Vol 2| Issue 2| 2012 | 77-86.

e-ISSN 2248 – 9142
print-ISSN 2248 – 9134

International Journal of
Current Pharmaceutical & Clinical Research

www.ijcpcr.com

CURRENT STATUS AND ADVANCED APPROACHES IN OCULAR DRUG DELIVERY SYSTEMS

K. Thamizhvanan*, R. Himabindu, K. Sarada, N. Hyndavi, K. Roopa Lahari

*Department of Pharmaceutical Biotechnology, Sree Vidyanikethan College of Pharmacy, Tirupathi-517102, Andhra Pradesh, India.

ABSTRACT

The purpose of this review is to provide an update on the current knowledge within this field of ocular drug delivery. Drug delivery to eye has always been a daunting task in the field of pharmaceutical research due to unique anatomy and physiology of the eye. Innovatory novel therapy for treatment of ocular diseases has emerged due to the recent advance in drug delivery approaches and material sciences. In the earlier periods, drug delivery to the eye has been limited to topical application, redistribution into the eye following systemic administration or directs intraocular/periocular injections. Conventional drug delivery systems: which include solutions, suspensions, gels, ointments and inserts, suffer with the problems such as poor drainage of instilled solutions, tear turn over, poor corneal permeability, nasolacrimal drainage, systemic absorption and blurred vision. Nano carrier based approaches seem to be most attracting and are extensively investigated presently.

Key words: Ocular drug delivery, Eye medications, Side effects.

INTRODUCTION

Ocular drug delivery has remained one of the most taxing tasks for pharmaceutical scientists. The unique structure of the eye restricts the entry of drug molecules at the required site of action. Innovatory novel therapy for treatment of ocular diseases has emerged due to the recent advance in drug delivery approaches and material sciences. In the earlier periods, drug delivery to the eye has been limited to topical application, redistribution into the eye following systemic administration or directs intraocular/periocular injections. Conventional drug delivery systems: which include solutions, suspensions, gels, ointments and inserts, suffer with the problems such as poor drainage of instilled solutions, tear turn over, poor corneal permeability, nasolacrimal drainage, systemic absorption and blurred vision. Nano carrier based approaches seem to be most attracting and are extensively investigated presently. It has been reported that particulate delivery system such as microspheres and nanoparticles; vesicular carriers like liposomes, niosomes, pharmacosomes improved the pharmacokinetic and pharmaco dynamic properties of various types of drug molecules. Emerging new controlled delivery systems such as dendrimers, micro emulsions, mucoadhesive polymers, iontophoresis, prodrug approaches have been developed for this purpose. The novel systems offer main fold advantages over conventional system as they increase the efficiency of drug delivery by improving the release profile and also to reduce drug toxicity. The rapid progress of the biosciences opens new possibilities to meet the needs. The review article briefly covers general outline of various conventional and recent past time formulations for ophthalmic drug delivery. It also provides the limitations of conventional delivery with a view to find modern approaches like nano technology, stem cell therapy as well as gene therapy, vesicular systems for the treatment of various ocular diseases [1,2].

Corresponding Author :- **K. Thamizhvanan** Email:- ktvanan2006@yahoo.co.in

Table 1. Eye Medications

Classification/Use/Indication	Medication	Specific Uses	Contra Indication (If Any)
Eye rinses USE: clean, rinse, flush INDICATIONS: clear mucus before instilling medications, remove debris from eye	Sterile, buffered isotonic solutions containing sodium citrate, sodium phosphate		
	Combinations of water, boric acid, zinc sulphate		
Relieve dryness Indication: keratoconjuctivitis sicca whenever general anesthesia is used in keratitis, ectropion.	Polyvinypyrrolidine Polyvinyl alcohol, Methyl cellulose, Ethylene glycol Polymers, Refined petrolatum, Refined lanolin Refined peanut oil		
MUCOLYTICS	Acetylcysteine		Very expensive
USE: prevent collagen break-down, break up mucus INDICATIONS: melting, corneal ulcers, chronic conjunctivitis, keratoconjuctivitis	Autologus plasma		Sometimes used in place of acetylcysteine
ANESTHETICS USE: Topical pain relief INDICATIONS: Minor surgery, eye Examination, diagnostic procedures, preoperative evaluation of entropion, removal of foreign bodies	Pilocarpine 0.5% Tetracycline HCL 0.5% Chloramphenicol 0.5%solution and 1% ointment	Susceptible bacteria may include	Never use therapeutically. May cause corneal irritation.
ANTIBIOTICS (SINGLE) USES: Preparation for an intraocular			
Treatment of infection (if possible, select specific agent for microbe; if testing is not possible, broad spectrum or combination antibiotic is preferred) Preventive pre and/or post-procedure. INDICATIONS: Treat susceptible infections contributing to uveitis, conjunctivitis, blepharitis, keratitis, keratoconjuctiviis sicca. Control secondary bacterial infections in conditions such as proptosis of the globe, entropion, corneal ulcer, corneal abrasion.	Bacitracin 500U/g ointment	Susceptible Bacteria may include Staphylococcus, Cornyebacterium, Pseudomonas, Proteus spp, Escherichia coli, Hemophilia, Enterobacter, Moraxella	
	Gentamycin0.3% Solution and 0.3% ointment		
	Tobramycin 0.3% Solution and 0.3% Ointment		
	Chlortetracycline 1% ointment		
	Erythromycin 0.5% ointment		
	Neomycin 0.35% ointment		
ANTIBIOTICS (COMBINATION) USE: same as single antibiotic When more than one type of microbe is present or when testing for specific identification is not possible INDICATIONS: same as single antibiotic	Neomycin sulfate, Polymyxin B sulfate, Bacitracin ointment	Preferable drug for broad spectrum coverage without culture/sensitivity	
	OxytetracyclineHCL, Polymyxcin B ointment		
ANTIINFLAMMATORY- STEROIDAL USES: All allergic ocular diseases. Nonpyrogenic inflammations of any ocular tissue. Reduction of scar tissue. Certain ocular surgeries. INDICATIONS: Blepharitis, Conjuctivitis, proptosis of the globe uveitis,entropion, prolapse of the gland of the 3rd eyelid, keratoconjuctivitis sicca, chronic superficial keratitis	Prednisolone acetate Suspension		Avoid when there is no specific indication for steroid use, treatment of corneal ulceration, viral infection and keratomalacia. May promote fungal infections. May alter insulin requirements in diabetic animals
	Dexamethosone		
	Triamcinolone (topical and injectable) Betamethasone (topical and injectable)		
	Methylprednisolone acetate (injectable)		

ANTIBIOTIC/STERIOD COMBINATIONS USES: Control inflammation and bacterial infection, treat acute and chronic inflammatory processes of the eye INDICATIONS: Acute or chronic conjunctivitis, inflammation, proptosis of the globe, entropion, uveitis	Neomycin sulfate, Polymycin B sulfate, Dexamethasone Solution and ointment, Hydrocortisone Acetate solution and ointment Prednisolone Solution and ointment, methyl prednisolone ointment, Gentamycin with betamethasone	Commonly used	
	Chloramphenicol		
TOPICAL NON-STEROIDAL ANTI-INFLAMMATORY USE: Reduce inflammation INDICATIONS: Uveitis, cataract surgery, panophthalmitis, corneal ulcers	Flurbiprofen Suprofen Diclofenac		May delay corneal healing
IMMUNOSUPRESSIVE DRUGS USE: Supress the immune response INDICATIONS: Keratoconjuctivitis sicca, corneal ulceration associated with keratoconjuctivitis sicca, nodular granulomatous episclerokeratitis, unresponsive uveitis	Cyclosporine Azathioprine (systemic)	Drug of choice for keratoconjuctivitis sicca	Use with extreme caution potentially toxic to liver and bone marrow
MYDRIATICS USE: Dilation of the pupil (mydriasis), Control ciliary spasm and the accompanying pain which causes eyelid spasm, photophobia and lacrimation INDICATIONS: Non-surgical treatment of axial leukoma (white spot on cornea) and axial cataracts. Pre-operative mydriasis for cataract surgery and other ocular surgery, corneal abrasions, corneal ulceration, keratitis, anterior uveitis, possibly proptosis of the globe.	Atropine sulfate	Not for routine eye Examination	May compromise tear production May predispose to local irritation. Contraindicated in glaucoma or in animals predisposed to glaucoma
	Tropicamide	Short-acting-used for eye examinations	
	Phenylephrine HCL	Combined with atropine	
MIOTICS USE: Cause contraction of the pupil, enhance aqueous flow. INDICATIONS: Keep luxated lens in posterior chamber, treat glaucoma	Demecarium bromide		Cholinesterase inhibitor, do not use with organophosphate insecticides
	Pilocarpine		May irritate the eye
	Carbachol		All miotics are contraindicated in glaucoma secondary to anterior uveitis
ADRENERGICS USE: Lower intraocular pressure. Control capillary bleeding during surgery INDICATIONS: Control/treat glaucoma		Agonist/increases outflow of aqueous humour	
	Timolol maleate	Betablocker/reduces aqueous formation	
CARBONIC ANHYDRASE INHIBITORS USE: Decrease aqueous humor production INDICATIONS: Control/treat glaucoma	Acetazolamide (given orally)		Metabolic acidosis and electrolye imbalances
	Methazolamide		
	Dichlorphenamide (given orally)		Use with caution in animals with sulfonamide sensitivity
	Ethoxzolamide		

CHOICE OF DRUGS FOR OCULAR DELIVERY

Eye medications can be delivered by several methods. Topical medications are applied directly to the eye surface. The topical medications may be available as eye drops and ointments. This method of administration is appropriate for both hospital and home treatment of eye diseases in cats. In addition, veterinarians may administer medications via injection into the eye. Common sites for these injections are sub conjunctival (beneath the conjunctiva), retro bulbar (behind the eye),or intraocular (into the eyeball).In addition, diseases of the eye may be treated with medications that are given directly to the cat, either by mouth or by injection. Finally, eye disease may not be limited to the eyes; they may be a sign of disease that is affecting the entire body. In this case the veterinarian will prescribe medication to treat the primary illness, as well as to control the problems in the eyes.

FORMULATIONS

Liquids –Eye Drops/Lotions

Eye drops may be solutions or suspensions and are comparatively convenient, safe, immediately active and acceptable to patients. An eye drop is sterile contains preservative (if not, single use only) is isotonic has a ph of about 7.4 for patient comfort and (if to be used more than once) has a limited shelf life after opening. Eye lotions are isotonic, sterile solutions for the irrigation of the eye, usually as a single use first aid treatment. Eye drops provide a pulse entry of the drug, followed by a rapid decline in drug concentration, the kinetics of which approximate to first order. Many patients particularly the young and elderly find eye drops difficult to apply and may not receive the correct dose. Inter and intra-subject variation in the therapeutic response is an inevitable consequence. Polymers are frequently added to ophthalmic solutions and suspensions in order to increase the viscosity of the vehicle; this prolongs contact with the cornea, after enhancing the bioavailability. It has been reported that an increase in the corneal penetration of a drug is at maximum if the viscosity of the eye drop solution is about 15to 150 m PaS. Any further increase in viscosity would have less effect on the drainage rate and tear film thickness and has been implicated with interference of the vision and resisting movement of eyelids [3].

Eye Ointments

Ointments are semisolid preparations intended for external application. They are usually formulated using mixtures of semisolid and hydrocarbons (paraffin's) which have a melting or softening point close to body temperature and are non-irritating to the eye. Ointments may be simple bases, where the ointment forms are continuous phase or compound bases where a two-phased system (eg: an emulsion) is employed. The medicinal agent is added to the base either as a solution or as a finely micronized powder. Upon installation into the eye, ointments break up into small droplets and remain as a depot of drug in the cul-de-sac for extended periods. Ointments are therefore useful in improving drug bioavailability and in sustaining drug release. Although safe and well tolerated by the eye, ointments suffer with relatively poor patient compliance due to blurring of vision and occasional irritation. For this reason they are often used as a means of night time medication [4].

Aqueous Gels

Aqueous gels consist of high molecular wt, hydrophilic cross linked polymers or co-polymers that form a three dimensional network in water. These gels have been shown to combine significantly longer residence times in the cul-de-sac with increased drug bioavailability. Typical gelling systems include cellulose derivatives, polyvinyl alcohol hyaluronic acid and carbomer .the in situ forming gels are viscous liquids that shift to a gel phase upon exposure to physical conditions. These systems are more acceptable for patients since they are administered into the eye as a solution, after which they undergo transition into a gel. Studies have shown that the precorneal residence times of some in situ gelling systems can be several hours. The polymers use for these exhibit reversible phase transitions. The change in viscosity can be due to a change in ph, temperature or ionic strength. In situ gel forming materials include gellan gum, poloxamer and cellulose acetate phthalate latex [5].

Ocuserts and Lacriset

Ocular inserts (ocuserts) are sterile preparations with solid or semisolid consisting and whose size and shape are especially designed for ophthalmic application. They offer several advantages as they increase ocular residence, possibility of releasing drug at a slow constant rate , accurate dosing and increased shelf life with respect to aqueous solutions. Pilocarpine ocular therapeutic system is the first product marketed by Alza incorporation USA from this category. Lacrisert is a sterile rod shaped device for the treatment of dry eye syndrome and keratitis sicca and was introduced by Merck, Sharp and Dhome in 1981. They act by imbibing water from the cornea and conjunctiva and form a hydrophilic film which lubricates the cornea [6].

ROUTES OF ADMINISTRATION

Topical

Topical administration is the usual route associated with ophthalmic drugs. Some of the many factors to consider selecting a drug for topical therapy are what is the target tissue and can the drug reach the targeted in therapeutic levels; is the drug available in more than one form; the desired frequency of administration and practically of it being administered; owner compliance; patient cooperation; comparative cost of medications; and potential side effects and toxicities.

In general, topical therapy will achieve therapeutic drug levels only on the ocular surface and a far posterior as the iris-ciliary body. Topical therapy should not be relied on posterior segment diseases. The frequency of therapy will vary with the severity of the condition, type vehicle used, and the duration of action of the drug administered. For instance, one installation of atropine in the normal eye will maintain mydriasis for 3-4 days, where as in an eye with iritis, mydriasis may require installation 3-4 times per day. Antibiotics used for minor infections or prophylaxis may be given q12-8h but for an infected corneal ulcer the concentration infusion which limits it applications [7].

Subconjuctival

Injection of the drug under the bulbar conjunctiva is also usually under tenon`s capsule and consequently the drug is deposited against the sclera, thus bypassing the lipid barrier that the intact cornea presents. Penetration of drug is mainly by diffusion through the sclera, although the leakage through the needle hole and topical absorption does occur. The use of reposital for long acting drugs can produce a prolonged therapeutic effect, but there is nothing inherent in the route that allows the drugs to last for long period of time. Most animals can have injection performed under topical anesthesia. Injection is the usual anterior location will achieve therapeutic levels only in the anterior segment, although if injected posterior, therapeutic retinal levels may be achieved. Injection of a drug sub conjuctivaly in the palpebral conjunctiva, as it is frequently performed in food animal medicine, loses the advantage of being absorbed through sclera.

Advantages include: aqueous products can be absorbed into the eye and if reposital type products are used, a prolonged drug level can be obtained without bother of frequent topical medication. Disadvantages include: perforation of the globe with the needle can occur; many drugs are irritating; if reposital products are used, it is difficult to discontinue therapy, for instance to stop steroids if they become contraindicated; increased systemic absorption and potential side effects [8].

Intraocular or Intracameral Administration

Intraocular injections are given when heroic means are needed to control a problem. The dangers of the trauma of injection plus the toxicity of many drugs to the corneal endothelium, lens and retina have to be balanced against the therapeutic benefit. The concentration of drugs is drastically reduced when intraocular injections ate utilized. The injection can be in either the anterior chamber (intracameral) or the vitreous or both depending on the condition. Intravitreal injections are often the only means of achieving significant drug levels in the vitreous. The most common drugs administered intracamerally are antibiotics for endopthalmitis and tissue plasminogen activator for fibrin formation [9].

Systemic Administration

Due to presence of BRB, systemic administration has achieved a limited success to deliver drugs to the vitreo-retinal tissues. Only 1-2% of plasma drug concentration is achieved in the vitreous humor and therefore requires frequent administration to maintain therapeutic drug level. This route of administration may also result in non-specific binding of drug to other tissues and cause systemic cytotoxicity. Even though not an ideal strategy for ocular complication, intravenous administration of ganciclorvir orfoscarnet sodium has been used in the treatment of acute CMV retinitis [10].

POLYMERS USED IN FORMULATIONS

The polymers used in liquid form to improve the ocular bio availability of drug, to increase the viscosity of the preparation, to reduce the drainage route. Polymer hydration results in the relaxation of stretched; twisted macro molecules with exposes the adhesive sites. The high molecular weight polymers capable of forming hydrogen bonds and cannot crosses the biological membrane can ultimately increase the residence time. About 1,00, 000 Da of molecular weight of polymer require for successful muco adhesion. The cellulose derivatives are employed in the liquid dosage forms as viscosity enhancing ophthalmic vehicle. The hydroxyl propyl methyl cellulose (HPMC) and hydroxyl propyl cellulose (HPC) are ph-sensitive polymers also exhibit surface –active properties influencing the blinking rate with ultimately alters the elimination of the drug instilled. The poly (acrylic acid) (PAA) and corbomers were the first muco adhesives polymers and the protonated form at an acidic pH responsible for the mucoadhesion. The polyacrylates or corbomers are used in dry eye syndrome as artificial tears. The natural polymer solutions of sodium hyluronase have been employed successfully as tear substitutes in severe dry eye disorders. Chitosan micro or nanoparticles have higher precorneal retention than chitosan solutions. The mucoadhesive property is higher in the chitosan suspension than in solution. Cyclodextrins (CDs) are shown to be nontoxic to the eye, but are well tolerated in eye drop formulation, eg.cypclosporin A. The polygalactoronic 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 tremendous increase in dispersion of medium. CDs are cyclic oligosaccharides commonly composed of 6-8 a-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*. found that dimethyl-b-cyclodextrin is toxic to

the cornea and thus should not be used for corneal ophthalmic formulations. Hence, extensive corneal sensitivity studies should be conducts while developing with new formulation of CDs.

Aktas *et al.* studied the effect of hydroxyl propyl b-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 b-cyclodextrin into the formulation. The highest ionic response was obtained with the formulation prepared in a vehicle of Carbopol 940.

Luma *et al*. 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. Among different described generations, (POE III) and (POE IV) are promising viscous and injectable material. The report by Ghelardi et al. 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 obtained with viscofied formulations [11].

SEMI SOLID 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 appear to be only by a change in temperature, ph, or electrolyte composition. Poloxamer 407 is a polymer with a solution viscosity that increases when its temperature is raised to the eye temperature. Cellulose acetophthalate, polymer undergoing coagulation when the original pH of the solution (4.5) is raised to7.4 by the tear fluid; these are used to formulate hydrogels. These hydrogels containing high concentrations of polymers re used in dry eye symptoms. But apart from the reproducible administration of a dose compared to the application of preformed gels, the hydrogels can cause discomfort at the day time and cause blurred vision. The methyl cellulose (MC), hydroxyl ethyl cellulose (HEC) is used along with the charged surfactant in the timolol (TM) controlled-release in the viscosity. Thus acrylic compounds can also use as hydrogels to treat ocular irritation. The gellan gum forms a clear gel in presence of mono or divalent cations suitable for gelling system in glaucoma therapy. The hyluronase and chitosan also used in dry eye syndrome. Alginic acid is insoluble in water, but its salts form clear gel (sodium alginate) can be used in various hydrogel formulations. Nyogel forms Novartis containing carbomer and polyvinyl alcohol (PVA) as eye gel are popular in UK.

Lin and sung, prepared carbopal - 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 1150. Unique characterization of this polymer is reverse thermal gelation and this can be for ophthalmic drug delivery. Desai *et al.* 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 formulation, which had no additive present. Wilson *et al.* developed the novel method of radio labeling carbomer gels, with minimum change to their rheology that had permitted the non invasive 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 [12].

Opthalmic Insert 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. The recent study has indicated that ocular inserts incorporating a bioadhesive polymer, thiolated PAA are most useful one. Sultana *et al.* developed ocular inserts using PVP K-30and Eudragit. Lee *et al*. formulated the ocular insert containing phenylephrine and tropicamide containing gel foam R. the gel foam is a versatile drug carrier for either local or systemic drug delivery via ophthalmic route. Gurny ET AL. 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-pyrolidone, poly (amido amine) dendrimers and poly (dimethyl siloxane). Hiratani *et al.* developed soft contact lenses of TM capable of prolonging the permanence of TM n the precorneal area, compared to conventional contact lenses and eye drops. Soft contact lenses considered of N, N-diethylacrylamide (DEAA; main component of the matrix) methacrylic acid (MAA; functional monomer) and ethylene glycoldimethacrylate (EGDMA; cross linker) were prepared. Grzeskowiak, formulated solid ocular inserts made of poly (vinyl alcohol) containing sulfadicramide [13].

Wang *et al*. studied in *vitro* and in *vivo* evaluation in rabbits of a controlled release 5-fluorouracil subconjunctival implant based on a poly (d, 1-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 intra chain disulfide bonds with in the polymeric network after hydration. Hornhof *et al.* formulated inserts (diameter 2 mm)consisting of PAA 450-cysteine conjugate, a thiolated PAA 450 kDa, were prepared by direct compression and evaluated by fluoro photometry. The irritation score indicated that the inserts were well accepted and tolerated. In humans, the Bionite lens that was made from hydrophilic polymer 92-hydroxyl ethyl methacrylate) has been shown to produce a greater penetration of fluorescein. Intra ocular 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 anti inflammatory drug fluocinolone acetonide (FA) due to their hydrophobicity and network density [14].

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 with the application of viscous or sticky preparations such as ointments. The later 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 non dissolving 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 location, leading to a decrease in the dose required and a decrease in side effects. So far, various synthetic and natural biocompatible polymers have been used to manufacture microspheres for ocular drug delivery. Particulates such as nanoparticles, nanocapsules, submicron emulsions, and nano suspensions 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.* used polycarboxylic acid carriers such as polyacrylic acids and polyaconic acid in sub colloidal, nanoparticulate hydrogel forms that have a strong potential for sustained release of a drug in ocular delivery. Leucata 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 solutions. 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.* 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 nano particles (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 four fold. The SLN dispersion was perfectly tolerated and there was no evidence of ocular irritation [15].

Ion Exchange Resins

Ion exchange is a reversible chemical reaction where in an ion from solution is exchanged for a similarly charged ion attached to an immobile solid particle. The solid ion exchange particles are either naturally occurring inorganic zeolites or synthetically produced organic resins. Jani et al. developed novel delivery system for ophthalmic drugs using an glaucoma 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 934Pas a polymer, to enhance the physical stability and ease of resuspendability of the product. Moreau *et al.* 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 x hydrochloride (LB x HCL), for use in the treatment of glaucoma. 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 x 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 micro particulates formed of an erodible bioadhesive polymeric matrix of poly and polyvinyl pyrrolidane where in the ratio of poly (methyl vinyl ether/maleic anhydride0 to poly vinyl pyrrolidone ranges from approximately 1:1 to4:1 by weight, incorporating at least one ion exchange resin said ion exchange resin particle having approximately 2-50wt.% of a pharmaceutical compound releasably bound [16].

Gene Therapy

Non viral 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. Using nonviral strategies, oligonucleotides (ODNs) can be delivered naked (less efficient0or 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. Moreover, a specific vector can be selected according to disease course and intensity of manifestations fulfilling specific requirements such astha duration of drug release and its level along with cells and tissues specific targeting nonviraldelivery 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. However, in developing nonviral gene carriers, those that are efficient *in vitro* often fail to show the same effiency 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*. 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.* developed, controlled release of gene therapy vectors from hydro gels using different polymers as a function of the physical properties for both the hydrogel and the vector. Hydro gels were formed by photo cross linking 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*. formulated, chemically cross linked hydro gels 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 forma 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. 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. The activated dendrimers are an efficient non viral vector capable of transducing corneal endothelial cells *ex viva*. 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 [17].

Iontophoresis

Iontophoresis is an active method of delivery, which uses a small electrical current to transport ionized drugs into and through body tissues. Iontophoresis offers a non invasive and reproducible means of delivering a model an ionic drug to eye tissues, specifically to the retina/choroid. 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*. 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 poly flux 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 (Iontophresis , 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 hydroxyl ethyl methacrylate (HEMA) hydro gel sponges and portable iontophoretic device by Baeyens *et al*. Dexamethasone levels in the rabbit cornea after a single transcorneal iontophoresis for 1min was up to 3-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. 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) hydro gels seems to be promising method achieving high concentrations of drug in the eye tissue [18].

RECENT TRENDS IN OCULAR DELIVERY

Liposomes: Liposomes are biocompatible and biodegradable lipid vesicles made up of natural lipids and

about 25-10000 nm in diameter. They are having an intimate contact with the corneal and conjuctival surfaces which is desirable for drugs they are having n intimate contact with the corneal and conjuctival surfaces which is desirable for drugs that are poorly absorbed, the drugs with low partition coefficient, poor solubility or those with medium to high molecular weights and thus increase the probability of ocular drug absorption. The corneal epithelium is thinly coated with negatively charged mucin to which the positive charged surface of the liposomes may bind.

Implants: For ocular diseases like cytomegalovirus retinitis, implants are effective drug delivery system. Earlier non biodegradable polymers were used but they needed surgical procedures for insertion and removal. Presently biodegradable polymers such as Poly lactic acid (PLA) are safe and effective to deliver drugs in the vitreous cavity and show no toxic signs. Intravitreal implants of fluocinolone acetonide were developed for the treatment of posterior segment and reported to control the ocular inflammation of retina.

Iontophoresis: In Iontophoresis direct current drives ions into cells or tissues. For iontophoresis the ions of importance should be charged molecules of the drug. Positively charged of drug are driven into the tissues at the anode and vice versa. Ocular iontophoresis delivery is not only fast, .painless and safe but it can also deliver high concentration of the drug to a specific site. Iontophoretic application of antibiotics in eye not only increases their bactericidal activity but also reduce the severity of disease. Similarly application of anti-inflammatory agents can reduce the severity of disease. Similarly application of anti-inflammatory agents can reduce vision threatening side effects.

Contact Lenses: Water soluble drugs soaked in drug solutions can be absorbed through contact lenses. The drug saturated contact lenses are placed in the eye which releases the drug in for a long period of time. For prolongation of ocular residence time of the drugs, hydrophilic contact lenses can be used. Greater penetration of fluorescein has been made from hydrophilic polymer (22-droxy ethyl methacrylate) in human.

Micro Emulsions: Micro emulsion is dispersion of water and oil stabilized using surfactant and co-surfactant to reduce interfacial tension and usually characterized by small droplet size (100nm), higher thermodynamic stability and clear appearance. Selection of aqueous phase, organic phase and surfactant/co surfactant systems are critical parameters which can affect stability of the system. Optimization of these components results in solubility of the drug molecule. eg; indomethacin, chloramphenicol for eye diseases.

Nanosuspensions: Nanosuspensions have emerged as a promising strategy for the efficient delivery of hydrophobic. Drugs because they enhanced not only the rate and extent of ophthalmic drug absorption but also the intensity of drug action with significant extended duration effect. For commercial preparation of nanosuspensions, techniques like media milling and high pressure homogenization have been used. The higher drug level was reported using Edragit RS 100 nanosuspensions for the ophthalmic controlled delivery of ibuprofen.

Prodrugs: The ideal prodrugs for ocular therapy not only increased lipophilicity and a high partition coefficient, but it must also have high enzyme susceptibility to such an extent that after corneal penetration or within the cornea they are either chemically or enzymatically metabolized to the active parent compound. The partition coefficient of Ganciclovir found to be increased using an acyl ester prodrug, with substantially increased the amount of drug penetration to the cornea winch is due to increased susceptibility of the Ganciclovir esters to unde4rgo hydrolysis by esterases in the cornea.

Gene Therapy: Along with tissue engineering .gene therapy approaches stand on the front line of advance biomedical research to treat blindness arising from corneal diseases, which are second only to cataract as the leading cause of the vision loss. Several kinds of viruses including adenoviruses, retroviruses, adeno-associated virus and herpes simplex virus, have been manipulated for use in gene transfer and gene therapy applications. Retroviral vectors have been widely used due to their high efficacy; however, they do not have the ability to transduce nondividing cells leads to restrict their clinical use.

Stem Cell Therapy: Emerging cell therapies for the restoration of sight have focused on two areas of the eye that are critical for visual function, the cornea and the retina. Current strategy for management of ocular conditions eliminating the injurious agent or attempting to minimize its effects. The most successful ocular application has been the use of limbal stern cells, transplanted from a source other than the patient for the renewal of corneal epithelium. The sources of limbal cells include donors, autografts, cadaver eyes and (recently) cells grown in culture. Stem cell therapy has demonstrated great success for certain maladies of the anterior segment.

Scleralplug Therapy: Scleral plug can be implanted using a simple procedure at the pars plana region of eye, made of biodegradable polymers and drugs, and it gradually releases effective doses of drugs for several months upon biodegradation. The release profiles vary with the kind of polymers used their molecular weights and the amount of drug in the plug. The plugs are effective for treating vitreoretinal diseases such as proliferative vitreoretinal diseases such as proliferative vitreoretinopathy, cytomegalovirus retinitis responds to repeated intravitreal injections and for vitreoretinal disorders that require vitrectomy.

Ribozyme Therapy: RNA enzymes or ribozymes are a relatively new class of single-stranded RNA molecules capable of assuming three dimensional conformations and exhibiting catalytic activity that induces site-specific

cleavage, ligation and polymerization of nucleotides involving RNA or DNA. They function by binding to the target RNA moiety through Watson-crick base pairing and inactivate it by cleaving the phosphodiester backbone at a specific cutting site. A disease named autosomal dominated retinitis pigmentosa (ADRP) is caused by mutations in genes that produce mutated proteins, leading to the apoptic death of photoreceptor cells. Lewin and Hauswirth have worked on the delivery of ribozymes in ADRP in rats shows promise for ribozyme therapy in many other autosomal dominant eye diseases, including glaucoma [19,20].

CONCLUSION

Ocular drug delivery systems provide local as well as systemic delivery of the drugs The novel advanced delivery of systems offer more protective and effective means of the therapy for the nearly inaccessible diseases or syndromes of eyes. The latest available targeted drug delivery system focuses on the delivery of the drugs as well as macromolecular substances like proteins, DNA to the internal parts of the eye. Farther developments are preferable which will eliminate the cons of these available advanced delivery systems sod readily acceptable with the regulatory authorities as well.

REFERENCES

1. Hughes PM, Mitra A.K.Overview of ocular drug delivery and iatrogenic ocular cytopathologies In: Mitra AK. Opthalmic Drug Delivery Ssystems.2nd ed. New York: M.Dekker Inc: 1993, pp 1-27.
2. Bourlais cl, Acar L, Zia H, Sado PA, Needham T, Leverge R. Ophthalmic drug delivery systems-recent advances. *Prog Rein Eye Res*, 17, 1998.
3. Kaur IP, Garg A, Singla AK, Aggarwal D. Vesicular systems in ocular drug delivery; an overview. *Int J Pharm*, 269, 2004.
4. Wadha S.Pailwal SR, Vyas SP. Nanocarriers in ocular drug delivery: an update review. *Current Pharmaceutical Design*, 15, 2009.
5. Mueller WH, Deardroff DL. Ophthalmic vehicles: the effect of methyl cellulose on the penetration of Homatropine hydro bromide through the cornea. *J Am Pharma Assoc*, 45, 1956.
6. Urtti A, Pipkin JD, Rork G, Sendo T, Finne U, Repta AJ. Controlled drug delivery devices for experimental ocular studies with timolol, Ocular and systemic absorption in rabbits. *Int J.Pharm*, 61, 1990.
7. Geroski DH, Edlhausker HF. Drug delivery for posterior segment eye diseases. *Invest Opthalmol Vis sci*, 41, 2000.
8. Sultana Y,Jain R,Aquil M, Ali A. Review of Ocular Drug Delivery. *Current Drug Delivery*, 3, 2006, 207-17.
9. Mishra DN, Gilhotra RM. Design and charecterisation of bioadhesive in-situ gelling ocular insert of gatifloxacin sesquihydrate. *DARU*, 16, 2008, 1-8.
10. Lawrenson JG, Edgar DF, Gudgeon AC, Burns JM, Geriant M, Nas BA. Comparision of the efficacy and duration of action of topically applied proymetacaine using a novel ophthalmic delivery system versus eye drops in healthy young volunteers. *Br J Opthalmol*, 50,005,167-182.
11. Ebrahim S, Peyman GA, Lee PJ. Applications of liposomes in ophthalmology. *Surv.Opthalmol*, 50, 2005, 167-182.
12. Kaur IP, Garg A, Singla AK, Aggarwal D. Vesicular systems in ocular drug delivery: An overview. *Int.J.Pharm*, 269, 2004, I-14.
13. Vyas SP, Mysore N, Jaitely V, Venkatesan N. Discoidal noisome based controlled ocular delivery of timolol maleate. *Pharmazine*, 53(7), 1998, 466-469.
14. Guinedi AS, Mortada ND, Mansour S, Hathout RM. Preparation and evaluation of reversephase evaporation and multilamellar niosomes as ophthalmic carriers of acetazolamide. *Int J.Pharm*, 306, 2005, 71-82.
15. Kaur IP, Kanwar M. Ocular preparations: The formulation approach, drug development. *Industrial pharmacy*, 28(5), 2202, 473-493.
16. Loftssona T, Jarvinen T. Cyclodextrins in ophthalmic drug delivery. *Adv.Drug Deliv. Rev*, 36, 1999, 59-79.
17. Kimura H, Ogura Y.Hashizoe M, Nishiwaki H, Honda Y, Ikad Y. A new vitreal drug delivery system using an implantable biodegradable polymeric device, invest ophthalmic carriers of acetazolamide. *Int J.Pharm*, 306, 2005, 71-82.
18. Taban M, Lowder CY, Kaiser PK. Outcome of fluocinolone acetonide implant (etisert trade mark) reimplantation for chronic non-infectious posterior uveitis. *Retina*, 28(9), 2008, 1280-1228.
19. Hill JM, O Calaghan RJ, Hobden JA. Ocular lontophoresis. In: Mitra AK. Ophthalmic Drug Delivery Systems. 2nd ed. New York M.Dekker Inc; 1993, pp. 331-354.
20. Rootman DS, Jantzen JA, Gonzalez JR, Fischer MJ, Beuerman R, Hill JM. Pharmacokinetics and safety of transcorneal iontophoresis of tobramycin in the rabbit. *Invest Opthalmol Vis Sci*, 29, 1998, 1397-1401.