritant materials and should be stable enough to achieve a reasonable shelf life.

Attention should be paid to the CMC of detergents used for micellar assembly, since high CMC often renders them toxic and irritant to ocular tissues. The non-ionic triblock copolymer polyethylene oxide–polypropylene oxide–polyethylene oxide (PEO–PPO–PEO) has been widely used in medicine and has shown low toxicity. The potential of a micellar carrier for topical ocular delivery using pilocarpine as a model drug was evaluated in another study [152]. Micellar solution of pilocarpine for topical ocular delivery was prepared by a simple method of drug dissolution within an aqueous solution of a surface-active high molecular weight triblock copolymer, Pluronic F127. For this purpose, an aqueous solution of Pluronic F127 was prepared in concentrations above the CMC, where the copolymer is supposed to form micelles.

Cyclodextrin-based formulations (Fig. 6.9) should not be missed by ophthalmic drug development groups [153, 154]. Their typical domain of use would be sparingly soluble drugs, e.g., sulfonamides inhibiting carbonic anhydrase for the treatment of glaucoma [155] or steroids against inflammation [156]. However, their action might be equivocal in some cases: a cyclodextrin solution of L 671,152 (dorzolamide hydrochloride, a topically active sulfonamide) induced—in rabbits—intraocular levels lower than the corresponding suspension. On the other hand auspicious results were reported for other inhibiting carbonic anhydrase drug (acetazolamide) in hydroxypropyl-ß-cyclodextrin (Fig. 6.10) formulations.

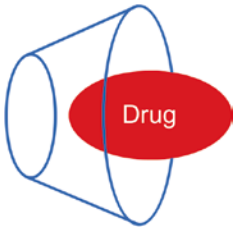

Fig. 6.9 Cyclodextrin-drug complex

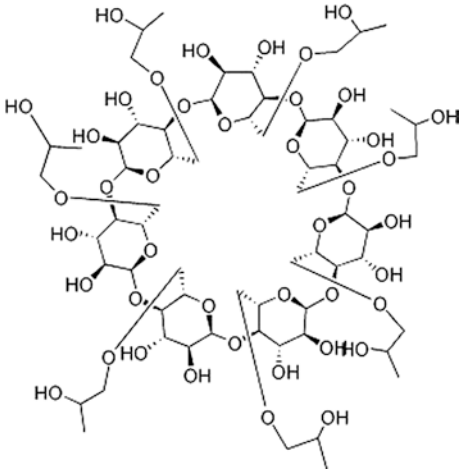

Fig. 6.10 Hydroxypropyl-ß-cyclodextrin

Hydroxypropyl-ß-cyclodextrin–acetazolamide–triethanolamine ternary complexes, showed better results in terms of in vitro corneal permeability and in vivo intraocular pressure reduction, in comparison with acetazolamide–triethanolamine complexes [157].

Conclusions

The eye presents unique challenges to the delivery of drugs. When the demand for sustained delivery to the target tissue is coupled with the desire to avoid systemic exposure, circumstances are ripe for creative approaches. Pharmaceutical research and development provides a pathway to achieve this, but it is governed by available technology, innovations, and regulatory constraints. Importantly, the cost of the finished product must be bearable by the individuals and/or communities who will use the product, and it has to be economically viable for the manufacturer. In the future, the use of ophthalmic drug delivery systems will certainly increase because of the development of new polymers, the emergence of new drugs having short biological half-lives or systemic side effects and the need to improve the efficacy of ophthalmic treatments by ensuring an effective drug concentration in the eye for several days.

References

1. Sieg, J.W., Robinson, J.R.: Vehicle effects on ocular drug bioavailability i: evaluation of fluorometholone. J. Pharm. Sci. **64**(6), 931–936 (1975)
2. Patton, T.F., Robinson, J.R.: Ocular evaluation of polyvinyl alcohol vehicle in rabbits. J. Pharm. Sci. **64**(8), 1312–1316 (1975)
3. Robinson, J.R., Mlynek, G.M.: Bioadhesive and phase-change polymers for ocular drug delivery. Adv. Drug. Deliv. Rev. **16**, 45–50 (1975)
4. Salminen, L., et al.: Prolonged pulse-entry of pilocarpine with a soluble drug insert. Graefes. Arch. Clin. Exp. Ophthalmol. **221**(2), 96–99 (1983)
5. Wilson, C.G., et al.: Structure and physiological functions. In: Touitou, E., Barry, B.W. (eds.) Enhancement in Drug Delivery. pp. 473–487. (2007)
6. Snell, R.S., Lemp, M.A.: Clinical Anatomy of the Eye, 2nd edn, p. 423. Blackwell Science, Malden (1998)
7. Norn, M.S.: Tear secretion in normal eyes. estimated by a new method: the lacrimal streak dilution test. Acta. Ophthalmol. (Copenh) **43**(4), 567–573 (1965)
8. Records, R.E: The tear film. In: Tasman, W., Jaeger, E.A.(eds.) Duane's Foundations of Clinical Ophthalmology, Lippincott Williams & Wilkins, Philadelphia (2005)
9. Patton, T.F., Robinson, J.R.: Quantitative precorneal disposition of topically applied pilocarpine nitrate in rabbit eyes. J. Pharm. Sci. **65**(9), 1295–1301 (1976)
10. Plazonnet, B., et al.: Pharmacokinetics and biopharmaceutical aspects of some anti-glaucoma drugs. In: Saettone, M.F., Bucci, M., Speiser, P. (eds.) Ophthalmic Drug Delivery; Biopharmaceutical, Technological and Clinical Aspects, pp. 117–139. Liviana Press/ Springer Verlag, Padova/New york (1987)
11. Gurny, R., Ibrahim, H., Buri, P.: The development and use of in situ formed gels, triggered by pH. In: Edman, P. (ed.) Biopharmaceutics of Ocular Drug Delivery, pp. 81–90. CRC Press, Florida (1993)

12. Tanaka, T.: Collapse of gels and the critical endpoint. Phys. Rev. Lett. **40**(12), 820–823 (1978)
13. Ahn, S.-K., et al.: Stimuli-responsive polymer gels. Soft. Matter. **4**(6), 1151–1157 (2008)
14. Swan, K.C.: Use of methyl cellulose in ophthalmology. Arch. Ophthalmol. **33**(5), 378–380 (1945)
15. Zaki, I., et al.: A comparison of the effect of viscosity on the precorneal residence of solutions in rabbit and man. J. Pharm. Pharmacol. **38**(6), 463–466 (1986)
16. Tous, S.S., Abd-El Nasser, K.: Acetazolamide topical formulation and ocular effect. STP Pharm Sci. **2**, 125–131 (1992)
17. Grove, J., et al.: The effect of vehicle viscosity on the ocular bioavailability of L-653,328. Int. J. Pharm. **66**(1–3), 23–28 (1990)
18. Ludwig, A., Van Ooteghem, M.: Influence of viscolysers on the residence of ophthalmic solutions evaluated by slit lamp fluorophotometry. STP. Pharma. Sci. **2**, 81–87 (1992)
19. Mueller, W.H., Deardorff, D.L.: Ophthalmic vehicles: the effect of methylcellulose on the penetration of homatropine hydrobromide through the cornea. J. Am. Pharm. Assoc. (Baltim) **45**(5), 334–341 (1956)
20. Haas, J.S., Merrill, D.L.: The effect of methyl-cellulose on responses to solutions of pilocarpine. Am. J. Ophthalmol. **54**, 21–24 (1962)
21. Hardberger, R., Hanna, C., Boyd, C.M.: Effects of drug vehicles on ocular contact time. Arch. Ophthalmol. **93**(1), 42–45 (1975)
22. Schoenwald, R.D., et al.: Inlfuence of high-viscosity vehicles on miotic effect of pilocarpine. J. Pharm. Sci. **67**(9), 1280–1283 (1978)
23. Saettone, M.F., et al.: Polymer effects on ocular bioavailability—the influence of different liquid vehicles on the mydriatic response of tropicamide in humans and rabbits. Int. J. Pharm. **20**, 187–202 (1984)
24. Deshpande, S.G., Shirolkar, S.: Sustained release ophthalmic formulations of pilocarpine. J. Pharm. Pharmacol. **41**(3), 197–200 (1989)
25. Patchan, M., et al.: Synthesis and properties of regenerated cellulose-based hydrogels with high strength and transparency for potential use as an ocular bandage. Mater. Sci. Eng. C. Mater. Biol. Appl. **33**(5), 3069–3076 (2013)
26. Peppas, N.A.: Hydrogels. In: Peppas, N.A.(ed.) Medicine and Pharmacy. CRC Press, Boca Raton (1987)
27. Davies, N.M., et al.: Evaluation of mucoadhesive polymers in ocular drug delivery. I. Viscous solutions. Pharm. Res. **8**(8), 1039–1043 (1991)
28. Balazs, E.A.: Ultrapure hyaluronic acid and the use thereof. US Patent #4,141,973 (1979)
29. Bernatchez, S.F., et al.: Use of hyaluronic acid. In: Edman P.(ed.) Biopharmaceutics of Ocular Drug Delivery, pp. 105–120. CRC Press, Boca Raton (1993)
30. Wysenbeek, Y.S., et al.: The effect of sodium hyaluronate on the corneal epithelium. An ultrastructural study. Invest. Ophthalmol. Vis. Sci. **29**(2), 194–199 (1988)
31. Camber, O., Edman, P., Gurny, R.: Influence of sodium hyaluronate on the meiotic effect of pilocarpine in rabbits. Curr. Eye. Res. **6**(6), 779–784 (1987)
32. Saettone, M.F., et al.: Mucoadhesive ophthalmic vehicles: evaluation of polymeric low-viscosity formulations. J. Ocul. Pharmacol. **10**(1), 83–92 (1994)
33. Saettone, M.F., et al.: Evaluation of muco-adhesive properties and in vivo activity of ophthalmic vehicles based on hyaluronic acid. Int. J. Pharm. **51**, 203–212 (1989)
34. Bernatchez, S.F., Tabatabay, C., Gurny, R.: Sodium hyaluronate 0.25 % used as a vehicle increases the bioavailability of topically administered gentamicin. Graefes. Arch. Clin. Exp. Ophthalmol. **231**(3), 157–161 (1993)
35. Calles, J.A., et al.: Novel bioadhesive hyaluronan-itaconic acid crosslinked films for ocular therapy. Int. J. Pharm. **455**(1–2), 48–56 (2013)
36. Edsman, K., Carlfors, J., Harju, K.: Rheological evaluation and ocular contact time of some carbomer gels for ophthalmic use. Int. J. Pharm. **137**(2), 233–241 (1996)
37. von der Ohe, N., et al.: How can the bioavailability of timolol be enhanced? A pharmacokinetic pilot study of novel hydrogels. Graefes. Arch. Clin. Exp. Ophthalmol. **234**(7), 452–456 (1996)

38. Schoenwald, R.D., Boltralik, J.J.: A bioavailability comparison in rabbits of two steroids formulated as high-viscosity gels and reference aqueous preparations. Invest. Ophthalmol. Vis. Sci. **18**(1), 61–66 (1979)
39. Ludwig, A., Unlu, N., van Ooteghem, M.: Evaluation of viscous ophthalmic vehicles containing carbomer by slit-lamp fluorophotometry in humans. Int. J. Pharm. **61**(1–2), 15–25 (1990)
40. Saettone, M.F., et al.: Semisolid ophthalmic vehicles III. An evaluation of four organic hydrogels containing pilocarpine. Int. J. Pharm. **31**, 261–270 (1986)
41. Amin, P.D., Bhogte, C.P., Deshpande, M.A.: Studies on gel tears. Drug. Dev. Ind. Pharm. **22**(7), 735–739 (1996)
42. Meseguer, G., et al.: Gamma scintigraphic study of precorneal drainage and assessment of miotic response in rabbits of various ophthalmic formulations containing pilocarpine. Int. J. Pharm. **95**(1–3), 229–234 (1993)
43. Albasini, M., Ludwig, A.: Evaluation of polysaccharides intended for ophthalmic use in ocular dosage forms. Farmaco (Societa chimica italiana: 1989) **50**(9), 633–642 (1995)
44. Burgalassi, S., Chetoni, P., Saettone, M.F.: Hydrogels for ocular delivery of pilocarpine: preliminary evaluation in rabbits of the influence of viscosity and of drug solubility. Eur. J. Pharm. Biopham. **42**, 385–392 (1996)
45. Felt, O., Buri, P., Gurny, R.: Chitosan: a unique polysaccharide for drug delivery. Drug. Dev. Ind. Pharm. **24**(11), 979–993 (1998)
46. Felt, O., et al.: Topical use of chitosan in ophthalmology: tolerance assessment and evaluation of precorneal retention. Int. J. Pharm. **180**(2), 185–193 (1999)
47. Felt, O., et al.: Chitosan as tear substitute: a wetting agent endowed with antimicrobial efficacy. J. Ocul. Pharmacol. Ther. **16**(3), 261–270 (2000)
48. Felt, O., Buri, P., Gumy, R.: Ocular bioavailability of tobramycin after topical administration of formulations based on polysaccharide. In: 2nd International Symposium on Experimental Clinical Ocular Pharmacology and Pharmaceutics (1997)
49. Qiu, Y., Park, K.: Environment-sensitive hydrogels for drug delivery. Adv. Drug. Deliv. Rev. **53**(3), 321–339 (2001)
50. Ron, E.S., Bromberg, L.E.: Temperature-responsive gels and thermogelling polymer matrices for protein and peptide delivery. Adv. Drug. Deliv. Rev. **31**(3), 197–221 (1998)
51. Kost, J., Langer, R.: Responsive polymeric delivery systems. Adv. Drug. Deliv. Rev. **46**(1–3), 125–148 (2001)
52. Ruel-Gariepy, E., Leroux, J.C.: In situ-forming hydrogels—review of temperature-sensitive systems. Eur. J. Pharm. Biopharm. **58**(2), 409–426 (2004)
53. Mazuel, C., Friteyre, M.C.: Ophthalmological composition of the type which undergoes liquid-gel phase transition, Google Patents (1989)
54. Kumar, S., Haglund, B.O., Himmelstein, K.J.: In situ-forming gels for ophthalmic drug delivery. J. Ocul. Pharmacol. **10**(1), 47–56 (1994)
55. Kumar, S., Himmelstein, K.J.: Modification of in situ gelling behavior of carbopol solutions by hydroxypropyl methylcellulose. J. Pharm. Sci. **84**(3), 344–348 (1995)
56. Ron, E.S.: Smart gel: a new thermogelling polymer mixture for drug delivery. Proceedings in international symposium of Controlled Rel Bioactive Materials. **23**, 23–24 (1996)
57. Zimmer, A.K., Zerbe, H., Kreuter, J.: Evaluation of pilocarpine-loaded albumin particles as drug delivery systems for controlled delivery in the eye I. in vitro and in vivo characterisation. J. Controlled. Release. **32**(1), 57–70 (1994)
58. Zimmer, A.K., et al.: Evaluation of pilocarpine-loaded albumin particles as controlled drug delivery systems for the eye. II. co-administration with bioadhesive and viscous polymers. J. Controlled. Release. **33**(1), 31–46 (1995)
59. Deasy, P.B., Quigley, K.J.: Rheological evaluation of deacetylated gellan gum (gelrite) for pharmaceutical use. Int. J. Pharm. **73**(2), 117–123 (1991)
60. Verschueren, E., Van Santvliet, L., Ludwig, A.: Evaluation of various carrageenans as ophthalmic viscolysers. S.T.P. Pharma. Sci. **6**, 203–210 (1996)
61. Cohen, S., et al.: A novel in situ-forming ophthalmic drug delivery system from alginates undergoing gelation in the eye. J. Controlled. Release. **44**(2–3), 201–208 (1997)

62. Kang, K.S., et al.: Agar-like polysaccharide produced by a pseudomonas species: production and basic properties. Appl. Environ. Microbiol. **43**(5), 1086–1091 (1982)
63. Mittal, N., Kaur, G.: In situ gelling ophthalmic drug delivery system: Formulation and evaluation. J. Appl. Polym. Sci. **131**(2) (2014)
64. Hoffman, A.S., Afrassiabi, A., Dong, L.C.: Thermally reversible hydrogels: II. delivery and selective removal of substances from aqueous solutions. J. Controlled. Release. **4**, 213–222 (1986)
65. Hoffman, A.S.: Applications of thermally reversible polymers and hydrogels in therapeutics and diagnostics. J. Controlled. Release. **6**(1), 297–305 (1987)
66. Bermudez, J.M., et al.: Challenges and opportunities in polymer technology applied to veterinary medicine. J. Vet. Pharmacol. Ther. **37**(2), 105–124 (2014)
67. Gilbert, J.C., et al.: The behaviour of Pluronic F127 in aqueous solution studied using fluorescent probes. Int. J. Pharm. **40**, 93–99 (1987)
68. Gilbert, J.C., et al.: The effect of solutes and polymers on the gelation properties of pluronic F-127 solutions for controlled drug delivery. J. Controlled. Release. **5**(2), 113–118 (1987)
69. Gilchrist, P., et al.: The precorneal residence of a thermally sensitive hydrogel. In: 137th British Pharmaceutical Conference Scarborough (1997)
70. Waring, G.O., Harris, R.R.: Double-masked evaluation of a poloxamer artificial tear in keratoconjunctivitis. In: Leopold, L.H., Burns, B.P. (eds.) Symposium on Ocular Therapy, pp. 127–140. Wiley, New York (1979)
71. Miller, S.C., Donovan, M.D.: Effect of Poloxamer 407 gel on the mitotic activity of pilocarpine nitrate in rabbits. Int. J. Pharm. **12**, 147–152 (1982)
72. Dumortier, G., et al.: Comparison between a thermoreversible gel and an insert in order to prolong the systemic absorption of morphine after ocular administration. S.T.P. Pharma. Sci. **2**, 111–117 (1992)
73. Zhang, R., et al.: A novel pH- and ionic-strength-sensitive carboxy methyl dextran hydrogel. Biomaterials **26**(22), 4677–4683 (2005)
74. El-Aasser, M.S.: Formation of polymer latexes by direct emulsification. Advances in emulsion polymerization and latex technology. In: 10th Annual Short Coarse (1979)
75. Ibrahim, H., et al.: Concept and development of ophthalmic pseudolatexes triggered by pH. Int. J. Pharm. **77**, 211–219 (1991)
76. Gumy, R., et al.: Recent developments in controlled drug delivery to the eye. In: Proceedings in International Symposium Controlled Rel Bioactive Materials (1985)
77. Ibrahim, H., et al.: Aqueous nanodispersions prepared by a salting-out process. Int. J. Pharm. **87**(1–3), 239–246 (1992)
78. Singh, J., Chhabra, G., Pathak, K.: Development of acetazolamide-loaded, pH-triggered polymeric nanoparticulate in situ gel for sustained ocular delivery: in vitro. ex vivo evaluation and pharmacodynamic study. Drug Dev. Ind. Pharm. **40**(9), 1223–1232 (2014)
79. Pathak, M.K., Chhabra, G., Pathak, K.: Design and development of a novel pH triggered nanoemulsified in-situ ophthalmic gel of fluconazole: ex-vivo transcorneal permeation, corneal toxicity and irritation testing. Drug. Dev. Ind. Pharm. **39**(5), 780–790 (2013)
80. Gurtler, F., Gurny, R.: Patent literature review of ophthalmic inserts. Drug. Dev. Ind. Pharm. **21**, 1–18 (1995)
81. Maichuk, Y.F.: Ophthalmic drug inserts. Invest. Ophthalmol. **14**, 87–90 (1975)
82. Friedrich, S.W., et al.: Pharmacokinetic differences between ocular inserts and eyedrops. J. Ocul. Pharmacol. Ther. **12**(1), 5–18 (1996)
83. Saettone, M.F.: Solid polymeric inserts/disks as drug delivery devices. In: Edman, P. (ed.) Biopharmaceutics of Ocular Drug Delivery, pp. 61–67. CRC Press, London (1993)
84. Saettone, M.F., Salminen, L.: Ocular inserts for topical delivery. Adv. Drug. Del. Rev. **16**, 95–106 (1995)
85. Urquhart, J.: Development of ocusert pilocarpine ocular therapeutic systems. In: Robinson J.R. (ed) Ophthalmic Drug Delivery Systems, pp. 105–108. American Pharmaceutical Association, Washington DC (1980)
86. Katz, I.M.: Shaped ophthalmic inserts for treating dry eye syndrome, Google Patents (1982)

87. Bawa, R.: Ocular inserts. In: Mitra, A.K. (ed.) Ophthalmic Drug Delivery Systems, pp. 223–260. Dekker, New York (1993)
88. Fyodorov, S.N., et al.: Ophthalmological collagen coverings, Google Patents (1990)
89. Bloomfield, S.E., et al.: Soluble gentamicin ophthalmic inserts as a drug delivery system. Arch. Ophthalmol. **96**(5), 885–887 (1978)
90. Friedberg, M.L., Pleyer, U., Mondino, B.J.: Device drug delivery to the eye. Collagen shields, iontophoresis, and pumps. Ophthalmology **98**(5), 725–732 (1991)
91. Phinney, R.B., et al.: Collagen-shield delivery of gentamicin and vancomycin. Arch. Ophthalmol. **106**(11), 1599–1604 (1988)
92. Sawusch, M.R., et al.: Use of collagen corneal shields in the treatment of bacterial keratitis. Am. J. Ophthalmol. **106**(3), 279–281 (1988)
93. Hwang, D.G., et al.: Collagen shield enhancement of topical dexamethasone penetration. Arch. Ophthalmol. **107**(9), 1375–1380 (1989)
94. Sawusch, M.R., O'Brien, T.P., Updegraff, S.A.: Collagen corneal shields enhance penetration of topical prednisolone acetate. J. Cataract. Refract. Surg. **15**(6), 625–628 (1989)
95. Gussler, J.R., et al.: Collagen shield delivery of trifluorothymidine. J. Cataract. Refract. Surg. **16**(6), 719–722 (1990)
96. Milani, J.K., et al.: Collagen shields impregnated with gentamicin-dexamethasone as a potential drug delivery device. Am. J. Ophthalmol. **116**(5), 622–627 (1993)
97. Fyodorov, S.N.: Efficiency of collagen covers: application in cases in keratotomy. In: Fydorov, S.N. (ed.) Eye Microsurgery, Research Institute of Eye Microsurgery, Moscow (1984)
98. O'Brien, T.P., et al.: Use of collagen corneal shields versus soft contact lenses to enhance penetration of topical tobramycin. J. Cataract. Refract. Surg. **14**(5), 505–507 (1988)
99. Pleyer, U., et al.: Use of collagen shields containing amphotericin B in the treatment of experimental Candida albicans-induced keratomycosis in rabbits. Am. J. Ophthalmol. **113**(3), 303–308 (1992)
100. Hobden, J.A., et al.: Treatment of experimental Pseudomonas keratitis using collagen shields containing tobramycin. Arch. Ophthalmol. **106**(11), 1605–1607 (1988)
101. Silbiger, J., Stern, G.A.: Evaluation of corneal collagen shields as a drug delivery device for the treatment of experimental Pseudomonas keratitis. Ophthalmology **99**(6), 889–892 (1992)
102. Callegan, M.C., et al.: Efficacy of tobramycin drops applied to collagen shields for experimental staphylococcal keratitis. Curr. Eye. Res. **13**(12), 875–878 (1994)
103. Chen, Y.F., et al.: Cyclosporine-containing collagen shields suppress corneal allograft rejection. Am. J. Ophthalmol. **109**(2), 132–137 (1990)
104. Simamora, P., et al.: Controlled delivery of pilocarpine. 2. In-vivo evaluation of Gelfoam device. Int. J. Pharm. **170**, 209–214 (1998)
105. Lee, Y.C., et al.: Formulation and in vivo evaluation of ocular insert containing phenylephrine and tropicamide. Int. J. Pharm. **182**(1), 121–126 (1999)
106. Negvesky, G.J., et al.: Ocular gelfoam disc-applicator for pupillary dilation in humans. J. Ocul. Pharmacol. Ther. **16**(4), 311–315 (2000)
107. Saettone, M.F., et al.: Controlled release of pilocarpine from coated polymeric ophthalmic inserts prepared by extrusion. Int. J. Pharm. **86**, 159–166 (1992)
108. Attia, M.A., Kassem, M.A., Safwat, S.M.: In vivo performance of [3H]dexamethasone ophthalmic film delivery systems in the rabbit eye. Int. J. Pharm. **47**(1–3), 21–30 (1988)
109. Kaga, Y., et al.: Ultraviolet-hardenable adhesive, Google Patents (1992)
110. Gurtler, F., et al.: Long-acting soluble bioadhesive ophthalmic drug insert (BODI) containing gentamicin for veterinary use: optimization and clinical investigation. J. Controlled. Release. **33**(2), 231–236 (1995)
111. Saettone, M.F., et al.: Application of the compression technique to the manufacture of pilocarpine inserts. Acta. Pharm. Technol. **1**, 15–19 (1990)
112. Harwood, R.J., Schwartz, J.B.: Drug release from compression molded films: preliminary studies with pilocarpine. Drug. Dev. Ind. Pharm. **8**(5), 663–682 (1982)

113. Baeyens, V., et al.: Optimized release of dexamethasone and gentamicin from a soluble ocular insert for the treatment of external ophthalmic infections. J. Controlled. Release. **52**(1–2), 215–220 (1998)
114. Gale, R.M., Ben-Dor, M., Keller, N.: Ocular therapeutic system for dispensing a medication formulation, Google Patents (1980)
115. Robinson, J.R.: Ocular drug delivery: mechanism(s) of corneal drug transport and mucoadhesive delivery systems. STP. Pharm. Sci. **5**(12), 839–846 (1989)
116. Drance, S.M., Mitchell, D.W., Schulzer, M.: The duration of action of pilocarpine ocusert on intraocular pressure in man. Can. J. Ophthalmol. **10**(4), 450–452 (1975)
117. Chien, Y.W.: Novel Drug Delivery Systems. Marcel Dekker, New York (1992)
118. Torron, C., et al.: Use of a new ocular insert versus conventional mydriasis in cataract surgery. Biomed. Res. Int. p. 849349 (2013)
119. Refojo, M.F.: Polymers in contact lenses: an overview. Curr. Eye. Res. **4**(6), 719–723 (1985)
120. Maddox, Y.T., Bernstein, H.N.: An evaluation of the Bionite hydrophilic contact lens for use in a drug delivery system. Ann. Ophthalmol. **4**(9), 789–790 (1972)
121. Praus, R., et al.: Hydrophilic contact lenses as a new therapeutic approach for the topical use of chloramphenicol and tetracycline. Ophthalmologica **165**(1), 62–70 (1972)
122. Hull, D.S., Edelhauser, H.F., Hyndiuk, R.A.: Ocular penetration of prednisolone and the hydrophilic contact lens. Arch. Ophthalmol. **92**(5), 413–416 (1974)
123. Wajs, G., Meslard, J.C.: Release of therapeutic agents from contact lenses. Crit. Rev. Ther. Drug. Carrier. Syst. **2**(3), 275–289 (1986)
124. Weiner, A.L.: Polymeric drug delivery systems for the eye. In: Domb, A.J. (ed.) Polymeric Site-Specific Pharmacotherapy, pp. 315–346. Wiley, Chichester (1994)
125. McMahon, T.T., Zadnik, K.: Twenty-five years of contact lenses: the impact on the cornea and ophthalmic practice. Cornea **19**(5), 730–740 (2000)
126. Jung, H.J., Chauhan, A.: Temperature sensitive contact lenses for triggered ophthalmic drug delivery. Biomaterials **33**(7), 2289–2300 (2012)
127. Kimura, H., Ogura, Y.: Biodegradable polymers for ocular drug delivery. Ophthalmologica **215**(3), 143–155 (2001)
128. Liu, W., Griffith, M., Li, F.: Alginate microsphere-collagen composite hydrogel for ocular drug delivery and implantation. J. Mater. Sci. Mater. Med. **19**(11), 3365–3371 (2008)
129. Bernards, D.A., et al.: Ocular biocompatibility and structural integrity of micro- and nanostructured poly(caprolactone) films. J. Ocul. Pharmacol. Ther. **29**(2), 249–257 (2013)
130. Gurny, R., Boye, T., Ibrahim, H.: Ocular therapy with nanoparticulate systems for controlled drug delivery. J. Controlled. Release. **2**, 353–361 (1985)
131. Lee, V.H., et al.: Ocular drug bioavailability from topically applied liposomes. Surv. Ophthalmol. **29**(5), 335–348 (1985)
132. Marchal-Heussler, L., et al.: Poly(epsilon-caprolactone) nanocapsules in carteolol ophthalmic delivery. Pharm. Res. **10**(3), 386–390 (1993)
133. Smolin, G., et al.: Idoxuridine-liposome therapy for herpes simplex keratitis. Am. J. Ophthalmol. **91**(2), 220–225 (1981)
134. Schaeffer, H.E., Krohn, D.L.: Liposomes in topical drug delivery. Invest. Ophthalmol. Vis. Sci. **22**(2), 220–227 (1982)
135. Law, S.L., Huang, K.J., Chiang, C.H.: Acyclovir-containing liposomes for potential ocular delivery. Corneal penetration and absorption. J. Controlled. Release. **63**(1–2), 135–140 (2000)
136. Seyfoddin, A., Al-Kassas, R.: Development of solid lipid nanoparticles and nanostructured lipid carriers for improving ocular delivery of acyclovir. Drug. Dev. Ind. Pharm. **39**(4), 508–519 (2013)
137. Lutfi, G., Muzeyyen, D.: Preparation and characterization of polymeric and lipid nanoparticles of pilocarpine HCl for ocular application. Pharm. Dev. Technol. **18**(3), 701–709 (2013)
138. Zimmer, A., Kreuter, J.: Microspheres and nanoparticles used in ocular delivery systems. Adv. Drug. Deliv. Rev. **16**(1), 61–73 (1995)
139. Losa, C., et al.: Design of new formulations for topical ocular administration: polymeric nanocapsules containing metipranolol. Pharm. Res. **10**(1), 80–87 (1993)

140. Desai, S.D., Blanchard, J.: Pluronic F127-based ocular delivery system containing biodegradable polyisobutylcyanoacrylate nanocapsules of pilocarpine. Drug. Deliv. **7**(4), 201–207 (2000)
141. Vezin, W.R., Florence, A.T.: Diffusion of small molecules in poly-N-alkyl cyanoacrylates [proceedings]. J. Pharm. Pharmacol. **30**(Suppl), 2P (1978)
142. Lenaerts, V., et al.: Degradation of poly (isobutyl cyanoacrylate) nanoparticles. Biomaterials **5**(2), 65–68 (1984)
143. Joshi, A.: Microparticulates for ophthalmic drug delivery. J. Ocul. Pharmacol. **10**(1), 29–45 (1994)
144. Genta, I., et al.: Bioadhesive microspheres for ophthalmic administration of acyclovir. J. Pharm. Pharmacol. **49**(8), 737–742 (1997)
145. Calvo, P., et al.: Polyester nanocapsules as new topical ocular delivery systems for cyclosporin A. Pharm. Res. **13**(2), 311–315 (1996)
146. Calvo, P., Vila-Jato, J.L., Alonso, M.A.J.: Evaluation of cationic polymer-coated nanocapsules as ocular drug carriers. Int. J. Pharm. **153**(1), 41–50 (1997)
147. Ibrahim, M.M., et al.: Natural bioadhesive biodegradable nanoparticles-based topical ophthalmic formulations for sustained celecoxib release. J. Pharm. Tech. Drug. Res. **2**(1), 7 (2013)
148. Muchtar, S., et al.: A submicron emulsion as ocular vehicle for delta-8-tetrahydrocannabinol: effect on intraocular pressure in rabbits. Ophthalmic. Res. **24**(3), 142–149 (1992)
149. Naveh, N., Muchtar, S., Benita, S.: Pilocarpine incorporated into a submicron emulsion vehicle causes an unexpectedly prolonged ocular hypotensive effect in rabbits. J. Ocul. Pharmacol. **10**(3), 509–520 (1994)
150. Schulz, M.B., Daniels, R.: Hydroxypropylmethylcellulose (HPMC) as emulsifier for submicron emulsions: influence of molecular weight and substitution type on the droplet size after high-pressure homogenization. Eur. J. Pharm. Biopharm. **49**(3), 231–236 (2000)
151. Hagigit, T., et al.: The influence of cationic lipid type on in-vitro release kinetic profiles of antisense oligonucleotide from cationic nanoemulsions. Eur. J. Pharm. Biopharm. **70**(1), 248–259 (2008)
152. Pepic, I., Jalsenjak, N., Jalsenjak, I.: Micellar solutions of triblock copolymer surfactants with pilocarpine. Int. J. Pharm. **272**(1–2), 57–64 (2004)
153. Loftssona, T., Jarvinen, T.: Cyclodextrins in ophthalmic drug delivery. Adv. Drug. Deliv. Rev. **36**(1), 59–79 (1999)
154. Bibby, D.C., Davies, N.M., Tucker, I.G.: Mechanisms by which cyclodextrins modify drug release from polymeric drug delivery systems. Int. J. Pharm. **197**(1), 1–11 (2000)
155. Gudmundsdottir, E., et al.: Methazolamide 1 % in cyclodextrin solution lowers IOP in human ocular hypertension. Invest. Ophthalmol. Vis. Sci. **41**(11), 3552–3554 (2000)
156. Kristinsson, J.K., et al.: Dexamethasone-cyclodextrin-polymer co-complexes in aqueous eye drops. Aqueous humor pharmacokinetics in humans. Invest. Ophthalmol. Vis. Sci. **37**(6), 1199–1203 (1996)
157. Palma, S.D., et al.: An efficient ternary complex of acetazolamide with HP-ss-CD and TEA for topical ocular administration. J. Controlled. Release. **138**(1), 24–31 (2009)