CHAPTER 2

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I. Ophthalmic Drug Delivery System

One of the first therapeutic delivery systems, the collyrium, noted in the writings of Celsus (20 B.C. to A.D. 50) was introduced by the Romans. That was a cake made of gum resembling a small bar of soap within which the drug was incorporated. For use, a small piece was taken and dissolved in water, oil or other available liquid and applied to the eye. Atropine containing gelatin wafers called "Lamellae" were described in the British Pharmacopoeia as early as 1948.

Mueller and Deardroff (1956) found that Methylcellulose prolonged the absorption of drugs like Homatropine. The viscosity of the methylcellulose solution prevents it from being washed rapidly from the eye and maintains the normal physiology i.e., lacrimation.

Krishna and Brown (1964) used polyvinyl alcohol as a viscosity enhancing agent in ophthalmic preparations. It was found that its solution gave longer retention times and prolonged effect of medicinal preparations.

Swanson et al., (1970) showed autoradiographic and liquid scintillation counting techniques can be used for the evaluation of influence of polyvinyl alcohol and methyl cellulose vehicles on the uptake of tritiated thymidine in component layers of normal corneal tissues.

Wattman and Patwicz (1970) examined the effects of hydroxy propyl methyl cellulose and polyvinyl alcohol on intraocular penetration of topical fluorescein in man. It was shown that 0.5 per cent methyl cellulose increases the intraocular penetration of topical fluorescein as compared to intraocular penetration with 1.4 percent polyvinyl alcohol or aqueous solutions.

Schoenwald and Smolen (1971) compared the pharmacological and bio-kinetic parameters characterizing the mydriatic behavior of tropicamide administered in
vehicles at pH 5.0 and 7.4. The biokinetic analysis of the pharmacological results permitted the mydriatic behaviour of tropicamide to be described quantitatively.

Thermis and Higuchi (1974) designed an osmotic dispensing device for releasing drugs to the eye. The release of drug was controlled by permeability of the wall and the osmotic pressure gradient across the wall of the device. The generic osmotic minipump (ALZET).

Refajo and Thomas (1975) evaluated biological activity of two common scleral buckling materials - gelatin film and solid silicone rubber impregnated with antibiotics and anti-cancer drugs.

Benedetto et al., (1975) demonstrated using slit lamp fluorophotometry that the rate of drainage of a vehicle placed in the eye increased with increased volume. He further showed that the polymer in solution increased the thickness of precorneal tear film.

Utah University (1996) discloses soluble ophthalmic drug inserts (SODI) using polymers of polyacrylamide, ethylacrylate and vinyl-pyrrolidone. SODI offered a number of advantages over eyedrops (aqueous solutions, viscous solutions of polymers and suspensions), ointments and subconjunctival injections. A simplified medication regimen of treatment with SODI is beneficial for the eyes and reduces the consumption of drugs used.

Hardberger (1975) administered $^{99m}$Tc in various vehicles e.g. in normal saline, 1% methyl cellulose, 1.4% polyvinyl alcohols and an ointment base (white petrolatum: mineral oil (6: 4)). It was found that longest contact time of the drug vehicle with the eye was afforded by use of an ointment vehicle and covering of both eyes.

Trueblood et al., (1975) used lacrimal microscintigraphy, in conjunction with computer system to evaluate the corneal contact times of three ophthalmic vehicles in 18 human subjects. These vehicles were saline, polyvinyl alcohol and hydroxy propyl methyl cellulose. Longest contact time was observed with hydroxy propyl methyl cellulose compared with other vehicles.
Sieg and Robinson (1976) used radiochemical techniques to study mechanism of corneal pilocarpine penetration. The results demonstrated a dual role for corneal epithelium both as a barrier to drug penetration and as a reservoir for drug in the intact cornea.

Seig and Robinson (1977) studied the influence of vehicle composition on ocular penetration of pilocarpine in the albino rabbits. Incorporation of pilocarpine into a petrolatum based ointment vehicle resulted in increased aqueous humour pilocarpine levels above those provided by equivalent doses of aqueous solution.

Katz and Blackman (1977) provided the first description of truly soluble ophthalmic delivery system being used in the U.S.A. Inserts without any drug were tested for dissolution and it was found that disappearance rate depended on size rather than shape. Similar types of inserts were used for dry eye syndrome. These devices are called slow release artificial tears (SR-AT).

Ticho et al., (1979) performed a clinical comparison of the effect of piloplex (an emulsion containing a new Pilocarpine polymer compound) to that of pilocarpine hydrochloride on the intra ocular pressure (I.O.P) of fifty-one open angle glaucoma cases. The results indicated that with piloplex, lower mean IOP with smaller variations in diurnal values were obtained.

Decerf and Ooteghem (1979) developed a method using diffusion cell to determine the drug release from viscous solutions simulating the blinking movements in the rabbit and human eye. For the solutions at rest, corresponding with the conditions at the surface of the rabbit cornea, the diffusion velocity decreases with increasing viscosity. It was found that when the solution was moved at a velocity corresponding to that of lacrimal fluid at the surface of the human eye, the influence of viscosity could be neglected.

Goldberg (1979) formulated a high viscosity gel containing pilocarpine to prolong contact time between the drug and the tear film. The preparation was tested in 15
patients and compared with eye drops. In all 15 patients gel was found to be more beneficial than eye drops. Side effects of the gel were low and did not limit its use.

Hosaka et al. (1979) developed hydrogel inserts showing constant rate of release of erythromycin estolate using ternary copolymers of Polyvinyl pyrrolidone (PVP), vinyl acetate, glycidyl methacrylate, methyl methacrylate and ethyl acrylate. In this method, polymeric inserts were prepared and drug was loaded by soaking them into a solution of erythromycin estolate in dioxane.

Gurny (1981) developed an ophthalmic delivery system with cellulose acetate phthalate of pilocarpine which maintained a constant miosis in the rabbits for up to 10 hours. The results were compared with pilocarpine eye drops.

Miller and Donovan (1982) conducted the study to evaluate poloxamer 407 gel for its suitability for use as a vehicle for ophthalmic drug delivery. 25% poloxamer gel formulation enhanced activity of pilocarpine compared to aqueous solution.

Mitra and Mikkelson (1982) obtained miosis - time profiles by instilling 25μl of 1.0% pilocarpine nitrate solution buffered at a pH of 4.75 with different concentration of citrate buffer, in the eyes of rabbits. The study demonstrated that a non drug formulation component such as a buffer system, can dramatically affect the relative pharmacological response from a simple ophthalmic dosage form.

Saettone et al., (1982) had shown the effect of different polymers on the pharmacological activity of pilocarpine in rabbit and man. The high molecular weight polyvinyl alcohol (PVA) solution produced ophthalmic bioavailability with non-viscous characteristics in the eye.

Harwood and Schwartz (1982) described an unusual technique, compression molding at a relatively high temperature (150°C) for the preparation of hydroxy propyl cellulose films (HPC) containing pilocarpine. In-vitro tests showed that release rate followed square root kinetics, was dramatically lower when matrices contained pilocarpine palmoate. The release rate was faster for matrices prepared with low viscosity grades of HPC.
Lee et al., (1983) studied the influence of semisolid vehicle composition on the ocular disposition of sodium cromoglycate (a drug used for allergic conjunctivitis where the target tissue was the conjunctiva). Three vehicles were investigated i.e. a water soluble base (15% PVA in water), an absorption base (10% acetylated lanolin in a paraffin base) and an oleaginous base (a polyethylene and mineral oil blend). Drug disposition was monitored in the ocular fluids and tissues of the rabbits at specific time intervals i.e. 30, 60 and 240 minutes, using radiotracer techniques. It was found that highest drug concentration in the tear pool was achieved in case of an absorption base.

Schoenwald and Huang (1983) studied the influence of physicochemical factors on the corneal penetration behaviour of β-blockers agents.

Ozawa et al., (1983) prepared ocular inserts impregnated with antibiotics (erythromycin and erythromycin estolate) using hydrogel for the treatment of trachoma. In-vitro experiments showed that the elution rate of the drug was found constant when the water content of the hydrogel insert was more than 30%.

Park and Robinson (1984) synthesized polymers of polycarbophil crosslinked with divinyl glycol and examined their utility in ocular progesterone delivery in rabbit’s eyes. The bioadhesive dosage form showed an area under the curve 4.2 times greater than the conventional non-bioadhesive suspension (AUC calculated from concentration vs.time curve), over the time course of the study.

Grass et al., (1984) prepared gels and dried films to examine the sustained release of a water soluble drug pilocarpine in the tear film. In in-vitro release studies significant prolongation of drug release from these systems was observed as compared with simple aqueous or viscous solutions.

Hui and Robinson (1985) synthesized polymers of acrylic acid crosslinked with divinyl glycol and 2, 5-dimethyl-1, 5-hexadiene and examined their utility in ocular drug delivery. The bioadhesive dosage form showed more bioavailability of the drug as compared to conventional dosage forms.
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Ahmad and Patton (1985) showed that noncorneal absorption route contributed significantly to drug penetration into intraocular tissues, using timolol and inulin as probe drugs. Results demonstrated that drugs absorbed by noncorneal route appeared to enter certain intraocular tissues by a mechanism which bypasses the anterior chamber.

Uriti et al. (1985) prepared matrices based on hydroxy propyl cellulose (HPC) and polyvinyl pyrrolidone (PVP) containing pilocarpine. It was found that the release of pilocarpine from matrices was accelerated with increased concentration of PVP and decreased molecular weight of HPC.

Ahmad and Chaudhari (1988) evaluated the buffer systems in ophthalmic product development. Two new buffer parameters, termed average buffer capacity and residual buffer capacity were introduced to elucidate the importance of buffer functionality and ionization values on the in-vivo time course of lacrimal fluid pH. Phosphate buffer was selected as buffer of choice for pilocarpine since it appears to be less irritating to the eye.

Attia et al. (1988) prepared and evaluated ocular inserts of Eudragits, cellulose acetate phthalate, polyvinyl alcohol and hydroxy propyl cellulose. These were compared to suspension dosage form and it was found that ocular films produced an increase in extent of drug absorption.

Vasantha et al. (1988) used collagen ophthalmic inserts for pilocarpine delivery to the eye. Collagen film proved to be the most promising carrier for ophthalmic drug delivery system due to its biological inertness, structural stability and good biocompatibility.

Rootman et al. (1988) employed iontophoresis for the treatment of experimental bacterial keratitis in rabbits. In pharmacokinetic studies iontophoresis resulted in higher and more sustained concentrations in the corneal epithelium, corneal stroma and aqueous humour as compared with eye drops and subconjunctival injections.
Ginsler et al. (1990) investigated the delivery of trifluoro thymidine (TFT) in collagen shields and in topical drops in the cornea of normal rabbits and corneas with experimental epithelial defects. It was found that highest drug concentrations were found in the eyes treated with shields as compared to eye drops.

Losa et al. (1991) used polycyanoacrylate nanoparticles to improve the corneal penetration of hydrophilic drugs as a carrier to retard rapid drug loss from the precorneal area.

Fume et al. (1991) studied the effects of polymer molecular weight and a basic additive on timolol release from matrices of monoesters of poly vinyl methyl ether maleic anhydride. It was found that the release of timolol from monoesters was controlled by polymer dissolution and thus, it was affected by the basic additive in the matrix.

Middleton and Robinson (1991) prepared sol to gel system with mucoadhesive property to deliver the steroid fluorometholone to the eye. The formulation gave better release of drug over a long period of time in the rabbit’s eye, as compared to conventional eye drops.

Kyyroinen et al., (1992) prepared films and microspheres from various esters of hyaluronic acid with methyl prednisolone. Polymeric films gave more sustained effect as compared to microspheres.

Mengi and Deshpande (1992) studied the release of flurbiprofen from carbopol 940 and pluronic F127 hydrogels. Unlike carbopol 940 gels, pluronic F127 gels revealed a rapid onset of action as early as 0.5 hour post administration.

Thermes et al., (1992) evaluated the effect of polyacrylic acid as a bioadhesive polymer on the ocular bioavailability of timolol.

Fitzgerald et al., (1992) studied release of \(^{99m}\)Te labelled sodium pertechnetate and sulphur colloid from polyvinyl alcohol films. Gamma scintigraphy was used to
monitor drug disposition in the eye tissues. It was found that polyvinyl alcohol prolonged the residence time of the drug in the eye tissues.

Saettone et al., (1992) developed coated polymeric inserts prepared by extrusion. Cylindrical inserts based on mixtures of polyvinyl alcohol, glyceryl behenate, xanthan gum, jota carrageenan containing pilocarpine nitrate were prepared by extrusion and were subsequently coated with a mixture of Eudragit® RL and RS. Zero order release kinetics was observed in all cases.

Durrani et al., (1992) developed a mucoadhesive liposomal ophthalmic drug delivery system of pilocarpine nitrate. It gave sustained release of drug over a long duration of time.

Yeshwant et al., (1993) synthesize and evaluated gellan based system for applications in ocular sustained release devices. A methylprednisolone (MP) ester of gellan (gellan-MP) was synthesized. Sustained release gellan-MP films and eye drops of MP suspended in a 0.6% w/w gellan dispersion in water was prepared. In vitro release of MP from the test dosage forms was determined at 32°C using a rotating bottle apparatus. The results shows that compared with the MP suspension control, the gellan-MP films yielded an approximately 4-fold higher area under tear fluid concentration vs time curve.

Kamath et al., (1993) prepared ocular inserts of ciprofloxacin hydrochloride using hydroxy propyl methyl cellulose (HPMC) 1.5cps, ethyl cellulose, Eudragit® and microcrystalline cellulose as polymers. The slow release pattern of the drug was found upto 8 to 9 hours in all types of ocular inserts.

Folkman et al., (1993) granted a U.S. Patent 5,227,372 for invention comprising complexing an ophthalmological drug or reagent with a sulfated glucan sulfate such as cyclodextrin sulfate and contacting the complex so formed with the ocular tissue.

Nandkarni and Yalkowsky (1993) examined the potential of Gelfoam® absorbable gelatin sponge for ophthalmic delivery of pilocarpine. The device released the drug in
Losa et al., (1993) investigated the potential of polymeric nanocapsules for ocular delivery of beta-blockers. Several formulations of polyisobutyl cyanoacrylate and polyethyl-capsabacetic acid nanocapsules containing metipranolol base were developed. A drastic reduction in the systemic side effects of the drug was observed for nanocapsules ophthalmic delivery system.

Weiner et al., (1993) developed a sustained release ocular insert of oxytetracycline HCl [OCUFIT SR™] using medical grade silicone elastomers and rubbers. The devices loaded with oxytetracycline hydrochloride did not exceed 1.9 mm in diameter and spanned the deep fornix from temporal to nasal canthus (25-30 mm in adult human) thus locking it in place. The successful in-vitro studies were carried out for over 14 days and a high level of in-vivo compliance (in human volunteers) was observed for 7 days.

Hill et al., (1993) found that direct current delivery i.e transcorneal iontophoresis overcomes the surface resistance of corneal epithelium and drives the drug through the semipermeable corneal epithelium and then into the corneal stroma and aqueous humor.

Chetoni et al., (1996) prepared and evaluated Ocular mini-tablets (MT’s) for controlled release of Timolol in rabbits. The MTs was prepared by compressing appropriate mixtures of powders with a standard tabletting machine. A thin, rate-controlling membrane was applied over the devices by spraying aqueous dispersions of acrylic copolymers. The MTs were tested for release of TiM to the lacrimal fluid, using commercial eyedrops (Timoptol 0.5%) as a reference standard. Results showed that at 8 h. The apparent mean residence time (MRT) of TiM in the aqueous humor was 1.3 h for the reference solution, 3.2 h for the uncoated MT and 5.7 h for the coated one.

Lindell and Engstrom (1993) studied in-vitro release of timolol maleate from in-situ gelling polymer system. It was found that in-vitro release rate was retarded with in-
Hume et al., (1994) studied ocular delivery of prednisolone using hyaluronic acid benzyl ester films. Circular pieces of the films, 4 mm in diameter, were used for drug content determination and in vivo studies. It was found that the films provided sustained release of the drug over a long period of time.

Kumar et al., (1994) developed in-situ forming gel for ophthalmic drug delivery which increased residence time of drug in the eye. A solution containing 1.5% methyl cellulose and 0.3% carbopol at pH 4.0 and 25°C was found to be an easily flowing liquid capable of administration as a drop and showed an increase in viscosity and conversion to a gel on changing pH to 7.4 by addition of 0.5 M NaOH.

Kumar and Himmelstein (1995) investigated that in-situ gelling behaviour of carbopol solution can be modified by addition of hydroxy propyl methyl cellulose. They found that hydroxy propyl methyl cellulose-polyacrylic acid could be formulated as an eye drop and upon instillation into the cul-de-sac of the eye can undergo in-situ transition to form gels capable of sustained drug release.

Collagen et al., (1995) compared transcorneal iontophoresis and corneal collagen shields for ocular delivery of gentamicin, tobramycin and ciprofloxacin in a pseudomonas model of bacterial keratitis. Corneal collagen shield was used as a protective device and also as a delivery system in the therapy of ocular infections. The ease of application and convenience of its use made it attractive therapeutic tools than current regimen. Besides the benefits of therapy, the absence of side effects in both delivery methods indicated the safety with which both techniques could be used.

Durrani et al., (1995) studied the influence of molecular weight and formulation pH on the precorneal clearance rate of hyaluronic acid in the rabbit’s eye. Hyaluronic acid is a natural polymer which, due to its water retaining capability, binds to cell membranes and can therefore be considered as a putative vehicle for controlled ocular delivery. It was found that bioadhesion was stronger for Herlon® at pH 5 than at pH
It was concluded that high molecular weight hyaluronic acid resides on the ocular surface for a long duration as compared to low molecular weight hyaluronic acid.

Saetone et al. (1995) prepared ophthalmic inserts (mini tablet) for sustained release of triamol by a standard compression and coating technique. It was found that an adequate control of the in-vitro drug release from the devices could be obtained by adjusting the type and amount of acrylic polymer coating.

Calvo et al. (1996) designed 3 different colloidal carriers viz. nanoparticles and nanocapsules made of poly-e-caprolactone and submicron emulsions. The in-vitro corneal penetration of the encapsulated drug was more than 3 fold that of the commercial eye drops. The main factor responsible for the favourable corneal transport of indomethacin was the colloidal nature of these carriers.

Kling et al., (1996) conducted a physicochemical study of a positively charged submicron emulsion containing piroxicam. The results of the study revealed that when the initial adjusted pH was 7.4 and the rate of hydrolysis of phospholipids was reduced, satisfactory conditions for preparation of positively charged submicron emulsion of piroxicam was established for its use as a parenteral and ocular dosage form.

Subonen et al., (1996) studied the ocular delivery of pilocarpine as bispilocarpic acid diesters in albino rabbits. It was found that the eye irritation increased with increasing lipophilicity of the prodrugs. The ocular bioavailability of pilocarpine and its duration of action can be improved by bispilocarpic acid diesters, but for predicting their performance, both lipophilicity and prodrug cleavage rate should be taken into account.

Calvo et al., (1997) developed two new colloidal systems, Poly-L-Lysine (PLL) coated and chitosan (CS) coated nanocapsules, which were successful in improving the ocular penetration of drugs. It was found that the presence of bioadhesive polymer CS around the nanocapsules provided an optimal corneal penetration of the encapsulated drug.
Davies et al. (1997) investigates the effect of hydroxypropyl-β-cyclodextrin (HPβ-CD) on the aqueous solubility and chemical stability of hydrocortisone (HC). It was found that the aqueous solubility of HC was markedly increased upon addition of HP-β-CD due to the formation of a soluble 1:1 inclusion complex. Cyclodextrins may be useful in the reformulation of ophthalmic suspensions as solutions there by overcoming many problems associated with formulation and use of ophthalmic suspensions.

Lee et al. (1997) developed sodium and zinc insulin ocular devices for the systemic delivery of insulin. The devices consisted of Gelfoam absorbable gelatin sponge, USP as an insulin carrier and did not contain any surfactant or absorption enhancer. The results indicated that insulin reached the systemic circulation and blood glucose concentration could be maintained in a uniform level (60% of initial) over a period of 8 hours.

Barath and Hiremath, (1999) prepared ocular films of pefloxacin mesylate with the objectives of reducing frequency of administration, improvement of patient compliance, obtaining controlled release and greater therapeutic efficacy in the treatment of eye infections such as conjunctivitis, keratoconjunctivitis, keratitis, corneal ulcers etc. Polymers such as HPC, HPMC, PVP and PVA were used in different ratios to prepare the ocular films.

Nagarsenker et al., (1999) entrapped tropicamide in liposomes. Various drug loaded liposomal forms were prepared i.e., neutral, positively charged; and neutral liposomes dispersed in 0.25% w/v polycarbophil gel. The positively charged liposomal formulation and liposome dispensed in polycarbophil gel were found to be more effective than neutral liposomal dispersion.

Saisivam et al., (1999) prepared ciprofloxacin hydrochloride ocular inserts using different polymers in various proportions and combinations. The results indicated a good correlation between in-vitro and in-vivo studies. The expected release for an extended period of 24 hrs was observed in one formulation (drug reservoir with 2% HPMC and 6% ethyl cellulose as rate controlling membrane).
Saxena (1999) granted a U.S. patent for inventing an ophthalmic formulation containing at least one pharmaceutically active substance, purified water, and an amount of gelling agent effective to form an aqueous gel. The gel has a viscosity of from 75,000 to 500,000 centipoise and does not contain an oil phase. The pharmaceutically active substance is solubilized in the formulation. The gelling agent consists essentially of cellulose or a water-soluble cellulose derivative.

Lee and Yalkowsky (1999) showed that insulin in acidified Gelfoam (absorbable gelatin sponge, USP) based ocular device, was delivered efficiently and absorbed into the systemic circulation without the aid of an absorption enhancer.

Lee and Yalkowsky (1999) prepared several Gelfoam® (Absorbable gelatin sponge, USP) based surfactant free devices containing either sodium or zinc insulin with dilute acetic or hydrochloric acid. The result indicated that the device prepared with up to 30% of acetic acid solution produced no eye irritation. A single device containing 0.2 mg of insulin was sufficient to control the blood glucose level in a uniform manner.

Desai et al., (2000) prepared a biodegradable polyisobutylcyanoacrylate (PIBCA) colloidal particulate system of pilocarpine, to incorporate it into a Pluronic F127 (PF127)-based gel delivery system, and to evaluate its ability to prolong the release of pilocarpine. Polyisobutylcyanoacrylate nanocapsules (PIBCA-NC) were prepared by interfacial polymerization. Physicochemical characterization was performed by measuring drug loading, particle size analysis, and scanning electron microscopy. Results indicated that PIBCA-NC of Pilocarpine dispersed in the PF127MC gel delivery system has great potential for achieving a prolonged delivery.

Andreas et al., (2000) developed mucoadhesive ocular insert for the controlled delivery of ophthalmic drugs and to evaluate its efficacy in vivo. Water uptake and swelling behavior of the inserts as well as the drug release rates of the model drugs fluorescein and two diclofenac salts with different solubility properties were evaluated in vitro. Results revealed that controlled release was achieved for the incorporated model drugs. The study indicates that ocular inserts based on thiolated poly (acrylic
acid) are promising new solid devices for ocular drug delivery.

Becirevic-Lacan, M., et al. (2000) studied the Effect of hydroxypropyl-beta-cyclodextrin on hydrocortisone dissolution from films intended for ocular drug delivery. The inclusion complex between hydrocortisone and hydroxypropyl-beta-cyclodextrin was prepared and evaluated for in vitro transfer rate. High molecular weight cellulose and PVA polymeric films were prepared. Results show that the drug and complex-polymer interaction in each system is responsible for the solubility of the drug, and different release behaviours of hydrocortisone and cyclodextrin inclusion complex from the films prepared.

Sznitowska et al., (2000) prepared submicron emulsions containing pilocarpine as ion pair with mono-dodecyl phosphoric acid. They found that the miotic effect observed in rabbits after application of the ion pair in aqueous solution or in submicron emulsion was the same which indicated that the drug distribution into the oily phase of the colloidal vehicle did not improve bioavailability.

Srividya et al., (2001) developed and evaluated Sustained ophthalmic delivery of ofloxacin from a pH triggered in situ gelling systems poor bioavailability. Polyacrylic acid (Carbopol 940) was used as the gelling agent in combination with HPMC (Methocel E50LV) which acted as a viscosity enhancing agent. The developed formulation was therapeutically efficacious, stable, non-irritant and provided sustained release of the drug over an 8-h period.

Liaw et al., (2001) investigated use of PEO-PPO-PEO non-ionic copolymeric micelles as a carrier for eye-drop gene delivery of plasmid DNA with lacZ gene in vivo. Using pyrene fluorescence probe methods, zeta potential, and dynamic light scattering test (DLS), the ability of micelle formation of these block copolymers with plasmid was studied. Results shows that efficient and stable transfer of the functional gene could be achieved with PEO-PPO-PEO polymeric micelles through topical delivery in mice and rabbits.

for oral administration comprising a carrier and, as active ingredient, an ophthalmologically active compound, characterized to promote pre-gastric absorption of the ophthalmologically active compound. A process for preparing such compositions and the use of such compositions for the treatment of ophthalmic diseases, particularly diseases caused by elevated intra-ocular pressure, such as ocular hypertension and glaucoma.

Schultz et al., (2002) granted U.S.Patent for inventing polymeric hydrogel contact lenses containing an anti-glaucoma medication, such as a beta adrenergic receptor antagonist, e.g., timolol maleate, or an alpha adrenergic receptor agonist, e.g., brimonidine tartrate, and methods of fabrication and uses thereof. A medication is passively transferred into a contact lens by absorption from a dilute aqueous solution. Such treated lenses are contacted with the ocular fluid of an individual to treat glaucoma.

Fulzele et al., (2002) studied and characterized Polymerized rosin (PR) for its application in drug delivery. Films were produced by a casting/solvent evaporation method from plasticizer free and plasticizer containing solutions. Films prepared from different formulations were studied for their mechanical (tensile strength, percent elongation and Young’s modulus), water vapour transmission and moisture absorption characteristics. Results shows that hydrophobic plasticizers, dibutyl sebacate and tributyl citrate, improved the mechanical properties of free films.

Vesna Zderic et al., (2002) investigated application of 1-s bursts of 20-kHz ultrasound, for enhancement of corneal permeability to glaucoma drugs of different lipophilicity (atenolol, carteolol, timolol and betaxolol). The results revealed that permeability of rabbit cornea increased by 2.6 times for atenolol, 2.8 for carteolol, 1.9 for timolol and 4.4 times for betaxolol (all p-values < 0.05), after 60 min of ultrasound (US) exposure in vitro.

Colo et al., (2002) studied the effects of chitosan hydrochloride on in vitro release of ofloxacin (OFX) from mucoadhesive erodible ocular inserts. Circular inserts of 6 mm in diameter were prepared by powder compression. Results showed that by the
addition of 10, 20 or 30% medicated CH-HCl microparticles to formulations based on poly(ethylene oxide) (PEO 900) or (PEO 2000) produced changes in the insert microstructure which accelerated OFX release from inserts. Results are also shows that in rabbit’s eye, insert produced no substantial increase of AUC in the aqueous humour.

Loftsson et al., (2002) reviewed the properties of cyclodextrins and their application in eye drop formulations. Cyclodextrins have been used to formulate eye drops containing corticosteroids, such as dexamethasone. Cyclodextrin-based dexamethasone eye drops are well tolerated in the eye and seem to provide a higher degree of bioavailability and clinical efficiency than the steroid eye drop formulations presently available. Cyclodextrins are useful excipients in eye drop formulations for a variety of lipophilic drugs. They will facilitate eye drop formulations for drugs that otherwise might not be available for topical use, while improving absorption and stability and decreasing local irritation.

Kim et al., (2002) studied chemically and physically stable rhEGF/poloxamer gel and investigated possibility of ophthalmic delivery. The rhEGF/HP-beta-CD complex was prepared and incorporated in poloxamer gel. The poloxamer gel was composed of poloxamer 407 (16%) and poloxamer 188 (14%). Results showed that the in vitro release of rhEGF from poloxamer gel containing 1:4 rhEGF/HP-beta-CD complexes was much slower than that of rhEGF solution and faster than that of 1:20 rhEGF/HP-beta-CD complex. Therefore, the poloxamer gel could be applicable for the development of effective ophthalmic delivery.

Schultz et al., (2002) granted U.S. Patent US 6,410,045 discloses preparation of drug delivery system for antiglaucomatous medications utilizing a polymeric hydrogel contact lens containing Timolol maleate in a concentration of between 0.05% and 0.25% by weight absorbed in said contact lens which is capable of being delivered into the ocular fluid.

Balasubramaniam et al., (2003) developed and evaluated ion activated in situ ophthalmic delivery system of the NSAID indomethacin. Gelrite gellan gum, a novel
ophthalmic vehicle, which gels in the presence of mono or divalent cations present in the lacrimal fluid, was used as the gelling agent. The insitu gel upon installation as drops into the eye undergo a sol-gel transition in the cul-de-sac. The results revealed that the developed formulations were therapeutically efficacious and provided sustained release of the drug over an 8-hour period in vitro.

Bourges et al., (2003) prepared and evaluate polylactide (PLA) nanoparticle (NP) for their potential to release encapsulated material. NPs localization within the intraocular tissues was studied by environmental scanning electron microscopy (ESEM), confocal microscopy, light microscopy histology, fluorescence microscopy, and immunohistochemistry. The results show that a steady and continuous delivery of drugs can be achieved.

Isowaki et al., (2003) developed prepared matrix-type transdermal therapeutic system for treating diseases of the eye using Prednisolone as a model drug. An in vivo study result using rats showed that the daily application of the patch maintained a constant therapeutic plasma concentration of the drug. Pharmacokinetic analysis indicated that the present transdermal therapeutic system may be clinically effective as a new treatment for ocular diseases.

Hitoshi et al., (2003) prepared and evaluated a unique one-side-coated insert that releases drug from only uncoated side. One-side-coated insert was prepared by attaching a polypropylene tape on the one side of the polymer disc of poly(2-hydroxypropyl methacrylate) (HPM) containing tilisolol as a model ophthalmic drug. At the adequate intervals, the tear fluid, plasma, aqueous humor, conjunctiva, and sclera were collected and the drug concentrations were determined by an HPLC. A release of tilisolol from the one-side-coated insert was twice slower than from the uncoated insert. SC insert showed higher drug concentrations in the aqueous humor and sclera, and lower drug concentrations in the plasma and conjunctiva.

De et al., (2003) prepared and evaluated brimonidine loaded polyacrylic acid nanoparticles for potential delivery in ophthalmic therapy. The particles were prepared by a reverse microemulsion polymerization technique. The results shows
that nanoparticles exhibit superior loading properties for brimonidine, and the formulation was stable and the drug was slowly released over several hours. Two-photon laser scanning microscopic studies of dye-conjugated polyacrylic acid nanoparticles demonstrated the accumulation of the particles on the surface and intercellular spaces of Caco-2 cells.

Ging-Ho et al., (2003) developed thermosensitive drug vehicles for glaucoma therapy. Thermosensitive ophthalmic drop was prepared by mixing linear poly (N-isopropylacrylamide-g-2-hydroxyethyl methacrylate) (PNIPAAm-g-PHEMA), PNIPAAm- g-PHEMA gel particles and antiglaucoma drug. The in vivo studies indicated that the intraocular pressure (IOP)-lowering effect for a polymeric eyedrop lasted for 26 h, which is significantly better than the effect of traditional eyedrop (8 h). It is proved that thermosensitive polymeric eyedrop with ability of controlled drug release exhibits a greater potential for glaucoma therapy.

Charoo et al.,(2003) prepared and evaluated Sol-to-gel systems of ciprofloxacin hydrochloride utilizing the phase transition properties of hydroxy propyl methyl cellulose K 15 M grade (HPMC) and carbopol 934. The sol-to-gel systems were sterilized by gamma radiation. The sol-to-gel systems were evaluated for rheological characteristics, in vitro release behavior, microbial efficacy, in vivo release behavior, and efficacy against induced bacterial conjunctivitis in rabbits' eyes. Results showed that the sol-to-gel system exhibited a zero-order drug release pattern over 24 h in in vitro release studies. The drug was active against selected microorganisms in microbial efficacy studies. Better improvement in artificially induced bacterial conjunctivitis in rabbits' eyes was observed in animals treated with the sol-to-gel system compared with marketed eye drops.

Kumar et al., (2003) prepared and evaluated In vitro and in vivo characterization of scleral implant of indomethacin. Film-type scleral implants of indomethacin using sodium alginate and PEG 400 and600 as plasticizers were fabricated by solvent casting. The prepared implants were cross-linked by treatment with calcium chloride solution. Uniformity of thickness, weight, and drug content and surface pH of the implants were evaluated. The influence of plasticizer type/concentration and
crosslinking time/concentration of calcium chloride on indomethacin release was studied. Selected batches of the implants were subjected to pharmacodynamic studies. Results shows that the release of indomethacin from the implants was influenced by the concentration and nature of plasticizers used. Chemical cross-linking with calcium chloride was successful in retarding the drug release. The pharmacodynamic studies showed a marked improvement in the various clinical parameters.

Kompella et al., (2003) studied effect of budesonide to inhibit expression of vascular endothelial growth factor (VEGF) in a retinal pigment epithelial cell line (ARPE-19) and evaluated budesonide nano and microparticles sustain retinal drug levels. The effects of budesonide were determined in ARPE-19 cells by ELISA, RT-PCR, and a cell-viability assay, respectively. DL-Polylactide (PLA) nano- and microparticles containing budesonide were prepared by a solvent evaporation technique, and the particles were characterized for size, morphology, encapsulation efficiency, and in vitro release. Results shows that at concentrations, budesonide inhibited VEGF secretion as well as mRNA expression in ARPE-19 cells in a dose-dependent manner. After subconjunctival administration, both budesonide-PLA nano- and microparticles produced sustained budesonide levels in the retina and other ocular tissues.

Eljarrat-Binstock et al., (2004) studied corneal iontophoresis of gentamicin sulfate was studied in healthy white rabbits by using drug-loaded disposable hydroxyethyl methacrylate (HEMA) hydrogel disk probes and a portable mini-ion device. The gentamicin concentration was assayed with a fluorescence polarization immunoassay. Results show that the peak gentamicin concentrations after a single iontophoresis treatment were 12 to 15 times higher than those obtained after gentamicin injection or after topical eye drop instillation.

Chowdary et al., (2004) reviewed mucoadhesive microspheres for controlled drug delivery. Mucoadhesive microspheres exhibit a prolonged residence time at the site of application or absorption and facilitate an intimate contact with the underlying absorption surface. Mucoadhesive microspheres have been developed for oral, buccal, nasal, ocular, rectal and vaginal routes for either systemic or local effects. The article also discusses development and evaluation of mucoadhesive microspheres and the
Wang et al., (2004) prepared and studied the effect of aqueous eye drops containing a high concentration of disulfiram (DSF) in a cyclodextrin-based drug delivery system. The DSF and hydroxypropyl-beta-cyclodextrin (HPβCD) inclusion (DSF/HPβCD) was studied using solubility methods, IR spectra and X-ray diffraction patterns. Formulations for DSF eye drops were first identified by a transcorneal penetration experiment in vitro. The ocular bioavailability was calculated by a transcorneal experiment of DSF in vivo. Results shows that formation of DSF/HPβCD inclusion and the addition of hydroxypropylmethylcellulose (HPMC), as a penetration enhancer, played very important roles in increasing the ocular bioavailability of DSF.

Wang et al., (2004) studied the formulation effects of aqueous eye drops containing a high concentration of zinc diethylidithiocarbamate (Zn-DDC). Zn-DDC and hydroxypropyl-beta-cyclodextrin (HPβCD) inclusion complex (Zn-DDC/HPβCD) was studied using the saturation solution method and characterized by differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (IR). Suitable formulations for Zn-DDC eye drops were established by means of in-vitro transcorneal penetration experiments. In the presence of 22% (w/v) HPβCD, the solubility of Zn-DDC in water was increased almost 850 fold , by the formation of Zn-DDC/HPβCD. Results showed that this drug delivery system increases both the drug solubility in aqueous eye drops and the permeability of drug through the rabbit cornea, by the formation of a drug-cyclodextrin inclusion complex and the addition of polymers and penetration enhancers.

Gavini et al., (2004) prepared and evaluated poly (lactide-co-glycolide) (PLGA) microspheres as carriers for the topical ocular delivery of a peptide drug vancomycin (VA). The microspheres were prepared by an emulsification/spray-drying technique. In vivo studies were carried out by assessing the pharmacokinetic profile of VA in the aqueous humor of rabbits after topical administration of aqueous suspensions of microspheres. The results show by increasing the viscosity of the microsphere suspension by addition of a suspending-viscosizing agent (hydroxypropylcellulose) did not produce an increase of the ocular bioavailability.
Orosz et al., (2004) studied a novel method of administration of antiangiogenic and antioxidant drugs through a nanoporous inorganic filter. The method involves encapsulation of drugs in implantable sustained release devices. Human retinal endothelial cells (HREC) were exposed to vitamin C or to endostatin delivered across the nanoporous filter. Growth of cells on the filter was considered an indication for biocompatibility. The result shows that vitamin C, acting directly or after diffusion across the filter, up to concentrations physiologically present in the eye, was a concentration dependent modulator of HREC’s ability to survive. The drug delivery method passes in vitro tests for diffusibility and biocompatibility.

Bonferoni et al., (2004) prepared and in-vitro evaluated Carrageenan-gelatin mucoadhesive systems of Timolol maleate for ion-exchange based ophthalmic delivery system. Carrageenan-gelatin complex is formed which releases the drug slowly. Both films and microspheres were prepared and tested in vitro. A microsphere formulation was also tested in vivo in albino rabbits. The results showed that the combination of carrageenan and gelatin in different ratios is useful in modulating the drug release profiles, the rheological and mucoadhesive properties. The drug concentration and bioavailability in the aqueous humour were significantly high in comparison with commercial formulations.

Bron et al., (2004) studies the efficacy and safety of a single daily instillation of nonpreserved timolol to a timolol maleate gel-forming solution in patients with chronic glaucoma or ocular hypertension already treated with latanoprost. A randomized, prospective, multicenter, open, parallel-group clinical trial was undertaken with 73 patients with chronic glaucoma treated with latanoprost and a timolol maleate gel-forming solution. The changes in intraocular pressure (IOP) were recorded as well as local and systemic tolerance and patient compliance. The results conclude that at 3 months, both regimens were found equivalent in maintaining IOP control. This short-term study has demonstrated the equivalence of nonpreserved timolol to timolol maleate gel-forming solution in terms of IOP control. Moreover, the local tolerance of nonpreserved timolol was better.
Zhidong et al., (2006) studied the whether poor bioavailability and therapeutic response exhibited by conventional ophthalmic solutions may be overcome by the use of in situ gel-forming systems that are instilled as drops into the eye and then undergo a sol–gel transition in the cul-de-sac using gatifloxacin based on the concept of ion-activated in situ gelation. Alginate was used as the gelling agent in combination with HPMC which acted as a viscosity-enhancing agent. The rheological behaviors of all formulations were not affected by the incorporation of gatifloxacin. Both in vitro release studies and in vivo pre-corneal retention studies indicated that the alginate/HPMC solution retained the drug better than the alginate or HPMC E50Lv solutions alone. These results demonstrate that the alginate/HPMC mixture can be used as an in situ gelling vehicle to enhance ocular bioavailability and patient compliance.

Hong-Ru Lin et al., (2000) develop and characterize a series of carbopol- and pluronic-based solutions as the in situ gelling vehicles for ophthalmic drug delivery. The rheological properties, in vitro release as well as in vivo pharmacological response of various polymer solutions, including carbopol, pluronic and carbopol/pluronic solution, were evaluated. It was found that the optimum concentration of carbopol solution for the in situ gel forming delivery systems was 0.3% (w/w), and that for pluronic solution was 14% (w/w). The mixture of 0.3% carbopol and 14% pluronic solutions showed a significant enhancement in gel strength in the physiological condition; this gel mixture was also found to be free flowing at pH 4.0 and 25°C. The rheological behaviors of carbopol/pluronic solution were not affected by the incorporation of pilocarpine hydrochloride. Both the in vitro release and in vivo pharmacological studies indicated that the carbopol/pluronic solution had the better ability to retain drug than the carbopol or pluronic solutions alone.

Kumar et al., (2002) compared the efficacy and safety profile of Timolol maleate 0.5% versus Timolol gel forming solution (GFS) 0.5% in open angle glaucoma in Indian eyes. In a prospective crossover study 52 patients of open angle glaucoma, well controlled intraocular pressure (IOP) Fstudy, side effects reported or observed was also compared. : Statistically significant difference was not observed in ocular
The hypotensive effect of the two treatments. The side-effects in both the treatment groups were similar except for higher incidence of blurring of vision in patients on timolol GFS.

A number of drugs are used in the development of ophthalmic drug delivery systems. The work done on various drugs is summarized in Table 5.

**Table 5. Research work done on ophthalmic drug delivery system**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage form</th>
<th>Polymers / Bases</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilocarpine</td>
<td>Ointment</td>
<td>Petrolatum bases</td>
<td>Sieg and Robinson (1976)</td>
</tr>
<tr>
<td>Pilocarpine</td>
<td>Emulsion</td>
<td>—</td>
<td>Ticho et al., (1979)</td>
</tr>
<tr>
<td>Pilocarpine</td>
<td>Sol to gel system</td>
<td>Cellulose acetate phthalate</td>
<td>Gurny (1981)</td>
</tr>
<tr>
<td>Dihydrorstreptomycin sulphate</td>
<td>Liposomes</td>
<td>Phospholipids</td>
<td>Singh and Mezei (1984)</td>
</tr>
<tr>
<td>Pilocarpine</td>
<td>Matrices</td>
<td>Hydroxyl propyl cellulose and Polyvinyl pyrrolidone</td>
<td>Urtti et al., (1985)</td>
</tr>
<tr>
<td>Pilocarpine</td>
<td>Hydrogel</td>
<td>Polyacrylic acid and Polyacrylamide</td>
<td>Saettone et al., (1986)</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Suspension</td>
<td>—</td>
<td>Attia et al., (1988)</td>
</tr>
<tr>
<td></td>
<td>Ocular insert</td>
<td>Cellulose acetate phthalate, Endragit RS. 100 and RL 100</td>
<td>Attia et al., (1988)</td>
</tr>
<tr>
<td>Pilocarpine nitrate</td>
<td>Ocular insert</td>
<td>Collagen</td>
<td>Vasantha et al., (1988)</td>
</tr>
<tr>
<td>Drug</td>
<td>Formulation</td>
<td>Adjuvants/Ingredients</td>
<td>Reference(s)</td>
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<tr>
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<tr>
<td>Pilocarpine nitrate</td>
<td>Gel</td>
<td>Polyacrylic acid</td>
<td>Saettone et al., (1993)</td>
</tr>
<tr>
<td>Timolol</td>
<td>Sol to gel system</td>
<td>Gelrite&lt;sup&gt;®&lt;/sup&gt;</td>
<td>Rozier et al., (1989)</td>
</tr>
<tr>
<td>Methyl Prednisolone</td>
<td>Films and Microspheres</td>
<td>Various esters of hyaluronic acid</td>
<td>Kyyronen et al., (1992)</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>Gels</td>
<td>Pluronic F 127</td>
<td>Mengi and Deshpande (1992)</td>
</tr>
<tr>
<td>Timolol Maleate</td>
<td>Solutions</td>
<td>Polyacrylic acid (bioadhesive polymer)</td>
<td>Thermes et al., (1992)</td>
</tr>
<tr>
<td>Pilocarpine</td>
<td>Nanoparticulate pseudolatex</td>
<td>Cellulose acetate phthalate</td>
<td>Gurny (1981)</td>
</tr>
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<td>Penicillin G</td>
<td>Liposomes</td>
<td>Phospholipids</td>
<td>Schaeffer and Krohn (1982)</td>
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<tr>
<td>Pilocarpine</td>
<td>Solution</td>
<td>Hyaluronic acid sodium salt</td>
<td>Camber and Edman (1989)</td>
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<td>Timolol maleate</td>
<td>&lt;i&gt;in-situ&lt;/i&gt; forming gel</td>
<td>Hydroxy propyl methyl cellulose and Polyacrylic acid</td>
<td>Kumar and Himmelstein (1995)</td>
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<tr>
<td>Gentamicin</td>
<td>Corneal</td>
<td>Collagen</td>
<td>Callegan et al.,</td>
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<tr>
<td>Drug</td>
<td>Formulation</td>
<td>Excipients</td>
<td>Reference</td>
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<tr>
<td>Tobramycin and ciprofloxacin</td>
<td>Collagen shield</td>
<td></td>
<td>(1995)</td>
</tr>
<tr>
<td>Pilocarpine</td>
<td>Solution</td>
<td></td>
<td>Suohonen et al., (1996)</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>Submicron emulsion</td>
<td>Poloxamer and Stearylamine as emulsifier</td>
<td>Klang (1996)</td>
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<tr>
<td>Indomethacin</td>
<td>Nanoparticles, Nanocapsules, Submicron emulsion</td>
<td>Poly-ε-caprolactone, Polyoxamer 188</td>
<td>Calvo et al., Davies (1989)</td>
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<tr>
<td>Hydrocortisone</td>
<td>Solution</td>
<td>Hydroxypropyl-β-cyclodextrin</td>
<td>Davies (1997)</td>
</tr>
<tr>
<td>Pilocarpine hydrochloride</td>
<td>Gels</td>
<td>Pluronic F127, Methyl cellulose, Hydroxypropyl methyl cellulose</td>
<td>Desai and Blanchard (1998)</td>
</tr>
<tr>
<td>Ciprofloxacin hydrochloride</td>
<td>Ocular insert</td>
<td>Hydroxy propyl methyl cellulose, Methyl cellulose, Ethyl cellulose and polyvinyl pyrrolidone</td>
<td>Saisivam et al., (1999)</td>
</tr>
<tr>
<td>Insulin</td>
<td>Ocular devices</td>
<td>Absorbable gelatin sponge, USP</td>
<td>Lee and Yalkowsky (1999)</td>
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<tr>
<td>Tropicamide</td>
<td>Liposomes dispersed in gel</td>
<td>Polycarbophil</td>
<td>Nagarsenker et al., (1999)</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Solution</td>
<td>Pluronic™ F68 and F127</td>
<td>Dimitrova et al.,</td>
</tr>
<tr>
<td>Patent No.</td>
<td>Title</td>
<td>Author &amp; Date</td>
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<td></td>
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<tr>
<td>U.S.4,952,581</td>
<td>Use of a prostaglandin in combination with an adrenergic blocking agent for reduction of intraocular pressure</td>
<td>Bito et al.,(1990)</td>
<td></td>
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<tr>
<td>U.S.5,296,228</td>
<td>Compositions for controlled delivery of pharmaceutical compounds</td>
<td>Chang et al., (1994)</td>
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<tr>
<td>U.S.5,578,638</td>
<td>Treatment of glaucoma and ocular hypertension with beta.sub.3-adrenergic agonists</td>
<td>Brazzell et al., (1996)</td>
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<tr>
<td>U.S.5,705,194</td>
<td>Pharmaceutical compositions containing polyalkylene block copolymers which gel at physiological temperature</td>
<td>Wong et al., (1998)</td>
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<td>U.S.6,242,442</td>
<td>Brinzolamide and brimonidine for treating ocular conditions</td>
<td>Dean et al., (2001)</td>
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<tr>
<td>U.S.6,316,441</td>
<td>Brinzolamide and brimonidine for treating glaucoma</td>
<td>Dean et al., (2001)</td>
<td></td>
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<tr>
<td>U.S.6,410,045</td>
<td>Drug delivery system for antiglaucomatous</td>
<td>Schultz et al.,</td>
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Table 6. Patents related to Ocular drug delivery systems
<table>
<thead>
<tr>
<th>Publication Number</th>
<th>Description</th>
<th>Inventor(s)</th>
<th>Date</th>
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<tr>
<td>U.S.20020071874</td>
<td>Acoustically active drug delivery systems</td>
<td>Olejnik et al., (2002)</td>
<td></td>
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<tr>
<td>U.S.6,071,875</td>
<td>TGF.alpha. for the treatment of ocular hypertension and glaucoma</td>
<td>Clark et al., (1996)</td>
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<tr>
<td>U.S.6,154,671</td>
<td>Device for the intraocular transfer of active products by iontophoresis</td>
<td>Pare et al., (2000)</td>
<td></td>
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<tr>
<td>U.S.6,217,896</td>
<td>Conjunctival inserts for topical delivery of medication or lubrication</td>
<td>Benjamin (2001)</td>
<td></td>
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<tr>
<td>U.S.6,319,240</td>
<td>Methods and apparatus for ocular iontophoresis</td>
<td>Beck (2001)</td>
<td></td>
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<tr>
<td>U.S.6,335,335</td>
<td>Prolonged-action eye drop</td>
<td>Higashiyama, et al. (2002)</td>
<td></td>
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<tr>
<td>U.S.6,579,519</td>
<td>Sustained release and long residing ophthalmic formulation and the process of preparing the same</td>
<td>Maitra et al., (2003)</td>
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<tr>
<td>Patent Number</td>
<td>Description</td>
<td>Authors</td>
<td>Year</td>
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<tr>
<td>U.S.20020114778</td>
<td>Reversible gelling system for <em>ocular drug delivery</em></td>
<td>Xia <em>et al.</em>,</td>
<td>2002</td>
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<td>U.S.20020119941</td>
<td><em>In-situ</em> gel formation of pectin</td>
<td>Ni <em>et al.</em>,</td>
<td>2002</td>
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<tr>
<td>U.S.20020197300</td>
<td>Drug delivery system for anti-glaucomatous medication</td>
<td>Schultz <em>et al.</em>,</td>
<td>2002</td>
</tr>
<tr>
<td>U.S.20030175324</td>
<td>Ocular therapeutic agent delivery devices and methods for making and using such devices</td>
<td>Robinson <em>et al.</em>,</td>
<td>2003</td>
</tr>
<tr>
<td>U.S.20030185892</td>
<td><em>Intraocular</em> delivery compositions and methods</td>
<td>Bell <em>et al.</em>,</td>
<td>2003</td>
</tr>
<tr>
<td>U.S.20030191426</td>
<td>Device for enhanced delivery of biologically active substances and compounds in an organism</td>
<td>Lerner <em>et al.</em>,</td>
<td>2003</td>
</tr>
<tr>
<td>U.S.20040037889</td>
<td>Stabilized, dry pharmaceutical compositions for drug delivery and methods of preparing same</td>
<td>Rodger <em>et al.</em>,</td>
<td>2004</td>
</tr>
</tbody>
</table>

WO 2006/039558 A2 discloses a composition for treating ocular disease comprising a hydrophilic polymer, active agent and a gelling component, wherein the composition gels in ocular environment and provides a sustained release.

EP 1137407 discloses an aqueous ophthalmic composition comprising a beta blocker and a gel forming substance like carbopol and pharmaceutical excipients, buffer and preservative.

US 6174524 & US 5958443 discloses pharmaceutical composition containing polysaccharide like xanthan gum which gels when come in contact with eye due to change in pH.

US 5599534 relates to thermally reversible gel forming composition containing pH sensitive gelling polymers like acrylic polymers.
WO 06039330A1 and US 20060068012 A1 disclose proves for the preparation of ocular insert using polyvinyl alcohol. During the manufacturing process the poly (vinyl alcohol) is cured. The poly (vinyl alcohol) may be in the form of separate pieces, a unitary sheet or may be incorporated into the drug delivery device at the time of curing. During the step of curing the humidity is controlled to ensure improved consistency during the curing process. The improved consistency results in inventories of drug delivery devices that have different cure times. The present also relates to a process for making a plurality of drug delivery devices for ocular delivery.

US 20060067978A1 discloses process for making a plurality of drug delivery devices for implantation in the eye of a patient. The plurality of drug delivery devices are made in part of poly (vinyl alcohol). During the manufacturing process the poly(vinyl alcohol) is cured. The poly (vinyl alcohol) may be in the form of separate pieces, a unitary sheet or may be incorporated into the drug delivery device at the time of curing. During the step of curing the humidity is controlled to ensure improved consistency during the curing process. The improved consistency results in inventories of drug delivery devices that have different cure times.

US 20060069256A1 and WO 06020003A2 discloses ophthalmic compositions of comprising potent potassium channel blockers or a formulation thereof in the treatment of glaucoma and other conditions which leads to elevated intraocular pressure in the eye of a patient. The invention also relates to the use of such compounds to provide a neuroprotective effect to the eye of mammalian species, particularly humans.

WO 0189578A1 discloses ophthalmic composition comprising acetazolamide solubilized in an aqueous medium in the presence of a cyclodextrin and a stabilising water soluble polymer, further comprising a polymer selected between a hydroxyethyl-cellulose and a methylcellulose.

EP 0540813B1 & EP 0540813A1 relates to a sustained release formulation of the anti-glaucoma drug acetazolamide with improved release characteristics, comprises
substantially spherical, essentially binder-free pellets of the drug which are coated with a release-controlling membrane.

US 5494901 & WO 9415582A1 discloses a topical composition comprising an amount of a carbonic anhydrase inhibitor and an amount of β-cyclodextrin derivative effective in increasing the bioavailability of the carbonic anhydrase inhibitor when coadministered topically to the eye.

US 5472954 & US 5324718 discloses a method for enhancing the complexation of a cyclodextrin with a lipophilic and/or water-labile active ingredient, cosmetic additive, food additive or agrochemical, comprising combining from about 0.1 to about 70% (weight/volume) of a cyclodextrin, from about 0.001 to about 5% (weight/volume) of a pharmacologically inactive water-soluble polymer, cosmetic, food or agricultural composition, and said lipophilic and/or water-labile active ingredient in an aqueous medium, the polymer and cyclodextrin being dissolved in the aqueous medium before the active ingredient is added. Related methods, co-complexes of active ingredient/cyclodextrin/polymer, pharmaceutical, cosmetic, food and agricultural compositions and cyclodextrin/polymer complexing agents are also provided.

WO 9317664A1 discloses combinations of at least one cellulosic polymer and at least one carboxy vinyl polymer have an unexpectedly high viscosity. Compositions containing these polymeric combinations have a number of applications, such as in pharmaceuticals, especially in the field of ophthalmics. Topical ophthalmic compositions containing these polymeric combinations are contemplated for the relief of the symptoms of dry eye syndrome.

EP 0126684B1 disclose an effect of body temperature and pH to induce a liquid to gel transition of the polymer which contains a drug or therapeutic agent. The goal of such a delivery system is to achieve a greater degree of bioavailability or sustained concentration of a drug to a body cavity. The drug delivery system can be used in any body cavity, or as an injectable, as a topical or dermal application and/or ophthalmic application.
US 4888168 and US 4474751 disclose stable ophthalmic aqueous composition for topical administration, comprising acetazolamide and either a pre-formed, pharmaceutically acceptable, aqueous gel or an aqueous gel-forming liquid capable of forming a pharmaceutically acceptable gel in situ when applied topically to a patient; said composition having a pH of less than 5.0.


US 20060177430A1 relates to an ophthalmic formulation is provided for the prevention and treatment of adverse ocular conditions. In one embodiment, the formulation contains at least 0.6 wt. % of a biocompatible chelating agent, an effective permeation enhancing amount of an ophthalmic permeation enhancer such as methylsulfonylmethane (MSM), an anti-AGE agent, i.e., a compound that serves to reduce the presence of advanced glycation endproducts (AGEs) in the eye, and a pharmaceutically acceptable ophthalmic carrier suited to the particular formulation type (e.g., eye drops or ointments). In another embodiment, the formulation contains an ophthalmologically active agent and MSM as a penetration enhancer.

US 20050244506A1 relates to Sustained release intraocular implants and methods for preventing retinal dysfunction. Biocompatible intraocular microspheres and implants include an alpha-2 adrenergic receptor agonist and a polymer associated with the alpha-2 adrenergic receptor agonist to facilitate release of the alpha-2 adrenergic receptor agonist into an eye for an extended period of time.

WO 9951273A1 relates to gelling ophthalmic compositions containing xanthan gum. Ophthalmic drug delivery vehicles which are administrable as a liquid and which gel upon contact with the eye are disclosed. The vehicles contain xanthan gum.

EP 0833609B1 disclose compositions and methods for reducing the decomposition rate of polymeric bioadhesives and viscosity enhancers, such as poly(acrylic acids). The compositions include at least one strong, stable chelating agent, preferably an
organophosphorous compound such as diethylene triamine penta(methylene phosphonic acid). These biocompatible compositions are especially useful in the ophthalmic field.

US 5795913 and EP 0752847B1 discloses an ophthalmic composition in the form of a topical aqueous solution consisting of ophthalmologically active agent, an ion sensitive, hydrophilic polymer, inorganic salts and buffers, a wetting agent a, water, and optionally a pH regulating agent in an amount sufficient to give a pH of 4.0 to 8.0 to the composition, the ratio between salt and polymer components being such that the solution exhibits a viscosity of less than 1000 mPas. The composition contains a sufficient polymer to provide for a controlled absorption of the drug into the eye.

II. Evaluation Methods of Ophthalmic Drug Delivery Systems

Ticho et al., (1979) evaluated the release of pilocarpine from ophthalmic emulsion using the dialysis bag technique. The dialysis bag was filled with the preparation and it was suspended in normal saline at 37°C. The saline samples were withdrawn at various time intervals and analyzed for drug content.

Miller and Donovan, (1982) administered pilocarpine 25% poloxamer gel to rabbit's eyes. The ocular activity of pilocarpine was assessed by measuring intraocular pressure.

Mitra and Mikkelson, (1982) obtained, miosis-time profile using rabbits following the instillation of 25.0 μl of 1% pilocarpine nitrate solution. It was found that the area under the miosis-time profiles and the maximum observed pupillary diameter changes, decreased as the citrate buffer concentration was increased.

Schoenwald and Huang, (1983) determined the permeability characteristics of a group of β-blocking agent across excised rabbit corneas. Various correlations were determined for the log permeability coefficient as a sum of log functions of the partition (or distribution) coefficient, molecular weight and/or degree of ionization.
Ahmad and Patton, (1984) utilized an in-vivo technique to study the effect of pH and buffer capacity on the precorneal disposition and ocular penetration of pilocarpine in the rabbit eyes. Test solutions were prepared in 0.0667 M phosphate buffer at various pH (4.5, 6.0 and 7.2) and at various phosphate buffer concentrations (0M, 0.00667 M, 0.0667 M, 0.1M) at pH 4.5. It appeared that following the instillation of pilocarpine nitrate solutions buffered below the physiological pH of the lacrimal fluid, the extent of depression of the tear film pH and the tear pH re-equilibration time depend not only on the pH of the solution but also on the precorneal fluid dynamics, and the buffer capacities of the instilled solution and that of the tears. In order to ensure optimum ocular penetration of pilocarpine, the system should not depress the tear film pH appreciably, and should allow rapid tear pH re-equilibration.

Saettone et al., (1984) tested mydriatic activity of 0.2% tropicamide in humans and rabbits using polymers carboxymethyl cellulose, low molecular weight hydroxypropyl cellulose, medium molecular weight hydroxy propyl cellulose, polyvinyl pyrrolidone and polyvinyl alcohol. All vehicles increased the ocular bioavailability of drug in both humans and rabbits when compared with a non-viscous solution.

Saettone et al., (1986) found that in rabbits, administration of pilocarpine in the hydrogel vehicles doubled the drug bioavailability (as expressed by the area under the miotic response vs time curve, AUC) with respect to aqueous solution of the drug, however, no statistical differences were apparent in AUC values of the hydrogels.

Ahmad et al., (1987) examined the diffusion of different drugs like propanolol, timolol, penbutol and nadolol across the isolated corneal and scleral membrane of the rabbit using a two chamber glass diffusion cells. The scleral permeability was found higher than the respective corneal permeability.

Ahmed and Chaudhari, (1988) prepared pilocarpine solutions with equimolar acetate, phosphate and citrate buffers. Four solutions in single 25 µl dose were given to 6 conscious rabbits and in-vivo tear pH was determined with pH sensitive paper at different time intervals and lacrimal fluid pH-time profiles were made. Phosphate buffer was used as a buffer of choice.
Grass and Robinson, (1988) conducted ultrastructural analysis to augment results of classical kinetic studies. Scanning electron microscopy (SEM) allowed visual inspection of cellular junctions on corneal epithelium and endothelium. Results suggested that hydrophilic compounds were preferentially located in intercellular spaces, whereas hydrophobic compounds were associated with the lipid structures of the tissue.

Attia et al., (1988) investigated the disposition of dexamethasone in different eye tissues following application of ophthalmic inserts and suspensions.

Vasantha et al., (1988) evaluated films of pilocarpine nitrate by placing them in the culture bottles containing phosphate buffer of pH 7.4. The culture bottles were shaken in a thermostatic water bath at 37°C. Samples were withdrawn and analyzed for drug contents.

Saettone et al., (1989) evaluated the ophthalmic vehicle based on hyaluronic acid and polyacrylic acid (solutions, gels and matrices) containing pilocarpine and tropicamide for muco-adhesion, ocular retention and biological activity (miosis, mydriasis) in rabbits.

Grove et al., (1990) instilled 1% solution of L-653.328 in different concentrations of hydroxy ethyl cellulose to rabbits and ocular concentrations were measured in cornea, aqueous humor, iris and ciliary body. It was found that maximum drug concentrations in all three ocular sites increased concomittantly with increase in viscosity of polymers.

Chast et al., (1991) described the various resorption sites of morphine when administered through the conjunctiva.

Finne et al., (1991) evaluated circular matrices of timolol maleate by rotating disc method. The matrices were attached to rotating disc with molten blockform paraffin. The disc was rotated at 100 r.p.m and suspended in phosphate buffer. The buffer was
withdrawn at various time intervals and analyzed for drug content.

Thermes et al., (1992) measured the ocular bioavailability of 0.5% Timoptol (in PVA and bioadhesive polymer-polyacrylic acid) in cornea, aqueous humour, iris and ciliary body of rabbit's eye. It was found that bioadhesive polymer gave highest timolol concentration in ocular tissues.

Fitzgerald et al., (1992) used scintigraphy to assess the precorneal residence of a new ophthalmic delivery system (NODS) in man. The *in-vitro* evaluation of PVA based NODS was done using a rotating paddle apparatus.

Jarvinen et al., (1992) evaluated the effects of two polymers (sodium carboxy methyl cellulose and carbopol 940) on systemic absorption of ophthalmic timolol in rabbits. Both polymers gave same types of results.

Maurice and Srinivas, (1992) tested gelrite in humans for its efficacy as an ophthalmic vehicle, by a noninvasive fluorometric technique.

Thermes et al (1992) demonstrated that PVA formulation increased transcorneal penetration of timolol.

Kyyronen et al., (1992) studied the methyl prednisolone concentrations in tear fluids of New Zealand rabbits after ocular application of films and microspheres.

Saettone et al., (1993) studied release of drug from flat, circular ophthalmic inserts from one side. To this purpose, uncoated and one-side coated hydroxypropylcellulose inserts containing timolol were prepared and evaluated. An acrylic copolymer (Eudragit RS) was used as coating material. Timolol release from inserts was studied both in vitro and in vivo. Results revealed that Timolol release in vitro from the coated inserts much slower than from the uncoated ones. However, one-side coated inserts failed to show significant improvements with respect to the uncoated samples.

Lisbeth et al., (1994) studied ocular sustained delivery of prednisolone using
hyaluronic acid benzyl ester films. Tear fluid concentration were measured in rabbits after administration of the test films. Drug release in-vivo was seen to depend qualitatively on the hydrophilicity of the polymer used to make the film.

Callegan et al., (1995) induced bacterial keratitis in rabbits and treated with antibiotics in collagen shield and iontophoresis. Significant t test was applied to different group of animal

Saettone et al.,(1995) carried out in-vitro dissolution studis of coated mini tablets (ophthalmic inserts prepared by compression) of timolol maleate by using an apparatus consisting of small, stainless steel woven wire ( 50 mesh ) basket (diameter 18mm, height 20mm), rotating at 20 rpm. Release rate studies were performed at 30°C. (temperature of the eye).

Sasaki et al., (1996) used a cylindrical cell to characterize the absorption properties of ocular membranes in-situ. Rabbits were anaesthetized and placed in a position to brought one eye in the upright position. A plastic cylindrical cell was then fitted over the cornea, sclera and conjunctiva of the eye. Tilisolol solutions were filled into the cells and samples of 0.5 μl was collected at 10 minutes and analyzed for drug content. It was found that in-situ method using a cylindrical cell was a useful method for investigation of the ocular absorption of ophthalmic drugs.

Desai and Blanchard, (1998) formulated gel preparations of pilocarpine hydrochloride with pluronic F127 and assessed the in-vivo performance of the formulations using miosis in albino rabbit as a measure of ocular bioavailability. An improvement in bioavailability of pilocarpine was obtained as compared to conventional eyedrops.


Dimitrova et al.,(2000) prepared an aqueous solution of indomethacin and evaluated it by using an absorption simulator for in-vitro diffusion studies. 2ml sample was placed in a modified donor phase compartment. The receptor phase was 100ml of phosphate
buffer of pH 7.5 and the membrane was placed in between the donor and the receptor compartment.

Parkinson et al., (2003) evaluate ocular iontophoresis tolerance in healthy volunteers using novel OcuPhor trademark hydrogel drug delivery. Safety and tolerance were determined by subjective and objective ophthalmic assessments. The applicators were well tolerated and no clinically significant changes in symptomology or in ophthalmic assessments were seen following exposure to 0.3-0.3 mA for 20 min or 1.5 mA for 40 min. At 4.0 mA 2 of 4 subjects reported a burning sensation under the applicator during dosing which resolved by 22 hr post-dose; superficial changes in fluorescein staining were observed at 1 hr, but not at 22 hr. The OcuPhor trade mark system has promise for noninvasive drug delivery to the eye.

III. Hydroxy Propyl β-Cyclodextrin in Ocular Drug Delivery:

Loftsson et al., (1996) investigated the effect on water-soluble polymers and ionization of the drug molecules of cyclodextrins, namely 2-HP-β-cyclodextrin on solubilization of drugs. It was found that the HPβCD solubilization of the drugs could be influenced/improved by ionization of drug molecule through pH adjustment and through the use of some water-soluble polymers namely HPMC, PVP and CMC.

Martin et al., (1994) studied inclusion complexes of ciprofloxacin, norfloxacin, tinidazole with P-cyclodextrin, which were incorporated in ocular implants to as sustained ocular preparation of anti-infective drugs for prolonged use. It was that the stability of drugs improved alters complexation. The release characteristics were also found to be better.

Loftsson et al., (1994 b) and Loftsson et.al. (1997) found that the solubilizing effect of 10% w/v HPβCD solution on a series of drugs and other compounds was observed and it was found to increase from 12% to upto 129% in some of the cases when 0.25% w/v PVP was added to the aqueous CD solutions. Similarly carboxymethylcellulose was also found to enhance the solubility of various drugs.
Loftsson et al., (1994a) observed that acetazolamide and other carbonic anhydrase inhibitors can show IOP lowering effect (in rabbits) by formulating the drugs in aqueous eye drop solutions containing 2% HPβCD and HPMC.

Aithal et al., (1995) prepared ciprofloxacin-(3-cyclodextrin complex and found 's.3Z in-vitro activity of ciprofloxacin on E. coll and S. aureus was better on complexation. The complexes were found to be very effective as a local antibacterial agent when used in dental implants.

Kristinsson et al., (1996) studied and found that addition, of 0.1% w/v HPMC, and heating, increases the apparent stability constant of the dexamethasone 2-HPβCD complex from 1230 M⁻¹ to 1550 M⁻¹. At the same time the heating also enhanced the dexamethasone delivery into the eye.

Udupa et al., (1996) studied the interaction between ciprofloxacin & β-CD, leading to formation of an inclusion complex, by phase solubility, UV, X-ray diffractrometry, DSC, DTA and IR spectrometry. Change in crystallinity coupled with improved stability of the drug was observed on complexation.

Aithal et al., (1996) prepared ciprofloxacin-βCD inclusion complex and showed that the dissolution and diffusion of ciprofloxacin-βCD inclusion complex in buffer solution of pH 7.2 and 1.2 was better compared to the plain drug.

Van Santvliet et al., (1998) prepared inclusion complexes of the free bases of antazoline and tetracaine with HPβCD in order to improve their tolerance in ophthalmic solution. The physicochemical property of the drug: HPβCD was determined and the inclusion complexes were characterized by 'H and ''C NMR spectroscopy. The relationship between surface tension of the solution and the tolerance was also observed.

Nagaraju et al., (1998) prepared biodegradable dental implants containing inclusion
complexes of ciprofloxacin and norfloxacin with β-cyclodextrin. Dental implants were formulated using poly (6-caprolactone), a biodegradable polymer the treatment of acute periodontitis. The drug complexation improved its stability.

Jayachandra Babu et al., (1999) studied the effect of ageing on the physicochemical stability of glibenclamide-cyclodextrin system and tablets made with cyclodextrin complexed with glibenclamide and it was found that age related dissolution problem of glibenclamide can be overcome by utilizing the glibenclamide cyclodextrin complex in the tablet dosage form.

Popovici et al., (1999) formulated four variants of ciprofloxacin HCl (equivalent ~ 0.3% ciprofloxacin base) ophthalmic solution using some auxiliary substances stabilizing and preserving role. In two of these variants, β-cyclodextrin was associated. The tolerance of the eye drop was determined by the eye irritation test on rabbit conjunctiva and in-vitro availability of ciprofloxacin assessed by microbial test.

Sukhiija et al., (1999) studied the interaction of sparfloxacin with β-cyclodextrin and role of β-cyclodextrin in sparfloxacin release from the tablet. A 1:1 complex was formed successfully by kneading technique. The complex formation resulted in improved solubility and dissolution rate and the tablets prepared with sparfloxacin-β-cyclodextrin complex also showed significantly increased dissolution of the drug.

Vavia et al., (1999) prepared inclusion complex of ketoprofen, a poorly soluble RAID agent, with β-cyclodextrin and HPβCD in 1:1 molar ratio. The complexes were characterized by UV, TIR, XRD, DSC and 1H-NMR spectroscopy. It was demonstrated that the aqueous solubility and dissolution rate of ketoprofen were significantly increased when complexed with freeze-drying technology.

Baboota & Agarwal, (2000) have reported the preparation and physical characterization of inclusion complex of Meloxicam with either β-cyclodextrin or HP-β-cyclodextrin. Inclusion complex of Meloxicam had faster dissolution and a reduced gastric ulceration thus creating a dosage form with improved delivery of the
Loftsson et al., (2007) discloses Cyclodextrins and their pharmaceutical applications. In the 1930s, Freudenberg identified γ-cyclodextrin and suggested that larger cyclodextrins could exist. Freudenberg and co-workers showed that cyclodextrins were cyclic oligosaccharides formed by glucose units and somewhat later Cramer and co-workers described their ability to form inclusion complexes. The first cyclodextrin-related patent was issued in 1953 to Freudenberg, Cramer and Plieninger.

Challa et al., (2005) published review article and highlights important CD applications in the design of various novel delivery systems like liposomes, microspheres, microcapsules, and nanoparticles. The article also focuses on various factors influencing inclusion complex formation.

IV. Marketed Ophthalmic Drug Delivery Systems:
A number of ophthalmic drug delivery systems have been introduced in the global market over the last many years. However none of this delivery system is available in the Indian market. A review of these marketed ocular drug delivery systems is presented as follows:

1. Ocular Inserts
   (a) Ocusert® (Alza Corporation)
The ocsers is a flat, flexible elliptical device consisting of three layers. Two outer layers of ethylene vinyl-acetate enclosed, the inner core of pilocarpine gelled with alginate (Urguhant, 1980) A retaining ring of ethylenevinyl-acetate, impregnated with titanium dioxide for visibility encloses the drug reservoir circumferentially. The ocsers is marketed in two sizes, ocsers Pilos-20 and ocsers Pilos-40, representation of two different release rates (20 and 40 µg/h).

   (b) Lacrisert®
The lacrisert is a sterile, rod shaped device made of hydroxy propyl cellulose without
any preservatives and it is used for the treatment of dry eye syndrome. It was introduced by Merck, Sharp and Dohme in 1981 (LaMotte et al., 1985). The device weighs 5 mg and measures 1.27 mm in diameter with a length of 3.5 mm.

(c) Soluble ophthalmic drug inserts (SODI) (Diversified Tech. Inc.)
The SODI (soluble ocular drug insert) is a small oval wafer which was developed by soviet scientists for cosmonauts who could not use eye drops in weightless conditions. Its dimensions are 9 mm x 4.5 mm with a thickness of 0.35 mm.

2. Contact Lenses
The primary use of contact lenses is for vision correction. In addition to this function, therapeutic soft contact lenses (Matoba et al., 1985) are often used to aid in corneal wound healing.
The drug release from contact lenses is extremely rapid, most of the drug being released within the first 30 min (Seattone et al., 1993).

3. Collagen Shields
Collagen Shields were originally developed by Fyodovov in the Soviet Union as bandages lenses to promote healing after radical keratotomy (Marmer et al., 1988).
There are presently three different types of Biocor collagen shields marketed by Bausch and Lomb Pharmaceuticals, Tampa, Florida. These are Biocor 12, 24, and 72, representing different times of dissolution in hours.

4. Sol to Gel Systems
Timoptic-XE™ (Merck and Co. Inc., 1994) Sterile ophthalmic gel forming solution is available in the market and it contains Timolol maleate. Timoptic–XE sterile ophthalmic gel forming solution is a colorless to nearly colorless, slightly opalescent and slightly viscous solution. It is supplied as a sterile, isotonic, buffered, aqueous solution of timolol maleate in two dosage strengths of 0.25% and 0.5%. Each ml of Timoptic 0.5% contains 5.0 mg of timolol maleate, inactive ingredients Gelrite® gellan gum, tromethamine, mannitol, water for injection and preservative benzododecinium bromide. When instilled in the eye, the solution is converted into gel form and release drug over a long period of time (Chein et al., 1992, Yusuf et al., 2006).