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A Review on Innovative Formulation Approach to Enhance Occular Bioavailability

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Abstract

Conventional eye drops shows relatively low bioavailability due to poor precorneal contact time. In situ hydrogel are of great importance in providing sustained ocular drug delivery due to their elastic properties hydrogel resist occular drainage leading to longer contact times. Sustained and Prolonged drug delivery approaches are very common in today. Formulation design and research work is still going on in achieving better drug product. Ophthalmic use of viscosity-enhancing agents, penetration enhancers and ocular inserts and ready existing drug carrier systems along with their application to ophthalmic drug delivery are very common to improve ocular bioavailability. Amongst these hydrogel systems are of very important. They help to increase in precorneal residence time of drug to a sufficient extent that an occular delivered drug can exhibit its maximum biological action. The concept of this innovative ophthalmic delivery approach to decrease the systemic side effects and create a more pronounced effect with lower doses of the drug. Many polymers are very useful with majority of hydrogel, which undergo reversible sol-gel phase transitions in the ocular cul-de-sac to form viscoelastic gels due to phase changes of polymers in response to the physiological environment and presence of ions in organism fluids. These *in situ* forming gels can be applied as solution and exhibit pseudo plastic behavior to minimize interference, increase pre corneal residence of the delivery system and enhanced ocular bioavailability. Now days in situ gels have been used as vehicles for the delivery of drugs for both local treatment and systemic effects.

Keywords: Bioavailability, Hydrogel, Precorneal, Insitugel, Ophthalmic drug delivery

Contents

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1. Introduction

Ophthalmic drug delivery is extremely interesting and highly challenging endeavors. The landscape of ophthalmic drug delivery is highly competitive and rapidly evolving. New classes of pharmaceuticals and biologics are fuelling the demand for novel drug delivery systems. The anatomy, physiology, and biochemistry of the eye render this

organ exquisitely impervious to foreign substances. The challenge to the formulator is to circumvent the protective barriers of the eye without causing permanent tissue damage[1] The extent of absorption of an ophthalmic drug is severely limited by physiological constraints. Among the factors that limit ocular absorption is the relatively impermeable corneal barrier. The cornea consists of three membranes, the epithelium, the endothelium and inner stroma which are the main absorptive barriers. The epithelium facing the tears with lipophilic cellular layers, acts as a barrier to ion transport. The tight junctions of the corneal epithelium serve as a selective barrier for small molecules and they prevent the diffusion of macromolecules via the paracellular route. The stroma beneath the epithelium is a highly hydrophilic layer making up 90% of the cornea. The corneal endothelium is responsible for maintaining normal corneal hydration. Clearly then, the more lipophilic the drugs are, the more resistance they will find crossing the stroma. The more hydrophilic a drug, the more resistant the epithelium, whereas the stroma and endothelium are limited in their resistance. The conjunctiva is a thin, vascularized mucus membrane that lines the inner surface of the eyelids and covers the anterior part of the sclera up to the cornea. Owing to the relative leakiness of the membrane, rich blood flow and large surface area, conjunctival uptake of a topically applied drug from tear fluid is typically an order of magnitude greater than corneal uptake[2]. The objective of the present review is to describe the various in situ-forming polymeric systems used to achieve prolonged contact time of drugs with the cornea and increase their bioavailability[3]

Recent Formulation Approaches to Improve Ocular Bioavailability

Various approaches that have been attempted to increase the bioavailability and the duration of therapeutic action of ocular drugs can be divided into two categories. The first is based on the use of the drug delivery systems, which provide the controlled and continuous delivery of ophthalmic drugs. The second involves, maximizing corneal drug absorption and minimizing pre corneal drug loss. The typical pulse entry type drug release behavior observed with ocular aqueous solutions (eye drops), suspensions, and ointments can be replaced by a more controlled, sustained, and continuous drug delivery, using a controlled release ocular drug delivery system. These systems can achieve therapeutic action with a smaller dose and a fewer systemic and ocular side effects. Such systems include implantable systems[4], ocuserts[5], collagen shields,[6] but the limitations of these systems include poor patient compliance, need of surgery, and difficulty in self-insertion. Particulate drug delivery systems, like nanoparticles and microspheres, can also be used to improve the residence time of the drug[7]. Upon administration to the eye.

The particles reside at the delivery site and the drug is released from the particles through diffusion, chemical reaction, polymer degradation, or ion-exchange mechanism. Smaller particles are better tolerated by the patients than larger particles and hence microspheres and nanoparticles represent very comfortable prolonged action ophthalmic drug delivery systems. However, some workers observed that nanoparticles consisting of poly damaged the corneal epithelium by disrupting the cell membrane[8] Capacity of some polymers to adhere to the mucin coat covering the conjunctiva and the corneal surfaces of the eye by a non-covalent bond[9] has been exploited to provide an intimate contact between the drug and the absorbing tissue, which may result in high drug concentration in the local area and hence, drug flux through the absorbing tissue[10]. Common disadvantage observed is that the adhesive often detaches itself from the rate controlling drug delivery device and causes premature release of drugs. Increasing the permeability of the corneal epithelial membrane can maximize the transport characteristics across the cornea[11]. Penetration enhancers or the absorption promoters can thus be used to increase the permeability of cell membrane or loosen the tight junctions or both[12]. large numbers of enhancers, like actin filament inhibitors, surfactants, bile salts, chelators, and organic compounds, have been used. However, the unique characteristics and great sensitivity of the corneal conjunctival tissues impose great caution in the selection of enhancers with regard to consideration of their capacity to effect the integrity of the epithelial surfaces.

There is evidence that penetration enhancers themselves can penetrate the eye and may, therefore, lead to unknown toxicological complications, e.g. benzalkonium chloride (BAC) was found to accumulate in the cornea for days[13] EDTA was found to reach the iris-ciliary body in concentrations high enough to alter the permeability of the blood vessels in the tract indirectly accelerating drug removal from aqueous humor[14] Bile salts and surfactants were found to cause irritation of the eye and nasal mucosa[15] Liposomes (vesicular/colloidal systems) are a potentially useful ocular drug delivery system due to the simplicity of preparation and versatility in physical characteristics, but suffer from the disadvantage of instability (due to the hydrolysis of phospholipids normally used in their preparation), limited drug loading capacity, and technical difficulties in obtaining a sterile liposomal preparation. It has been reported that the stearylamine used to prepare positive liposomes was toxic to the cells and also appeared to be irritating to the eye[16]

a. Even though various drug delivery systems mentioned above offer a numerous advantages over conventional drug therapy.
b. Poor patient compliance and difficulty of insertion as in ocular inserts,
c. Tissue irritation and damage caused by penetration enhancers and collagen shields,

d. Toxicity caused by insertion of foreign substances, like albumin and polybutylcyanoacrylate, as in case of nanoparticles and microspheres,
e. Change in pharmacokinetic and pharmacodynamics of the drug as caused by altering the chemical structure of the drug (prodrug approach), and Cell toxicity and ocular irritation caused by stearylamine positive liposomes[17]

Hydrogels

The most common way to improve drug retention on the corneal surface is undoubtedly by using polymers to increase solution viscosity. Hydrogels are polymers endowed with an ability to swell in water or aqueous solvents and induce a liquid–gel transition. Currently, two groups of hydrogels are distinguished, namely preformed and in situ forming gels. Preformed hydrogels can be defined as simple viscous solutions which do not undergo any modifications after administration. In situ forming gels are formulations, applied as solutions, sols, or suspensions, that undergo gelation after instillation due to physic-chemical, changes inherent to the eye[18]. The objective of this review is to describe the various temperature, pH, and ion induced, in situ-forming polymeric systems used to achieve prolonged contact time of drugs with the cornea and increase their bioavailability.

In Situ-Forming Hydrogel

The use of preformed hydrogel 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.[18] In situ-forming hydrogels are liquid upon instillation and undergo phase transition in the ocular cul-de-sac to form visco elastic gel and this provides a response to environmental changes[19]. Three methods have been employed to cause phase transition on the surface: change in temperature55, pH 56 and electrolyte composition[20]

Temperature Induced Gelation

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[21] Different thermal setting gels have been described in this review, including for example Poloxamers, cellulose derivatives, and xyloglucan.

Poloxamers

The Poloxamers consist of more than 30 different non-ionic surface active agents. These polymers are ABA-type tri block copolymers composed of polyethylene oxide (A) and polypropylene oxide (B). The Poloxamer series covers a range of liquids, pastes, and solids, with molecular weights and ethylene oxide–propylene oxide weight ratios varying from 1100 to 14,000 and 1:9 to 8:2, respectively[22]. Poloxamers, commercially available as Pluronic, are the most commonly used thermal setting polymers in ophthalmic technology. They are formed by central hydrophobic part (polyoxypropylene) surrounded by hydrophilic part (ethylene oxide). Depending on the ratio and the distribution along the chain of the hydrophobic and hydrophilic subunits, several molecular weights are available, leading to different gelation properties.

Pluronic F-127, which gives colorless and transparent gels, is the most commonly used polymer in pharmaceutical technology. Concentrated aqueous solutions of Poloxamer form thermo reversible gels. The gelation mechanism of Poloxamer solutions has been investigated extensively, but is still being debated. Ultrasonic velocity, light-scattering and small-angle neutron scattering measurements of aqueous Poloxamer solutions have clearly indicated a micellar mode of association. Micelle formation occurs at the critical micellization temperature as a result of block dehydration. With increasing temperature, micellization becomes more important, and at a definite point, micelles come into contact and no longer move. In addition, the formation of highly ordered structures, such as cubic crystalline phase, has been proposed as the driving force for gel formation, but this hypothesis has been questioned recently[23].

Thus, packing of micelles and micelle entanglements may be possible mechanisms of Poloxamer solution gelation with increased of temperature[24] Furthermore, it has suggested that intra molecular hydrogen bonds might promote gelation[25] The muco mimetic property of Poloxamers is proposed to be due to their hydrophobic and hydrophilic sequences simulating mucin action by adsorption of the aqueous layer of tears on the hydrophobic epithelium. Owing to their protective and muco mimetic action, Poloxamers have also been evaluated for the treatment of dry eye. For example, Flow Base, containing 18% of Poloxamer 407, sodium chloride, and potassium chloride has been shown to possess clinically advantageous properties as a tear substitute. The major drawback of this product is the

formation of solid residues on the eyelids after instillation of 50 µL of solution, this problem being overcome by instillation of smaller volumes[26].Poloxamers have been widely investigated as ocular drug delivery systems. The enhanced activity of pilocarpine in Poloxamer 407 gels when compared with a simple solution has been reported [27] Studying the influence of some parameters on the release rate of solutes from Pluronic F-127 hydrogels in vitro, it is pointed out that increasing polymer concentration decreased the release rate of the drug, whereas increasing drug lipophilicity decreased the release rate[28].

Cellulose Derivatives

Thermo reversible gels can be prepared with naturally occurring polymers. Most natural polymer aqueous solutions form a gel phase when their temperature is lowered. Classic examples of natural polymers exhibiting a sol–gel transition include gelatin and carrageenan. At elevated temperatures, these polymers adopt a random coil conformation in solution. Upon cooling, a continuous network is formed by partial helix formation[29] .Aqueous solutions of ethyl (hydroxyethyl) cellulose also exhibit thermo sensitive behavior. However, their viscosity decreases with temperature. It is reported that the addition of an ionic surfactant, like sodium dodecyl sulfate or cetyl triammonium bromide, to semidilute (1–4 wt.%) EHEC solutions completely changed their thermal behavior. These systems underwent sol–gel phase transition upon heating from room temperature to 30–40 °C, resulting in the formation of stiff and clear gels.[30] The EHEC/surfactant system has been evaluated for the local delivery of anesthaetic agents to the periodontal pocket.[31] They incorporated small amounts of lidocaine and prilocaine into the solution without affecting gelation behavior. The tested formulations showed sustained drug release over a minimum of 60 min, making them interesting for short-term pain control. From a toxicological point of view, the need for inclusion of an ionic surfactant in such a formulation may, however, impair its clinical development.

Xyloglucan

Xyloglucan is the principal hemi cellulose of primary cell walls of dicots and in about half of the monocots. It is structurally related to cellulose as it shares the same backbone of β linked glucose residues. The main repeating unit contains four glucose units. Three out of four glucose units are substituted with α xylose residues. Some xylose units are further substituted by galactose through a β bond. In addition to these sugar units, the galactose residues can be further substituted with α furctose. The XG side chains give raise to radically different physical properties of the polymer compared to cellulose; xyloglucan is highly water soluble and cannot form ordered crystalline microfibrils as cellulose[32] Xyloglucan, a polysaccharide derived from tamarind seed, forms thermo responsive gels in water, under certain conditions. Xyloglucan is composed of aβ-Dglucan backbone chain (GLU) which presents α-D-xylose branches (XYL) partially substituted by (1-2)-β-D-galactoxylose (GAL). Tamarind seed xyloglucan is composed of three units of xyloglucan oligomers with hepta saccharide, octa saccharide and nonasaccharide, which differ in the number of galactose side chains. When xyloglucan is partially degraded by β-galactosidase, the resultant product exhibits thermally reversible gelation in dilute aqueous solutions. Such behavior does not occur with native xyloglucan. Gelation is only possible when the galactose removal ratio exceeds 35%. Xyloglucan formulations were assessed for ocular delivery of pilocarpine; using Poloxamer 407 as a positive thermo sensitive control. The 1.5 wt.% xyloglucan formulation enhanced the miotic response to a degree similar to that of a 25 wt.% Poloxamer 407 gel.72

pH Induced Gelation

Pseudolatexes

Pseudolatexes can be described as artificial latexes prepared by the dispersion of a pre-existing polymer in an aqueous medium. In situ gelling pseudo latexes for ophthalmic use can be described as aqueous colloidal dispersions of polymer, which become viscous gels after instillation in the conjunctival cul-desac due to modification of the pH. Pseudolatexes are obtained by dispersion of an organic solution of a preformed polymer in an aqueous medium, leading to an O/W emulsion. Solvents from the internal phase are then evaporated to obtain a fluid dispersion of polymeric particles with a size generally smaller than 1 µm. Two principal methods are commonly used to prepare ophthalmic pseudo latexes, the solvent evaporation process and the salting out process. Both methods allow the production of a lyophilized and easily redispersible powder. Thus, pseudo latexes have the advantage of ensuring the physical stability of the latex as well as the stability of active compounds such as pilocarpine, which is sensitive to aqueous media. In addition, such systems avoid the use of organic solvents, which can cause problems such as toxicity and pollution. Some prerequisites necessary for an optimal formulation of ophthalmic pseudo latex are listed below:

a. Solubility of the polymer selected in organic solvents as well as insolubility in water.
b. Existence on the macromolecule of ionizable groups, which can react with the electrolytes of the lachrymal fluid.
c. Use of a high molecular weight polymer.

d. Rapid coagulation process after instillation to avoid precorneal drainage of the instilled formulation before the phenomenon of gelation appears.
e. Compatibility of the different components of the colloidal dispersion with precorneal tissues.[33]

Cellulose acetate phthalate latex

First preliminary investigations of pH sensitive nano particulate system for ophthalmic administration began in the early 1980s. The choice of this polymer was determined by the compatibility of the polymer with the active compound, the ability of the CAP latex to be a free-running solution at pH 4.2 and a gel at 7.2, and finally, the latex stability at relatively low pH which is a prerequisite to ensuring the stability of pilocarpine. The gelation capacity of CAP latexes has been visualized in vitro by scanning electron microscopy and in vivo in rabbits by incorporating methylene blue in ophthalmic formulations. The efficacy of a preparation based on pseudolatex has been evaluated by measuring pharmacological responses and precorneal residence time by γ scintigraphy. This technique has clearly demonstrated the superiority of CAP latex over a solution to prolong the corneal residence time of pilocarpine. Finally, it is important to note that irritation tests on rabbits including examination of the cornea, the iris and the conjunctiva have demonstrated that the investigated pseudolatexes did not induce irritation. However, a sensation of discomfort seems to be unavoidable after the coagulation of the solution in the cul-de-sac as is the case for any semisolid preparation[34]

Carbomer

Carbopol 934 is a synthetic polymer composed of 62% of carboxyl groups with a high molecular weight (approximately 3×106) formed by repeating units of acrylic acid, cross-linked with either allylsucrose or allylethers of pentaerythritol[35] Carbopol offers the advantage of exhibiting excellent mucoadhesive properties when compared with other polymers (e.g. cellulose derivatives, and polyvinyl alcohol).

The mechanisms involved in the mucoadhesion ability of Carbopol have been investigated previously. Four mechanisms of interaction between mucin and poly (acrylic acid) have been described: electrostatic interaction, hydrogen bonding, hydrophobic interaction, and inter diffusion. These mechanisms can be explained by the similar features of the mucus network and the cross-linked poly (acrylic acid): macromolecular expanded network, negative charges, and significant hydration in aqueous media and significant number of carboxyl groups[36] The efficacy of Carbopol in enhancing precorneal residence time has been extensively studied by incorporating tracers such as sodium fluorescein[37]or active compounds such as pilocarpine or prednisolone.[38.] Carbopol is a polyacrylic acid (PAA) polymer, which shows a sol to gel transition in aqueous solution as the pH is raised above its pKa of about 5.5.[39]. They have also developed a similar delivery system by a combination of Carbopol and hydroxypropylmethylcellulose. For both systems it was found that a reduction in the Carbopol concentration without compromising the in situ gelling properties as well as overall rheological behaviors can be achieved by adding a suitable viscosity enhancing polymer[40]

Osmotically induced gelation

In this method, gelling of the solution instilled is triggered by change in the ionic strength[41]

Gelrite

Gellan gum is a linear, anionic hetero polysaccharide secreted by the microbe Sphingomonas elodea (formerly known as Pseudomonas elodea). The polysaccharide can be produced by aerobic fermentation and then isolated from the fermentation broth by alcohol precipitation. The polymer backbone consists of glucose, glucuronic acid, and rhamnose in the molar ratio 2:1:1.[42].These are linked together to give a tetrasaccharide repeat unit. The native polysaccharide is partially esterified with L-glycerate and acetate [43], but the commercial product Gelrite has been completely de-esterified by alkali treatment.[44] Gelrite is one of the most interesting in situ gelling polymers that has been tested since it seems to perform very well in humans. Gelrite has been granted regulatory approval as pharmaceutical excipient and is marketed by Merck in a controlled-release glaucoma formulation called Blocarden Depot. Formulations with the Gelrite can be administered to ocular mucosa as a lowviscosity solution. On contact with cations in tear fluid theformulation will form a clear gel[45] This is caused by cross linking of the negatively charged polysaccharide helices by monovalent and divalent cations (Na+, K+, Ca+). Several models have been presented to explain gellan gum gelation.

The model proposed by Robinson[46] will be discussed in more detail here and it will be partially supplemented to describe a more pharmaceutically relevant situation. In an ion free aqueous medium, Gelrite forms double helices at room temperature. This solution has a viscosity close to that of water and the helices are only weakly associated with each other (by vander Waals attraction). When gel-promoting cations are present, some of the helices associate into cation-mediated aggregates, which cross-link the polymer. On heating the polysaccharide in an ionfree environment, the polysaccharide becomes a disordered coil. However, on heating a sample with cations present, the

nonaggregated helices melt out first, and the aggregated helices melt out at a higher temperature in a second transition. The divalent ions such as magnesium or calcium were superior to monovalent cations in promoting the gelation of the polysaccharide.86 However the concentration of sodium in tears (2.6 g/L) is quite sufficient to induce the gelation. Corneal contact time of formulations based on gellan gum has been investigated using two main methods, which are fluorometry [47] and γ scintigraphy[48]. Both technique have demonstrated improved residence times with Gelrite when compared with saline or various commercial solutions.

Gelrite has also provided corneal residence times superior to those of other hydrogel preparations based on polymers such as cellulosic derivatives or xanthan gum. The rheological properties of gellan gum such as thixotropy, pseudoplasticity, and thermoplasticity are further advantages for its use in ophthalmology: the fluidity of the solution can be increased simply by shaking or slightly warming the preparation[49] Carrageenans, a group of natural, water-soluble, sulphatedgalactans extracted from red seaweed, showed similar features to gellan gum regarding their rheological behavior, gelling properties, and tolerance. This suggested that they could be interesting polymers for prolonging the residence time of topical ocular formulations[50]

Alginates

Alginates consist of linked β-D-mannuronic acid and α-Lguluronic acid residues of widely varying composition and sequence. By partial acid hydrolysis, alginate was separated into three fractions[51] Two of these contained almost homo polymeric molecules of G and M, respectively, while a third fraction consisted of nearly equal proportions of both monomers and was shown to contain a large number of MG dimer residues. It was concluded that alginate could be regarded as a true block copolymer composed of homo polymeric regions of M and G, termed M- and G-blocks, respectively, interspersed with regions of alternating structure. It was further shown that alginates have no regular repeating unit and that the distribution of the monomers along the polymer chain could not be described by Bernoullian statistics. Knowledge of the monomeric composition is hence not sufficient to determine the sequential structure.of alginates.[52,53]

Alginate with a high guluronic acid content will improve the gelling properties and reduce the total polymer to be introduced into the eye. The alginate forms 3-dimensional ionotropic hydrogel matrices, generally by the preferential interaction of calcium ions with the G moieties resulting in the formation in homogeneous gel. The characteristic properties of these hydrogels, such as mechanical strength and porosity, are dependent upon the G:M ratios, type of ionic crosslinker (bioor poly-valent cations), concentration and viscosity of the initial alginate solution. Calcium-crosslinked alginate gels have shown good mechanical properties even when prepared from relatively low solution concentrations of the polymer, 0.5% w/v, and they can physically entrap a whole array of molecules, and sustain their release[54]

Table 1: Formulation of marketed products[55]

Formulation Approach	Polymer/base	Product	Company
Suspensions/ Micropaticulates	Carbomer ion exchange resin	Betoptic S	Alcon
Ointments	Wool fat, liquid paraffin, white soft paraffin,	Polyvisc	Alcon
Viscosity enhancers	PEG,PG.HP-guar, Dextran, HPMC, Na CMC,PVA,Hyaluronic acid	Systane Bion tears Refresh Hy-drops	Alcon Alcon Allergan Bausch & Lomb
Insitu gelling systems	Gellan gum Xanthan gum	Timoptic XE Timoptic GFS	Merck Alcon
Prodrugs	Dipivefrin HCl (epinephrine prodrug)	Propine	Allergan
Ocular inserts	Alginic acid Hydroxypropyl cellulose Silicone elastomer Collagen shield	Ocusert Lacrisert Ocufit SR MediLens	Alza Corp. Merck. Escalon Medical Corp. Chiron.

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3. Conclusion

The development of ophthalmic drug delivery systems is easy because we can easily target the eye to treat ocular diseases and complicated at the same time because the eye has specific characteristics, which make the development of ocular drug delivery systems extremely difficult. The most widely developed drug delivery system is represented by the polymeric hydrogels. Hydrogels generally offer a moderate improvement of ocular drug bioavailability despite their favorable bioadhesive properties. One of the disadvantages is that hydrogel may result in blurred vision as well as foreign body sensation to patients. In situ activated gel-forming systems seem to be preferred as they can be administered in drop form and create significantly less problems with vision. Moreover, they provide good sustained release properties. Over the last decades, an impressive number of novel temperature, pH, and ion induced in-situ forming solutions have been described in the literature. Each system has its own advantages and drawbacks. The choice of a particular hydrogel depends on its intrinsic properties and envisaged therapeutic use.

4. References

1. Ashim KM; Ophthalmic drug delivery system. Marcel Dekker: New York; USA; **1993**; 58:105-110.
2. Indu P, Kaur AG, Anil KS, Deepika A. Vesicular systems in ocular drug delivery an overview. Int J Pharm. **2004**; 269: 1-14.
3. Saettone M.F. Progress and problems in ophthalmic drug delivery. **2002**; 167-172.
4. Kunou N, Ogura Y, Hashiozoe M, Controlled intraocular delivery of ganciclovir with use of biodegradable scleral implant in rabbits, J. Control. Release. **1995**,37, 143–150.
5. Saettone M.F, Salimen L, Ocular inserts for topical delivery, Adv. Drug Deliv. Rev. **1995**,16, 95–106.
6. Poland D.E, Kaufman H.E, Uses of collagen shields, J. Cataract Refract. Surg. 14 1988,14, 489–491.
7. Kreuter J, Bioadhesive Drug Delivery Systems, CRC Press, Boca Raton, FL, **1990**, pp. 203–212.
8. Zimmer A.K., Kreuter J, Studies on the transport pathway of PBCA nanoparticles in ocular tissues, J. Microencapsules.**1991**,8, 497–504.
9. Hui H.W, Robinson J.R, Ocular delivery of progesterone using a bioadhesive polymer, Int. J. Pharm. **1985,**26, 203–207.
10. Park K, Robinson J.R, Bioadhesive polymers as platform for oral controlled drug delivery: method to study bioadhesion, Int. J. Pharm. **1984**, 191,107–110.
11. Lee V.H, Precorneal and postcorneal factors, in: A.K. Mitra (Ed.), Ophthalmic Drug Delivery Systems, Marcel Dekker, New York, **1993**, pp. 59–82.
12. Kaur I.P.,Smitha R, Penetration enhancers and ocular bioadhesives: two new avenues for ophthalmic drug delivery, Drug Dev. Ind. Pharm. **2002**,28,353–369.
13. Green K, Chapman J.M, Cheeks J.L, Ocular penetration of pilocarpine in rabbits, J. Toxicol. **1987**, 2, 89–107.
14. Grass J.M., Robinson J.R., Relationship of chemical structure to corneal penetration and influence of low viscosity solution on ocular bioavailability, J. Pharm. Sci.**1984**, 73,1021–1027.
15. Merkus F, Schipper N,Hermeus W, Absorption enhancers in nasal drug delivery: efficacy and safety, J. Control. Release 1993,24, 201–208.
16. Kaur I.P., Kanwar M, Ocular preparations: the formulation approach, Drug Dev. Ind. Pharm. **2002**,28(5), 473–493.
17. Bourlais C.L., Acar L, Zia H, Sado P.A, Needham T, Leverge R, Ophthalic Drug Delivery Systems-Recent advances, Prog. Retin. Eye Res. **1998**,17, 33–58.
18. Kumar S, Haglund B.O.,Himmelstein K.J, In situ-forming gels for ophthalmic drug delivery, J. Ocul. Pharmacol.**1994**,10(1) 47–56.
19. Miller S.C., Donovan M.D., Effect of poloxamer 407 gel on the miotic activity of pilocarpine nitrate in rabbits, Int. J. Pharm. **1982**, 12,147–152.
20. Gurny R, Boye T, Ibrahim H, Ocular therapy with nanoparticulate systems for controlled drug delivery, J. Control. Release, **1985**, 2, 353–361.
21. Moorhouse R, Colegrove G.T, Sandford P.A, Baird J.K, a new gel-forming polysaccharide, in: D.A. Brant (Ed.), Solution Properties of Polysaccharides. ACS Symposium series, Washington-DC, **1981**, pp. 111–124.
22. Hoffman A.S., Afrassiabi A, Dong L.C., Thermally reversible hydrogels: II. Delivery and selective removal of substances from aqueous solutions, J. Control. Release, **1986**, 4, 213–222.
23. Gariepy E.R, Leroux J.C, In situ-forming hydrogels—review of temperature-sensitive systems, Eur. J. Pharm. Biopharm. **2004,** 5 8, 409–426.
24. Cabana A, Ait-Kadi A., Juhasz J, Study of the gelation process of polyethylene oxide-polypropylene oxide–polyethylene oxide copolymer (poloxamer 407) aqueous solutions, J. Colloid Interface Sci.**1997**,190, 307–312.

25. Miller S.C, Drabic B.R., Rheological properties of poloxamer vehicles, Int. J. Pharm. **1984**, 18,269–276.
26. Waring G.O, Harris R.R, Symposium on Ocular Therapy, Wiley, New York, **1979**, pp. 127–140.
27. Gilbert J.C, Hadgraft J, Bye A, Brookes L.G, Drug release from Pluronic F-127 gels, Int. J. Pharm. **1986**, 32, 223–228.
28. Schmolka I.R., Artificial skin 1. Preparations and properties of Pluronic F-127 gels for treatment of burns, J. Biomed. Mater. Res. **1972**, 6, 571–582.
29. Kamel A.H., In vitro and in vivo evaluation of Pluronic F127-based ocular delivery system for timolol maleate, Int. J. Pharm. **2002**, 241, 47–55.
30. Harrington W.F, Hippel P.H., The structure of collagen and gelatin, Adv. Protein Chem. 1961,16, 1–138.
31. Carlsson A.,Karlstrom G.,Lindman B.,Stenberg O., Interaction between ethyl(hydroxyethyl)cellulose and sodium dodecyl sulphate in aqueous solution, Colloid Polym. Sci. **1988**, 266,1031–1036.
32. Scherlund M., Brodin A., Malmstem M., Nonionic cellulose ethers as potential drug delivery systems for periodontal anesthesia, J. Colloid Interface Sci. **2000**, 229,365 -374.
33. Fry S.C, The structure and functions of xyloglucan, J. Exp. Bot.**1989**, 40, 1–11.
34. Shirakawa M., Yamatoya K., Nishinari K, Tailoring xyloglucan properties using an enzyme, Food Hydrocoll. **1998**, 22, 25–28.
35. Miyazaki S., Suisha F., Kawasaki N., Shirakawa M., Yamatoya K., Attwood D, Thermally reversible xyloglucan gels as vehicles for rectal drug delivery, J. Control. Release, **1998**, 56, 75–83.
36. Miyazaki S., Suzuki S., Kawasaki N., Endo K., Takahashi A. , Attwood W., In situ gelling xyloglucan formulations for sustained release ocular delivery of pilocarpine hydrochloride, Int. J. Pharm. **2001**, 229, 29–36.
37. McGinity J.M., Harris M.R., Patel K, Davis S.S., Carbomer. Handbook of Pharmaceutical Excipients. American Pharmaceutical Association. Washington-DC, USA. The Pharmaceutical Society of Great Britain, England, **1986**, pp. 41–42.
38. Leung S.S., Robinson J.R., The contribution of anionic polymer structural features to mucoadhesion, J. Control. Release, **1988**,5, 223–231.
39. Chrai S.S., Robinson J.R., Ocular evaluation of methylcellulose vehicle in albino rabbits, J. Pharm. Sci. **1974**, 63, 1218–1222.
40. Saettone M.F., Giannaccini B., Guiducci A., Savigni P., Semisolid ophthalmic vehicles. III. An evaluation of four organic hydrogels containing pilocarpine, Int. J. Pharm. **1986**, 31, 261–270.
41. Davies N.M., Farr S.J., Hadgraft J.,Kellaway I.W., Evaluation of mucoadhesive polymers in ocular drug delivery. I. Viscous solutions,Pharm. Res. **1991**, 8(8): 1039–1043.
42. Patton T.F., Robinson J.R., Ocular evaluation of polyvinyl alcohol vehicle in rabbits, J. Pharm. Sci.**1975**, 64(8): 1312–1316.
43. Kumar S., Himmelstein K.J., Modification of in Situ Gelling Behavior of Carbopol Solutions by Hydroxypropyl Methylcellulose, J. Pharm. Sci.**1995**, 84(3): 344–348.
44. Bhaskaran S., Lakshmi P.K., Harish C.G., Topical ocular drug delivery— a review, Ind. J. Pharm. Sci. **2005**, 67(4): 404–408.
45. Jansson. P.E., Lindberg B., Structural studies of gellan gum, an extracellular polysaccharide elaborated by Pseuomonas elodea, Carbohydr. Res.**1983**, 124: 135–139.
46. Kuo M.S., Mort A.J., Dell A., Identification and location of L-glycerate, an unusual acyl substituent in gellan gum, Carbohydr. Res. **1986**,156: 173–187.
47. Morris V.J., Bacterial polysaccharides, and Food polysaccharides and their application, Marcel Dekker, New York, **1995**, pp. 341–375.
48. Rozier A., Mazuel C., Grove J., Plazonnet B., a novel ionactivatedin situ gelling polymer for ophthalmic vehicles. Effect on bioavailability of timolol, Int. J. Pharm. **1989**, 57:163–168.
49. Robinson G, Manning C.E, Morris E.R., Conformation and physical properties of the bacterial polysaccharides gellan, welan and rhamsan, in: E. Dickinson (Ed.), Food polymers, gels, and colloids, Royal Society Chemistry, London, **1991**, 7, 342-349.
50. Kang K.S., Veeder G.T., Mirrasoul P.J., Kaneko T., Agar like polysaccharide produced by a Pseudomonas species: production and basic properties, Appl. Environ. Microbiol. **1982**, 43: 1086–1091.
51. Maurice D.M., Srinivas S.P., Use of fluorometry in assessing the efficacy of a cation-sensitive gel as an ophthalmic vehicle: comparison with scintigraphy, J. Pharm. Sci. **1992**, 81: 615–618.
52. Meseguer G., Gurny R., Buri .P, Rozier A., Plazonnet B., Gamma scintigraphic study of precorneal drainage and assessment of mioticresponse in rabbits of various ophthalmic formulations containingpilocarpine, Int. J. Pharm. **1993**, 95, 229–234.
53. Deasy P.B., Quigley K.J., Rheological evaluation of deacetylated gellangum (Gelrite) for pharmaceutical use, Int. J. Pharm. **1991**,73: 117–123.

54. Haug A., Larsen B., Smidsrod O. , A study of the constitution of alginic acid by partial hydrolysis, Acta Chem. Scand. **1966**, 20: 183–190.
55. Painte T.J., Smidsrod O.,Haug A., A computer study of the changes in composition distribution occurring during random depolymerisation of a binary linear heteropolysaccharide, Acta Chem. Scand. **1968**, 22: 1637–1648.