

Polymers used in ocular dosage form and drug delivery systems

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Topical application of drugs to the eye is most popular and well-accepted route of administration for the treatment of various eye disorders. A variety of ocular dosage form and drug delivery systems, including a controlled release of the drug, drug targeting, and penetration enhancement of the drug, have been investigated. Polymers have been widely used as the drug carrier for controlled-release systems. Polymers release the drug as they themselves degrade and are sometimes finally absorbed within the body. In this article, several ocular drug delivery systems have discussed using different kinds of polymers and their acceptance over conventional.

Key words: Ocular dosage form, ocular drug delivery systems, polymers

INTRODUCTION

The need for ophthalmic medications is continuously increasing as the populations of the industrialized nations age. The development of new products for treatment of ophthalmic diseases is facing a double challenge: pharmacology and drug delivery. In addition to factors concerning the high tolerability/comfort requirements, the eye^[1-3] presents two difficult and challenging problems for drug delivery: the first is specific to hydrophobic new chemical entity (NCEs), which usually lack suitable vehicles. The second obstacle is general to all ocular products: the low ocular bioavailability of topically applied drugs - a well known and extensively - reviewed issue.

Whenever an ophthalmic drug is applied topically to the anterior segment of the eye, only a small amount (5%) actually penetrates the cornea and reaches the internal anterior tissue of the eyes. Rapid and efficient drainage by the nasolacrimal apparatus, noncorneal absorption, and the relative impermeability of the cornea to both hydrophilic and hydrophobic molecules, all account for such poor ocular bioavailability. The various approaches that have been attempted to increase the bioavailability and the duration of the therapeutic action of ocular drugs can be divided into two categories. The first one is based on the use of sustained drug delivery systems, which provide the

controlled and continuous delivery of ophthalmic drugs, such as implants, inserts, and colloids.^[4] The second involves maximizing corneal drug absorption and minimizing precorneal drug loss through viscosity and penetration enhancers, prodrugs, and colloids. Recently, one of the approaches developed is the drug incorporation into cationic submicron vectors, which bind the anionic charges present at the corneal surface for the increased residence time and penetration.^[5] Drug delivery to the posterior eye, where 40% of main ocular diseases are located, is another great challenge in ophthalmology. To date, invasive treatments are used due to the lack of alternatives, requiring the most careful assessment to guarantee biocompatibility and lack of toxicity to the internal structure of the eye. In addition to invasive approaches, topically applied drugs were shown to reach the back-of-eye tissues through trans-conjunctival-scleral diffusion after multiple instillations.^[6]

POLYMERS USED IN CONVENTIONAL OCULAR DOSAGE FORM (ODF)

Liquid dosage forms

The polymers used in liquid form to improve the ocular bioavailability of drug, to increase the viscosity of the preparation, to reduce the drainage rate. Polymer hydration results in the relaxation of stretched; twisted macromolecules which exposes the adhesive sites. The high molecular weight polymers capable of forming hydrogen bonds and cannot cross the biological membrane can ultimately increase the residence time. About 1,00,000 Da of molecular

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weight of polymer require for successful mucoadhesion. The cellulose derivatives are employed in the liquid dosage forms as viscosity enhancing ophthalmic vehicle. The hydroxypropylmethyl cellulose (HPMC) and hydroxypropyl cellulose (HPC) are pH-sensitive polymers also exhibit surface-active properties influencing the blinking rate with ultimately alters the elimination of the drug instilled.^[7] The poly(acrylic acid) (PAA) and carbomers were the first mucoadhesives polymers and the protonated form at an acidic pH responsible for the mucoadhesion.^[8] The polyacrylates or carbomers are used in dry eye syndrome as artificial tears. The natural polymer solution of sodium hyaluronase have been employed successfully as tear substitutes in severe dry eye disorders.^[9] Chitosan micro or nanoparticles have higher precorneal retention than chitosan solutions. The mucoadhesive property is higher in the chitosan suspension than in solution.^[10] Cyclodextrins (CDs) are shown to be nontoxic to the eye, but are well tolerated in eye drop formulation, e.g. cyclosporin A.^[11,12] The polygalacturonic acid, xyloglucan, xanthan gum, and gellan gum show delay of clearance of the instilled solution. Thiomers are capable of cross-linking with mucins results in a tremendous increase in dispersion of medium. CDs are cyclic oligosaccharides commonly composed of 6-8 α -D-glucose units that have a shape like a truncated cone. The complex has a hydrophobic interior that is capable of encapsulating poorly soluble drugs. The hydrophilic exterior allows for solubilization, thus making these complexes useful for formulation of hydrophobic drugs. The ability of CDs to solubilize hydrophobic drugs and provide a hydrophilic exterior makes it useful for ocular applications. The sensitive nature of corneal epithelium precludes the use of certain CDs due to their toxicity. Jansen *et al.*^[13] found that dimethyl- β -cyclodextrin is toxic to the cornea and thus should not be used for corneal ophthalmic formulations. Hence, extensive corneal sensitivity studies should be conducted while developing new formulations of CDs.

Aktas *et al.*^[14] studied the effect of hydroxypropyl β -cyclodextrin on the corneal permeation of pilocarpine nitrate using isolated rabbit cornea. Corneal permeation of pilocarpine nitrate was found to be four times higher after adding β -cyclodextrin into the formulation. The highest miotic response was obtained with the formulation prepared in a vehicle of Carbopol 940.

Luma *et al.*^[15] invented two new surface-active polymers of different molecular weight for ophthalmic irritation potential *n*-octenylsuccinate starch (AS). Poly(ortho esters) (POE) are hydrophobic and biodegradable polymers that have been investigated for pharmaceutical use.^[16] Among different described generations, (POE III) and (POE IV) are promising viscous and injectable material. The report by Ghelardi *et al.*^[17] describes the efficacy of a novel mucoadhesive polymer, the tamarind seed polysaccharide, as a delivery system for the ocular administration of hydrophilic and hydrophobic

antibiotics. The result showed that there is increasing in the residence time and prolonged drug elimination phase obtained with viscosified formulations.

Semisolid dosage forms

The *in situ* gels formed when liquid vehicles undergo a viscosity increase upon instillation in the eye, thus favoring precorneal retention. However, these appears to be only by a change in temperature, pH, or electrolyte composition.^[18,19] Poloxamer 407 is a polymer with a solution viscosity that increases when its temperature is raised to the eye temperature.^[20] Celluloseacetophthalate,^[21] polymer undergoing coagulation when the original pH of the solution (4.5) is raised to 7.4 by the tear fluid, these are used to formulate hydrogels. The hydrogels containing high concentrations of polymers are used in dry eye symptoms. But apart from the reproducible administration of a dose compared to the application of performed gels, the hydrogels can cause discomfort at the daytime and cause blurred vision. The methyl cellulose (MC), hydroxy ethyl cellulose (HEC) are used along with the charged surfactant in the timolol (TM) controlled-release formulation. Poly(acrylic acid) forms hydrogen bonds between its -COOH groups and -sialic-COOH groups of the mucin glucoprotein which can cause a significant increase in the viscosity. Thus acrylic compounds can also used as hydrogels to treat ocular irritation.^[22] The gellan gum forms a clear gel in presence of mono or divalent cations suitable for gelling system in glaucoma therapy.^[23,24] The hyaluronase and chitosan also used in dry eye syndrome.^[25-27] Alginate is insoluble in water, but its salts form clear gel (sodium alginate) can be used in various hydrogel formulations.^[28] Nyogel from Novartis containing carbomer and polyvinyl alcohol (PVA) as eye gel are popular in UK.^[6]

Lin and Sung,^[29] prepared carbopol-pluronic phase change solution for ophthalmic drug delivery. The gel mixture of carbopol/pluronic can be used as an *in situ* gelling vehicle to enhance the ocular bioavailability. The pluronic F-127 gels consists of approximately 70% ethylene oxide and 30% propylene oxide with an average molecular weight of 11500. Unique characterization of this polymer is reverse thermal gelation and this can be used for ophthalmic drug delivery. Desai *et al.*^[30] developed pluronic F127 (PF127)-containing formulations of pilocarpine hydrochloride (PHCL) suitable for controlled-release ocular delivery of PHCL. It was observed that the PEG- and PVP-containing PF127 formulations of PHCL dissolved the quickest and released the drug at a significantly faster rate than the control PF127 formulation, which had no additive present. Wilson *et al.*^[31] developed the novel method of radiolabelling carbomer gels, with minimum change to their rheology that had permitted the noninvasive evaluation of precorneal residence of the gel in volunteers using gamma scintigraphy. The technique was used to evaluate the precorneal clearance of the liquid phase and of a suspended particulate in Gel Tears.

OCULAR DRUG DELIVERY SYSTEMS (ODDS)

Ophthalmic inserts/films

The dry formulation achieved by adhesion via dehydration of the local mucosal surface. The ocular inserts, ocular films, wafers, and rods are solid devices which are placed in the cornea, *cul-de-sac*. These are having advantages over liquid formulation of longer retention time, accurate dosing, increased stability, and shelf life.^[32] The recent study has indicated that ocular inserts incorporating a bioadhesive polymer, thiolated PAA are most useful one. Sultana *et al.*^[33] developed ocular inserts using PVP K-30 and Eudragit. Lee *et al.*^[34] formulated the ocular insert containing phenylephrine and tropicamide containing Gelfoam R. The Gelfoam is a versatile drug carrier for either local or systemic drug delivery via ophthalmic route. Gurny *et al.*^[35] prepared bioadhesive ophthalmic drug inserts of gentamycin using HPMC, ethyl cellulose. The water-soluble cellulose derivatives and PVA are also used in preparing inserts by solvent casting method. The Poly(ethylene oxide) developed gel-forming erodible inserts for controlled delivery of drugs. Other nonbiodegradable bio-adhesive materials for drug release have been used, are vinyl-pyrrolidone, poly(amidoamine) dendrimers, and poly(dimethyl siloxane). Hiratani *et al.*^[36] developed soft contact lenses of TM capable of prolonging the permanence of TM in the precorneal area, compared to conventional contact lenses and eyedrops. Soft contact lenses consisted of *N,N*-diethylacrylamide (DEAA; main component of the matrix), methacrylic acid (MAA; functional monomer), and ethyleneglycol dimethacrylate (EGDMA; cross linker) were prepared. Grzeskowiak,^[37] formulated solid ocular inserts made of poly (vinyl alcohol), containing sulfadiazine.

Wang *et al.*^[38] studied *in vitro* and *in vivo* evaluation in rabbits of a controlled release 5-fluorouracil subconjunctival implant based on poly(D,L-lactide-co-glycolide). Thiomers, which can form covalent disulfide bridges with cysteine rich subdomains of mucin, have used to prepare ocular inserts. Inserts made of thiomers were not soluble and had good cohesive properties, due to the formation of inter- and/or intrachain disulfide bonds within the polymeric network after hydration. Hornhof *et al.*^[39] formulated inserts (diameter 2 mm) consisting of PAA 450-cysteine conjugate, a thiolated PAA 450 kDa, were prepared by direct compression and evaluated by fluorophotometry. The general irritation score indicated that the inserts were well accepted and tolerated. In humans, the Bionite lens that was made from hydrophilic polymer (2-hydroxy ethyl methacrylate) has been shown to produce a greater penetration of fluorescein. Intraocular drug delivery systems made from biodegradable polymers also hold great potential to effectively treat chronic diseases of the posterior segment of the eye. The cross-linked poly(propylene fumarate) (PPF)-based matrices are suitable long-term delivery devices for the sustained release of the antiinflammatory drug fluocinolone acetonide (FA) due to their hydrophobicity and network density.^[40]

Microspheres and nanoparticles

These colloidal particles have the advantage that they may be applied in liquid form just like eye drop solutions. Thus they avoid the discomfort that is combined with the application of viscous or sticky preparations such as ointments. The latter preparations lead to a total blurring of vision if they are properly utilized. Large inserts, on the other hand, are difficult to administer or if they are designed as nondissolving inserts they are even more difficult to remove, especially by elderly patients. Another potential advantage is the targeting of the drug to the site of action, leading to a decrease in the dose required and a decrease in side effects.^[41] So far, various synthetic and natural biocompatible polymers have been used to manufacture microspheres for ocular drug delivery [Table 1].^[42] Particulates such as nanoparticles, nanocapsules, submicron emulsions, and nanosuspensions improved the bioavailability of ocularly applied drug. Chitosan is a cationic natural polymer that has been used to produce complexes as well as micro and nanoparticles drug delivery systems intended for topical ocular drug delivery. De *et al.*^[43,44] used polycarboxylic acid carriers such as polyacrylic acid and polyitaconic acid in subcolloidal, nanoparticulate hydrogel form that have a strong potential for sustained release of a drug in ocular delivery. Leucuta studied *in vitro* kinetic and miotic response in rabbits reported the prolonged effect of drugs (pilocarpine, piroxicam) incorporated in albumin particles compared to commercial preparations or aqueous and viscous solutions.^[45] Topical application of hydrocortisone-loaded albumin particles in rabbits led to a lower tissue concentration compared to a solution, due to the strong binding of the drug to the particles. Kyyronen *et al.*^[46] evaluated the release of methyl prednisolone from particles consisting of hyaluronic acid (HA) esters has been *in vitro* and *in vivo* on rabbits. The drug was physically dispersed in the matrix or covalently bound to the polymer. When chemically bound to the HA backbone, the drug release was slower when compared to a suspension *in vitro*, but caused a sustained drug concentration in the tear film in rabbits. Cavalli *et al.* evaluated the use of solid lipid nanoparticles (SLN) as carriers for tobramycin. Compared to commercial eye drops, the tobramycin-loaded SLN produced a significantly higher bioavailability: C_{max} increased 1.5-fold and area under curve fourfold. The SLN dispersion was perfectly tolerated and there was no evidence of ocular irritation.^[47]

Table 1: Nano- and microparticulate polymers in ophthalmology

Drug	Polymer
Amikacin	Poly(butyl) cyanoacrylate
Betaxolol	Poly(epsilon) caprolacton
	Poly(isobutyl) cyanoacrylate
	Poly(lactic-co-glycolic acid
Carteolol	Poly(epsilon) caprolacton
Chloramphenicol	Poly(lactic acid
Hydrocortisone	Albumin
Indomethacin	Poly(epsilon) caprolac
Pilocarpin	Albumin

Ion exchange resins

Ion exchange is a reversible chemical reaction wherein an ion from solution is exchanged for a similarly charged ion attached to an immobile solid particle. These solid ion exchange particles are either naturally occurring inorganic zeolites or synthetically produced organic resins.^[48,49] Jani *et al.*^[50] developed novel delivery system for ophthalmic drugs using an antiglaucoma agent betaxolol hydrochloride. Delivery system involved both the binding and release of drug from ion exchange resin particles. The amount of resin concentration was selected to obtain optimum binding of the drug. Drug resin particles were then incorporated into the structured vehicle, containing Carbomer 934P as a polymer, to enhance the physical stability and ease of resuspendability of the product. Moreau *et al.*^[51] employed an experimental rabbit model of Staphylococcus keratitis, compared the effectiveness of two commonly prescribed formulations of fluoroquinolones to an experimental formulation, ciprofloxacin with polystyrene sulfonate (ciprofloxacin-PSS), ciprofloxacin, and ofloxacin. Lele and Hoffman developed a new mucoadhesive drug delivery formulation based on an ionic complex of partially neutralized PAA and a highly potent beta blocker drug, levobetaxolol \times hydrochloride (LB \times HCl), for use in the treatment of glaucoma.^[52] Complexes were prepared with varying degrees of drug loading, such that the same PAA chain would have free -COOH groups for mucoadhesion along with ionic complexes of LB \times H⁺ with COO⁻ groups. Chang formulated a sustained release pharmaceutical compound delivery composition having improved delivery characteristics and enhance long-term storage stability, said composition comprising nonionic liquid suspension of microparticulates formed of an erodible bioadhesive polymeric matrix of poly and polyvinylpyrrolidone wherein the ratio of poly(methylvinylether/maleic anhydride) to polyvinylpyrrolidone ranges from approximately 1:1 to 4:1 by weight, incorporating at least one ion exchange resin said ion exchange resin particle having approximately 2-50 wt.% of a pharmaceutical compound releasably bound.^[53]

Gene delivery

Nonviral vectors for potential gene replacement and therapy have been developed to overcome the drawbacks of viral vectors. The diversity of nonviral vectors allows for a wide range of various products, flexibility of application, ease of use, low-cost of production, and enhanced “genomic” safety.^[54] Using nonviral strategies, oligonucleotides (ODNs) can be delivered naked (less efficient) or entrapped in cationic lipids, polymers or peptides forming slow release delivery systems, which can be adapted according to the organ targeted and the therapy purposes. Changing by physical or chemical means can further enhance tissue and cell internalization.^[55] Moreover, a specific vector can be selected according to disease course and intensity of manifestations fulfilling specific requirements such as the duration of drug release and its level along with cells and tissues specific targeting nonviral delivery systems have

been developed with the hope of overcoming some of the problems associated with viral gene delivery. In nonviral methods, some types of lipid vehicle, usually a cationic liposome, chitosan, or a cationic biopolymer, etc. are used as gene carriers.^[56] However, in developing nonviral gene carriers, those that are efficient *in vitro* often fail to show the same efficiency when applied *in vivo*. The reasons for poor efficacy *in vivo* could be the sensitivity of the carrier to serum, the stability of complex formation between DNA and the carrier and unknown mechanisms of cellular uptake, and intracellular trafficking of the complex. Liaw *et al.*^[57] studied *in vivo* gene delivery into ocular tissues by eye drops of Poly (ethylene oxide)-b poly(propylene oxide)-b-poly(ethylene oxide) (PEO-PPO-PEO) polymeric micelles. Julie *et al.*^[58] developed, controlled release of gene therapy vectors from hydrogels using different polymers as a function of the physical properties for both the hydrogel and the vector. Hydrogels were formed by photocrosslinking acryl-modified HA with a 4-arm poly(ethylene glycol) (PEG) acryl. The polymer content and relative composition of HA and PEG modulated the swelling ratio, water content, and degradation, which can influence transport of the vector through the hydrogel. Chun *et al.*^[59] formulated, chemically cross-linked hydrogels composed of Pluronic, water-soluble tri-block copolymers of poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide), were synthesized by a photo-polymerization method to achieve controlled DNA release. Pluronic F127 was di-acrylated to form a macromer and cross-linked to form a hydrogel structure in the presence and absence of vinyl group-modified (HA UV irradiation). Urtti investigated the permeation of liposomal and polymeric gene delivery systems through neural retina into retinal pigment epithelium (RPE) and determined the roles of various factors in permeation and subsequent uptake of the delivery systems by RPE.^[60] Results suggest that the neural retina forms a substantial barrier for positively charged molecules including polymeric and liposomal gene carrier complexes. Hudde *et al.* studied the efficiency of activated polyamidoamine dendrimers, to transfect rabbit and human corneas in *ex vivo* culture. In addition to assessing the expression of a marker gene they have demonstrated that this approach can be used to induce the production of TNF receptor fusion protein (TNFR-Ig), a protein with therapeutic potential.^[61] The activated dendrimers are an efficient nonviral vector capable of transducing corneal endothelial cells *ex vivo*. They may have applications in gene-based approaches aimed at prevention of corneal all graft rejection or in treatment of other disorders of corneal endothelium.

Iontophoresis

Iontophoresis is an active method of drug delivery, which uses a small electrical current to transport ionized drugs into and through body tissues. Iontophoresis offers a noninvasive and reproducible means of delivering a model anionic drug to eye tissues, specifically to the retina/choroid.^[62] These

studies serve as the basis for future clinical studies aimed at delivering therapeutic drugs to the back of the eye for treatment of ocular diseases. Stamatialis *et al.*^[63] developed, of a gel reservoir for a TM transdermal iontophoretic delivery system is investigated. TM gel is prepared using HPC and the permeability of TM from the gel through an artificial membrane (Polyflux) and pig stratum corneum (SC) is studied. For a constant TM donor concentration, the TM transport across the Polyflux membrane alone decreases when the concentration of the gel increases due to increase of the gel viscosity. For constant gel concentration, however, the TM permeation across the membrane increases when the TM donor concentration increases. In addition, no effect of the electrical current (Iontophoresis, current density 0.5 mA cm⁻²) on the TM permeation is found, the application of electrical current enhances the TM delivery 13-15 times in comparison to passive (no current) transport. Iontophoresis of dexamethasone phosphate was studied in healthy rabbits using drug-loaded disposable hydroxyethyl methacrylate (HEMA) hydrogel sponges and portable iontophoretic device by Baeyens *et al.*^[64] Dexamethasone levels in the rabbit cornea after a single transcorneal iontophoresis for 1 min was up to 30-fold higher compared to those obtained after frequent eye drop instillation. Also, high drug concentrations were obtained in the retina and sclera 4 h after transscleral iontophoresis. Raiskup-Wolf *et al.* evaluated, the use of solid hydrogel as a probe for the drug delivery to the rabbit eye upon application of low current iontophoresis.^[65] HEMA cross-linked with EGDMA was prepared to form solid hydrogels. The concentration of gentamicin sulfate in different segments of the rabbit eye after transconjunctival and transscleral iontophoresis were also studied. The delivery of gentamicin to the eye via iontophoresis with solid HEMA/EGDMA (ethylene glycol dimethacrylate) hydrogels seems to be promising method achieving high concentrations of the drug in the eye tissue.

CONCLUSION

Just as nature has used biological polymers as the material of choice, mankind will chose polymeric materials as the choice material. Humans have progressed from the Stone Age, through the Bronze, Iron, and Steel Ages into its current age, the Age of Polymers. An age in which synthetic polymers are and will be the material of choice. Polymeric materials have a vast potential for exciting new applications in the foreseeable future. Ocular polymer uses are being developed in number of ODFs and drug delivery systems. Polymers like CDs, cross-linked polyacrylic acid, HEMA, EGDMA, HPC, EC, Pluronic F-127, hyaluronic acid, poly(ethylene oxide), Carbopol 940, and POE will have a great future in ocular drug delivery research.

ACKNOWLEDGMENT

The author Mr. Vijay D. Wagh is thankful to the Indian Council of

Medical Research, New Delhi, for their Senior Research fellowship award of this research work. The authors are also thankful to management and principal of Y. B. Chavan College of Pharmacy.

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Source of Support: Nil, **Conflict of Interest:** None declared.