Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Der Pharmacia Lettre, 2010, 2(4): 100-115
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Ophthalmic Drug Delivery system –A Review

Hitesh A.Patel, Jayvadan K. Patel, Kalpesh N. Patel, Ravi R.Patel

Nootan Pharmacy College, S.P.Sahkar Vidhyadham, Kamana Crossing, Visnagar 384315, Mehsana, Gujarat, India

---

Abstract

Ocular drug delivery has been a major challenge to pharmacologists and drug delivery scientists due to its unique anatomy and physiology. Static barriers (different layers of cornea, sclera, and retina including blood aqueous and blood–retinal barriers), dynamic barriers (choroidal and conjunctival blood flow, lymphatic clearance, and tear dilution), and efflux pumps in conjunction pose a significant challenge for delivery of a drug alone or in a dosage form, especially to the posterior segment. Identification of influx transporters on various ocular tissues and designing a transporter-targeted delivery of a parent drug has gathered momentum in recent years. Parallelly, colloidal dosage forms such as nanoparticles, nanomicelles, liposomes, and micro emulsions have been widely explored to overcome various static and dynamic barriers. Novel drug delivery strategies such as bioadhesive gels and fibrin sealant-based approaches were developed to sustain drug levels at the target site. Designing noninvasive sustained drug delivery systems and exploring the feasibility of topical application to deliver drugs to the posterior segment may drastically improve drug delivery in the years to come. Current developments in the field of ophthalmic drug delivery promise a significant improvement in overcoming the challenges posed by various anterior and posterior segment diseases.

Keywords: Eye, Ocufit, Ocusert, Minidisk Ocular Therapeutic Systems, New ophthalmic delivery system.

INTRODUCTION

Eye is most interesting organ due to its drug disposition characteristics. For ailments of the eye, topical administration is usually preferred over systemic administration, before reaching the anatomical barrier of the cornea, any drug molecule administered by the ocular route has to cross the precorneal barriers. These are the first barriers that slow the penetration of an active ingredient into the eye and consist of the tear film and the conjunctiva. The medication, upon

instillation, stimulates the protective physiological mechanisms, i.e., tear production, which exert a formidable defense against ophthalmic drug delivery. Another serious concomitant of the elimination of topically applied drugs from the precorneal area is the nasal cavity, with its greater surface area and higher permeability of the nasal mucosal membrane compared to that of the cornea [1]. Normal dropper used with conventional ophthalmic solution delivers about 50-75µl per drop and portion of these drops quickly drain until the eye is back to normal resident volume of 7µl. Because of this drug loss in front of the eye, very little drug is available to enter the cornea and inner tissue of the eye. Actual corneal permeability of the drug is quite low and very small corneal contact time of the about 1-2 min in humans for instilled solution commonly lens than 10% [2]. Consequently only small amount actually penetrates the cornea and reaches intraocular tissue [3]. Controlled drug delivery to the eye is restricted due to these limitation imposed by the efficient protective mechanism [4].

Most of ophthalmic drugs are administered topically in the form of eye drops, a dosage form consisting of buffered, isotonic, aqueous solution or suspensions of the drug. Ophthalmic CDDS have been mainly prepared as gels, ointments, liposomes, micro and nanoparticles, microspheres and ocular minitablets (MT) or films or inserts [5].

Ideal ophthalmic drug delivery must be able to sustain the drug release and to remain in the vicinity of front of the eye for prolong period of time. Consequently it is imperative to optimize ophthalmic drug delivery, one of the way to do so is by addition of polymers of various grades, development of viscous gel, development of colloidal suspension or using erodible or non erodible insert to prolong the precorneal drug retention [6]. Bioadhesive systems utilized can be either microparticle suspension [7] or polymeric solution. For small and medium sized peptides major resistance is not size but charge, it is found that cornea offers more resistance to negatively charged compounds as compared to positively charged compounds.

Following characteristics are required to optimize ocular drug delivery system:
· Good corneal penetration.
· Prolong contact time with corneal tissue.
· Simplicity of instillation for the patient.
· Non irritative and comfortable form (viscous solution should not provoke lachrymal secretion and reflex blinking)
· Appropriate rheological properties and concentrations of the viscous system.

Following mucoadhesive polymers are used most of the times in various ophthalmic drug delivery systems.

1.2.1 Polyacrylic Acid

1.2.1.1 Corbopol

Cross linked polyacrylic acid to have excellent mucoadhesive properties causing significant enhancement in ocular bioavailability. Carbopol 934 P is high cross link water swellable acrylic polymer with molecular weight approximately 3000000 Da. which is appropriate to use in pharmaceutical industry. Park Robinson and Ponchel et al. reported that poly acrylic acid interact with functional group of mucus glycol protien via carboxylic group [8]. Precorneal residence of carpool solution found to be grater than that of PVA solution when devis et al. evaluated corneal

clearance of pilocarpine in carpool 934P solution compare to that of end equiviscous non mucoadhesive PVA solution and buffer (PBS) in the rabbits.

Saettone et al. carried out much experiment with pilocarpine, the poly acrylic acid (5%w/v) carbopol 941P form a stable precorneal film and with less solubility. Drug duration of stable film effect significantly increases as compare to pilocarpine [9]. Weinreh et al. found that suspension beta hexabol base on the poly acrylic acid provided a more constant release of betaxol that its solution. Thermos et al. evaluated ocular bioavailibity of timolol in isoviscous solution of PVA (PAA and timolol PAA salt). The result suggested that PAA polymer produce lower ocular concentration that those after PVA and slower the release of timolol and resulting in longer retention of vehicle in cunjuctivital sac by mucoadhesion.

Use of carpool in ophthalmic drug delivery having following advantages and disadvantages:
Gel prepared for ophthalmic administration using carbopol are more comfortable than solution, or soluble inserts though they are instilled like ointment less blurring of vision occurred as compare to ointment. However, disadvantages are no rate control on drug instability and it leads to matted lids [10].

1.2.1.2 Polycarbophil:
It is cross linked poly acrylic acid polymer which is insoluble in water but swells and can incorporate large quantity of water. Carbophil cross linked with divinyl glycol found to give good bioadhesion as compare to conventional non bioadhesive suspension.

1.2.2 Carboxymethyl cellulose:
Sodium CMC found to be excellent mucoadhesive polymer. Ophthalmic gel formulated using NaCMC, PVP and corbopol on the in vivo studies on the gel showed diffusion coefficient in corbopol 940 1%> NaCMC 3%> PVP 23%. Recent research suggests that adhesive strength increases as molecular weight increases up to 100000 da.

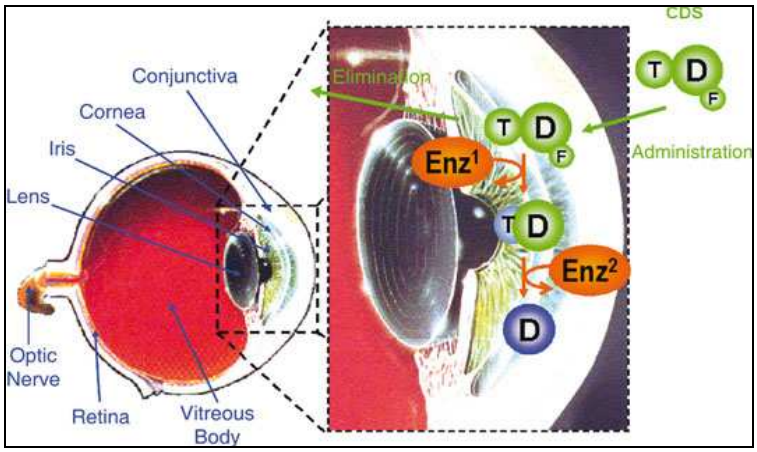

Fig: 1 Morphology of Eye

1.5 classifications of ocular drug delivery systems

A multitude of ocular dosage forms are available for delivery of drugs to the eye. These can be classified on the basis of their physical forms as follows:

1. **Liquids:** Solutions, Suspensions, Sol to gel systems, Sprays
2. **Solids:** Ocular inserts, Contact lenses, corneal shield, Artificial tear inserts, Filter paper strips
3. **Semi-solids:** Ointments, Gels
4. **Miscellaneous:** Ocular iontophoresis, Vesicular systems, Mucoadhesive dosage forms, Particulates, Ocular penetration.

1.7.1 Liquids

Liquids are the most popular and desirable state of dosage forms for the eye. This is because the drug absorption is fastest from this state. The slow release of the drug from the suspended solids provides a sustained effect for a short duration of time.

1.7.1.1 Solutions and Suspensions

Solutions are the pharmaceutical forms most widely used to administer drugs that must be active on the eye surface or in the eye after passage through the cornea or the conjunctiva. The drug in the solution is in the solved state and may be immediately active. This form also have disadvantages; the very short time the solution stays at the eye surface, its poor bioavailability (a major portion i.e. 75% is lost via nasolacrimal drainage), the instability of the dissolved drug, and the necessity of using preservatives. A considerable disadvantage of using eye drops is the rapid elimination of the solution and their poor bioavailability. This rapid elimination is due to solution state of the preparation and may be influenced by the composition of the solution. The retention of a solution in the eye is influenced by viscosity, hydrogen ion concentration, the osmolality and the instilled volume.

Extensive work has been done to prolong ocular retention of drugs in the solution state by enhancing the viscosity or altering the pH of the solution [11].

1.7.1.2 Sol to gel Systems

The new concept of producing a gel in situ (eg. in the cul-de-sac of the eye) was suggested for the first time in the early 1980s. It is widely accepted that increasing the viscosity of a drug formulation in the precorneal region will leads to an increased bioavailability, due to slower drainage from the cornea. Several concepts for the in situ gelling systems have been investigated. These systems can be triggered by pH, temperature or by ion activation. An anionic polymeric dispersion shows a low viscosity upto pH 5. 0, and will coacervate in contact with tear fluid due to presence of a carbonic buffer system which regulates the pH of tears. In situ gelling by a temperature change is produced when the temperature of polymeric dispersion is raised from 25 to 37°C. Ion activation of polymeric dispersion occurred due to the presence of cations in the tear fluid.

Wei et al. Developed a thermosetting gel with a suitable phase transition temperature by combining Pluronic analogs and examined the influence of incorporating mucoadhesive polysaccharide, sodium hyaluronate (HA-Na), on the ocular retention of the gel by dynamic rheological method and single photon emission computing tomography (SPECT) technique.

1.7.1.3 Sprays

Although not commonly used, some practitioners use mydriatics or cycloplegics alone or in combination in the form of eye spray. These sprays are used in the eye for dilating the pupil or for cycloplegic examination.

1.7.2 Solids

The concept of using solids for the eye is based on providing sustained release characteristics.

1.7.2.1 Ocular inserts

Ocular inserts are solid dosage form and can overcome the disadvantage reported with traditional ophthalmic systems like aqueous solutions, suspensions and ointments. The typical pulse entry type drug release behavior observed with ocular aqueous solutions (eye drops), suspensions and ointments is replaced by more controlled, sustained and continuous drug delivery using a controlled release ocular drug delivery system. The eye drops provided pulse entry pattern of drug administration in the eye which is characterized by transient overdose, relatively short period of acceptable dosing, followed by prolonged periods of under dosing. The ocular inserts maintain an effective drug concentration in the target tissues and yet minimize the number of applications consonant with the function of controlled release systems. Limited popularity of ocular inserts has been attributed to psychological factors, such as reluctance of patients to abandon the traditional liquid and semisolid medications, and to occasional therapeutic failures (e.g. unnoticed expulsion from the eye, membrane ruptures etc.). A number of ocular inserts were prepared utilizing different techniques to make soluble, erodible, nonerodible, and hydrogel inserts [12].

1.7.2.2 Contact lenses

Contact lenses can absorb water soluble drugs when soaked in drug solutions. These drug saturated contact lenses are placed in the eye for releasing the drug for long period of time. The hydrophilic contact lenses can be used to prolong the ocular residence time of the drugs. In humans, the Bionite lens which was made from hydrophilic polymer (2-hydroxy ethyl methacrylate) has been shown to produce a greater penetration of fluorescein.

1.7.2.3 Corneal shield

A non cross-linked homogenized, porcine scleral collagen slice is developed by a company (Bio-cor (Bausch and Lomb pharmaceuticals). Topically applied antibiotics have been used in conjunction with the shield to promote healing of corneal ulcers. Collagen shields are fabricated with foetal calf skin tissue and originally developed as a corneal bandage. These devices, once softened by the tear fluid, form a thin pliable film that confirms exactly to the corneal surface, and undergoes dissolution up to 10, 24 or 72 hours. Collagen film proved as a promising carrier for ophthalmic drug delivery system because of its biological inertness, structural stability and good biocompatibility. Gussler et al 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.

1.7.2.4 Artificial tear inserts

A rod shaped pellet of hydroxypropyl cellulose without preservative is commercially available (Lacrisert). This device is designed as a sustained release artificial tear for the treatment of dry eye disorders. It was developed by Merck, Sharp and Dohme in 1981[13].

1.7.2.5 Filter paper strips

Sodium fluorescein and rose Bengal dyes are commercially available as drug impregnated filter paper strips. These dyes are used diagnostically to disclose corneal injuries and infections such as herpes simplex, and dry eye disorders.

1.7.3 Semi-solids

A wide variety of semisolids vehicles are used for topical ocular delivery which falls into two general categories: simple and compound bases. Simple bases refer to a single continuous phase. These include white petrolatum, lanolin and viscous gels prepared from polymers such as PVA, carbopol etc. Compound bases are usually of a biphasic type forming either water in oil or oil in water emulsions. A drug in either a simple or compound base provide an increase in the duration of action due to reduction in dilution by tears, reduction in drainage by way of a sustained release effect, and prolonged corneal contact time. The most commonly used semisolid preparation is ointments consisting of dispersion of a solid drug in an appropriate vehicle base.

Semi-solids dosage forms are applied once or twice daily and provide sustained effects. The primary purpose of the ophthalmic ointment vehicle is to prolong drug contact time with the external ocular surface. But they present a disadvantage of causing blurring of vision and matting of eyelids. Ophthalmic gels are similar in viscosity and clinical usage to ophthalmic ointments. Pilopine HS is one of the ophthalmic preparations available in gel form and is intended to provide sustained action of pilocarpine over a period of 24 hours. Semi-solids vehicles were found to prolong the ocular contact time of many drugs, which ultimately leads to an enhanced bioavailability [14].

1.8 Recent developments in ophthalmic drug delivery

Most conventional ophthalmic dosage forms are simplistic. It is usual that water-soluble drugs are delivered through topical administration in an aqueous solution, and water-insoluble drugs are administered topically as an ointment or aqueous suspension. The major deficiencies of these conventional dosage forms include poor ocular drug bioavailability, pulse-drug entry after topical administration, systemic exposure because of nasolacrimal duct drainage, and a lack of effective systems for drug delivery to the posterior segment of ocular tissue. Poor ocular drug bioavailability is the result of ocular anatomical and physiological constraints, which include the relative impermeability of the corneal epithelial membrane, tear dynamics, nasolacrimal drainage, and the high efficiency of the blood–ocular barrier [15]. It is standard for only 1% or less of a topically applied dose to be absorbed across the cornea and thus reach the anterior segment of the eye [16]. Pulse entry is a common, and yet highly undesirable, pharmacokinetic characteristic associated with eye drops. The initial high drug concentration found in tears, followed by a rapid decline, poses a potential risk of toxicity, and suggests a requirement for frequent dosing. Attempts to overcome the toxicity associated with the high initial concentration without a requirement for frequent dosing form a challenging task, particularly in the case of potent drugs. Nasolacrimal drainage is the major factor for precorneal drug loss that leads to poor ocular bioavailability. It is also the major route of entry into the circulatory system for drugs that

are applied through topical administration. For potent drugs, the systemic exposure through nasolacrimal drainage after topical administration can be sufficiently high to cause systemic toxicity. A recognized example is timolol; systemic toxicity has been reported for the ophthalmic solution of timolol following topical administration [17]. The delivery of drugs to the posterior segment of ocular tissue is prevented by the same factors that are responsible for the poor ocular bioavailability. In addition, the blood–retinal barrier limits the effectiveness of the intravenous route in posterior drug delivery. To date, the most acceptable method for posterior drug delivery is intravitreal injection, and yet although effective, the intravitreal injection procedure is associated with a high risk of complications.

2. Ophthalmic preparation characteristics

Clarity- ophthalmic solution by definition contains no undissolved ingredients and is essentially free from foreign particles. Clarity may be enhanced in some cases by filtration. It is essential that the filtration equipment be clean and well rinsed so that particulate matter is not contributed to the solution by equipment designed to remove it. Operations performed in clean surroundings, the use of laminar-flow hoods, and proper non shedding garments will contributes collectively to the preparation of clear solutions essentially free from foreign particles. In many instances clarity and sterility may be achieved in the same filtration step. If viscosity-imparting polymers are used, a polish-filtering step may be required prior to the final filtration.

Both container and closure must be thoroughly clean, sterile, and non shedding, neither contributing particulate matter to the solution during prolonged contact for the duration of the shelf life. Normally this is established by thorough stability testing, which also will indicate if insoluble particles are generated by drug degradation (by-products with lower solubility). Solution formulations also may contain viscosity imparting polymers that can diminish clarity. In these situations it may be important both to define the visual clarity of the product and monitor its stability. The European pharmacopoeia describes visual clarity and recommends that can be used for clarity specifications [18].

2.1 Stability

The stability of a drug in an ophthalmic product depends on a number of factors including the chemical nature of the drug substance, whether it is in solution or suspension, product pH, method of preparation (particularly temperature exposure), solution additives, and type of packaging. A pharmaceutical manufacturer strives for a shelf-life measured in years at controlled room temperature conditions whereas the compounding pharmacist often is not certain about the shelf life of his preparation and thus provides relatively small quantities at one time and assigns a shelf life in terms of days or weeks and may specify refrigerated storage as a further precaution. The attainment of optimum stability often imposes some compromises in the formulation, packaging and preparation of the final product. The product's pH is often the stability-controlling factor for many drugs. Drugs such as pilocarpine and physostigmine are both active and comfortable in the eye at a pH of 6.8; however, at this pH chemical stability (or instability) can be measured in days or months. With either drug, a substantial loss in chemical stability will occur in less than 1 year. On the other hand, at pH 5 both drugs are stable for a period of several years.

In addition to optimal pH, if oxygen sensitivity is a factory, adequate stability may require inclusion of an antioxidant or special packaging. Plastic packaging, ie, the low-density

polyethylene containers such as the Drrop-Tainer (Alcon) that represents a patient convenience, may prove detrimental to stability by permitting oxygen permeation resulting in oxidative decomposition of the drug substance. To develop an epinephrine solution with 2 to 3 years stability in a plastic package requires the use as a pH of about 3 for protection from oxidation whereas an epinephrine borate solution formulated at a pH of about 7, which is more comfortable to the patient, requires an antioxidant system and the use of glass packaging. The prodrug of epinephrine, dipivefrin, significantly increases ocular bioavailability and is effective at one-tenth the concentration of epinephrine. The structure of the chemical derivative protects the active epinephrine portion from oxidation enabling it to be packaged in plastic. However, the prodrug introduces a labile ester linkage and as a result must be formulated at a pH of about 3 to minimize hydrolysis and still can only achieve a room temperature shelf life of less than 18 months.

Pharmaceutical manufacturers conduct comprehensive stability programs to assure the assigned expiration dating for each product. In addition to the standard chemical and physical stability of the pharmaceutical. The stability of the preservative is monitored by chemical means or by actual challenge of the preservative efficacy with appropriate test organisms. Sterility is not stability parameter per se but each container closure system can be tested by microbial challenge to assure integrity of the package against environmental contamination prior to opening.

Some of the newer classes of ophthalmic drugs, like prostaglandins are very hydrophobic and have very low concentrations. For example, in the product Xalatan latanoprost is present at .005% and in the product Travatan travoprost is present at 0.004% Actives at such low concentration present a challenge for formulators since the loss of even small amounts of drug, e.g., from adsorption losses to packaging, may become significant. Pharmacia's Xalatan requires refrigerated storage, and as indicated earlier, temperature cycling also can reduce the concentration of active> It is important for the pharmacist to know the properties of the drug substance so that product to know the properties of the drug substances so that product quality is maintained is maintained throughout the shelf life of the product.

2.2 Buffer and pH

Ideally, ophthalmic preparations should be formulated at a pH equivalent to the tear fluid of 7.4. Practically this seldom is achieved. The large majority of active ingredients used in ophthalmology is salts of weak bases and are most stable at an acid pH. This generally can be extended to suspensions of insoluble corticosteroids. Such suspensions usually are most stable at acid pH.

Optimum pH adjustment generally requires a compromise on the part of the formulator. The ph selected should have capacity adequate to maintain ph within the stability range for the duration of product shelf life. Buffer capacity is the key in this situation.

In generally is accepted that a low (acid) pH necessarily will not cause stinging or discomfort on instillation. If the overall pH of tears, after instillation, reverts rapidly to pH 7.4, discomfort is minimal. On the other hand, if the buffer capacity if sufficient to resist adjustment by tear fluid and the overall eye ph remains acid for an appreciable period of time, then stinging and discomfort may result. Consequently, buffer capacity should be adequate for stability but

minimized, so far as possible, to allow the overall pH of the tear fluid to be disrupted only momentarily. Special care in formulating intraocular products is required regarding their pH and buffer capacity. The corneal endothelium can tolerate much less deviation from physiological conditions compared to the external corneal epithelium.

2.3 Tonicity

Tonicity refers to the osmotic pressure exerted by salts in aqueous solution. An ophthalmic solution is isotonic when the magnitudes of the colligative properties of the solution are equal. An ophthalmic solution is considered isotonic when its tonicity is equal to that of a 0.9% sodium chloride solution (290 mOsm). However, the osmotic pressure of the aqueous intraocular fluid is slightly higher than tears measuring about 305 mOsm.

In actuality the external eye is much more tolerate of tonicity variations that was at one time suggested and usually can tolerate solutions equivalent to a range of 0.5 to 1.8% sodium chloride. Given a choice, isotonicity is desirable and particularly is important in intraocular solutions. However, in certain cases a non-isotonic topical product is desirable. Tear fluid in some cases of dry eye is reported to be hypertonic and a hypotonic artificial tear product is used to counteract this condition. Hypertonic ophthalmic products are used to relieve corneal edema and solutions and ointments containing 2% or 5% sodium chloride are available for this use.
The tonicity of ophthalmic solutions has been investigated intensively over the years. These studies have resulted in the accumulation and publication of a large number of sodium chloride equivalents that are useful in calculating tonicity values.

2.4 Viscosity:-

Ophthalmic solution and suspension eye drops may contain viscosity-imparting polymers to thicken the tear film and increase corneal contact time, i.e., reduce the rate of tear fluid drainage. For suspensions, the increased viscosity also serves to retard the settling of particles between uses and at the same time maintains their suspension for uniform dosing. However, added viscosity may make initial resuspension more difficult particularly in a suspension that has a tendency to cake during storage. The hydrophilic polymers most often used for these purposes are methylcellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose and polyvinyl alcohol. They are used at concentrations that produce viscosities in the range of about 5 to 100 cps. These polymers are also used themselves as the active ingredients in artificial tear solutions for their lubrication and moisturizing properties in dry eye therapy. Viscosity agents can have several disadvantages in that they sometimes produce blurring of vision and can leave a residue on the eyelids. These effects are most often seen at the higher end of the viscosity range. The added viscosity can make filtration more difficult particularly for the small pore size filters used to sterilize solutions.

Newer ophthalmic dosage forms such as gel-forming solutions and semi-solid aqueous gels utilize increased viscosity and gel elasticity to improve significantly drug bioavailability and duration of effect. With these advances, the frequency of dosing can be reduced and patient compliance improved. These newer dosage forms utilize novel polymer systems with special rheological properties to enhance their effect. Their complex rheology and intricate dependence on environment, however, increase the complexity of the sterile manufacturing process.

2.5 Additives:
Additives or pharmaceutical excipients are used as inactive ingredients in most ophthalmic dosage forms. Because of the need for tissue compatibility, the use of additives is perhaps more limited in ophthalmic, particularly in intraocular products.

The most common inactive ingredient is the product's vehicle. For topical dosage forms, Purified Water USP is used. Because of the requirement for nonpyrogenicity, Water for Injection USP is used for intraocular products. While a mineral oil and petrolatum combination is the vehicle used for ophthalmic ointments, nonaqueous liquids are rarely used in topical eye drops due to their potential for ocular irritation and poor patient tolerance. Some mineral and vegetable oils have been used for very moisture-sensitive or poorly water-soluble drugs. The purest grade of oil such as those used for parenteral products should be used.

Microbiological preservatives are commonly used in multiple dose topical ophthalmic products and will be discussed in a later section. Other commonly used additives in topical eye products are ingredients to adjust and buffer pH and adjust tonicity in addition to the viscosity agents previously discussed. Ingredients to adjust pH and tonicity and buffer pH are essentially the same as those used in parenteral products. Less commonly used additives are antioxidants such as sodium bisulfite, ascorbic acid and acetylcysteine.

Surfactants are sometimes used in topical eye products for dispersing insoluble ingredients or to aid in solubilization. They are used in the smallest concentration possible to perform the desired function since they can be irritating to sensitive ocular tissues. Nonionic surfactants are used most often since they are generally less irritating than ionic surfactants. Polysorbate 80 is used in the preparation of an ophthalmic emulsion. Polyoxyl 40 stearate and polyethylene glycol have been used to solubilize a drug in an anhydrous ointment so that it can be filter sterilized. Surfactants are often used to stabilize more hydrophobic drugs, for example preventing loss to adsorption on the container walls. For example, a nonionic surfactant like polyoxyl 40 hydrogenated castor oil (HCO-40) has been used to stabilize travoprost, a prostaglandin derivative. Similarly Cremophore EL has been used to stabilize diclofenac in the Voltaren formulation marketed by Novartis.

3. Ocular drug delivery devices
Ocular drug delivery devices include matrix type drug delivery systems, capsule type drug delivery systems and implantable drug delivery pumps [19].

3.1 Matrix-type Drug Delivery Systems:-
3.1.1 Hydrophilic Soft Contact Lenses
Hard contact lenses, soft contact lenses and intraocular lenses are popular for correction of refractive errors of the eye and several kinds of polymer have been used for the preparation theses lenses. Because they are easy to fit and tolerate and rapidly tolerance, hydrophilic soft contact lenses are more popular. They made up of hydrogels that absorb certain amounts of aqueous solutions, because of this property they have also been found useful for drug delivery to anterior segment of the eye.

The hydrophilic contact lenses, Bionite® was developed by Griffin laboratory, and Soflens®, was developed by Bausch & Lomb, as devices for maintaining high concentration in anterior chamber of the eye. They used fluoresce in as a model drug. They have achieved four times greater concentration than those from frequent administration of drops in the case of Bionite® lens presoaked with the drug as well as a presoaked Soflens® also. They have also performed human studies and found that a Bionite® could maintain the flourscein concentration in the ocular tissues for 24 h despite the known rapid clearance of flourescein from the eye. Kaufman et al., studied the usefulness of soft contact lenses for antiviral idoxuridine (IDU), polymyxin B and pilocarpine as drug delivery devises to the eye.

Hull et al., 1992 studied the ocular penetration of predinsolone sodium phosphate in rabbit eye and the effect of a hydrophilic contact lens on the penetration. The contact lenses made from PHP (hefilcon-A) copolymer (80% 2-hydroxyethylmethacrylate and 20% N-vinyl-2-pyrrolidone), were of 16 mm in diameter and 0.3 mm thickness, and their hydration was 40% to 45%. The lenses were presoacked in predinsolone sodium phosphate for 2 min., they were able to maintain the aqueous and corneal levels two to three times higher, at 4 hr, than the levels obtained after topical administration of plane predinsolone solution.

The ability of the available disposable soft contact lenses to absorb various ocular therapeutic agents and release them. After a 2 h or 4 h presoaking time, they measured the amount drug released into fresh saline baths for up to 3 h Ciprofloxacin hydrochloride, predinsolone sodium phosphate, and cromolyn sodium were found to be released from the disposable contacts at a rate that provided higher concentrations of drug for a longer period of time than would be expected with drops. Depending on the lens used these drugs were released continuously for a period of up to 3 h.

Disposable lenses soaked in pilocarpine hydrochloride or idoxuridine released drug for 30 min or less. They found that disposable contact lenses could provide an acceptable means of drug delivery for some situations and overcome drawbacks associated with the use of nondisposable hydrogel lenses.

3.1.2 Soluble Ocular Inserts

Soluble ocular inserts, such as the poly(vinyl alcohol) insert (PVAI), the soluble ophthalmic drug insert (SODI) and polypeptide devises are matrix type polymeric devises used for drug delivery to eye. Poly(vinyl alcohol) inserts are characteristically thin, elastic and oval shaped plates and impregnated with antibiotics, sulfonamides, pilocarpine, atropine, or other drugs used in ophthalmology. Pilocarpine impregnated discs of polyvinyl alcohol and hydroxypropyl cellulose inserts were studied to develop prolonged release pattern of pilocarpine. However, the limitations are poor patient compliance and difficulty of self-insertion. SODIs are thin, elastic, oval plates and made from polymers and copolymers of polyacrylamide, ethylacrylate, and vinylpyrrolidone SODIs are well tolerated by eye tissues. When a SODI inserted into the conjunctival sac, it absorbs tears rapidly, swells and dissolves in about 30 to 90 min., releasing the active substance in a controlled manner. The dissolution property of the SODIs frees the patient from task of removing the device after the drug has been released completely.

Hull et al., 1992 studied the insert composed of cross-linked polypeptide matrix which 10 mg hydrocortisone was uniformly dispersed and designed to release the drug at the rate of 10 mg/hr. The device was visibly opaque, flexible and elliptical in shape (8×5×0.4 mm). The insert gradually eroded in the eye and dissolved out completely after about three weeks of wear.

A structural polysaccharide, poly (N-acetyl-D-glucosamine) (chitin) converts enzymetically to a decomposed form, which can serve as a matrix for the ocular insert. The insert (1×10×1.02), containing 50 mg pilocarpine nitrate, when placed on the rabbit eye degraded by lysozyme contained in normal tears. The pilocarpine, which is released from the eroding surface of the insert, produced papillary response for 6 hours.

3.1.3 Scleral Buckling Materials

In some of the cases scleral buckling materials cause postoperative infections as they are used in retinal detachment surgery .To prevent this complication, scleral buckling materials can be made to absorb an antibiotic. Refojo and Thomos evaluated two common scleral buckling materials, gelatin film and solid silicone rubber impregnated with antibiotics, for their biological activity using agar plate method. They used commercial antibiotics preparations of chloramphenicol and lincomycin. Antibiotic impregnated gelatin disc and silicone rubber were prepared by immersing these devices into an aqueous antibiotic solution and then dried. They found sustained release of antibiotics form these devices. Refojo also investigated the sustained release of chloramphenicol sodium succinate and lincomycin hydrochloride from closed-cell silicone rubber scleral buckling material (sponge). These antibiotic-impregnated materials used in conjunction with standard pre- and postoperative therapy, can reduce the degree of infection in scleral buckling procedures.

3.2 Capsular-type Drug Delivery Systems:-

These are the devices that have a therapeutic agent encapsulated within a closed compartment surrounded by a polymeric membrane.

3.2.1 Ocusert® and Related Devices

A truly continuous, controlled release and zero order kinetic fashion was achieved using ocusert. First marketed by Alza Corporation of California, pilocarpine ocuserts specifically improved the non-compliance problems, low intraoculor drug bioavailability and potential systemic side effects of pilocarpine.The system consists of a pilocarpine-alginate core (drug) sandwiched between two transparent, rate-controlling ethylene-vinyl acetate copolymer membranes. When this is placed under the upper or lower eyelid, the pilocarpine molecules dissolved in the lacrimal fluid are released through the rate-controlling membranes at predefined rates. A mixture of pilocarpine and alginic acid as the drug reservoir provides the drug for almost one week. A thin membrane of ethylene-vinyl acetate (EVA) copolymer encloses the reservoir above and below. A retaining ring of the same material impregnated with titanium dioxide encloses the drug reservoir circumferentially. The dimensions of the elliptical devise are: major axis, 13.4 mm, minor axis, 5.7 mm, thickness, 0.3 mm. Two types of Ocusert® are available, Ocusert® Pilo-20 and Ocusert® Pilo-40. The Ocusert® Pilo-20 can release pilocarpine at a rate of 20 µg/h for 7 days (total amount of drug released, 3.4 mg) and Ocusert® Pilo-40 at a rate of 40 µg/h for 7 days (total amount of drug released, 6.7 mg). Ocusert® Pilo-20 contains 5 mg drug and Ocusert® Pilo-40, 11 mg of drug to maintain a constant release rate from the drug reservoir. Ocusert® Pilo-40 contains

about 90 mg of di(2-ethylhexyl) phthalate as flux enhancer to maintain the higher release rate (40 µg/h).

3.2.2 Implantable Silicone Rubber Devices

Ocusert® is a drug delivery device for hydrophilic drugs. Refojo et al., 1978 developed a constant release rate implantable silicone rubber device for hydrophobic drug, BCNU (1, 3-bis (2-chloroethyl)-1-niurosourea an intraocular malignancy agent. This device consists of two sheets of silicone rubber (Silastic® 500-1, 0.13 mm thick) glued together only at the edges with silicone adhesive). A tube of the same material (0.3 mm in diameter) extends from device. The device released BCNU at a nearly constant rate (about 200-400 µg/h) for a time determined by amount of drug in the device.

3.3 Implantable Drug Delivery Pumps

3.3.1 Osmotic Mini pump and Implantable Infusion System

Intravitreal drug delivery has been developed to treat posterior segment diseases because the blood-ocular barrier disallows treatment by topical, systemic, or subconjunctival routes as attaining therapeutic levels in the vitreous are not attained. Endophthalmitis, uveitis, proliferative virreoretinopathy, and viral retinitis are treated by intravitreal injection. Efforts to sustain drug delivery have included encapsulation of drugs in liposomes (made of lipids) or microspheres (made of polymers). In many instances the toxicity of drug to the retina was reduced and the clearance time was slowed. However, these methods cause clouding of the vitreous and can prolong drug delivery for only one month. Implantable devices, which have been developed and used, include an osmotic minipump, a drug pellet coated with polyvinyl alcohol and ethylene vinyl acetate, and polysulfone capillary fiber.

The generic osmotic minipump (ALZET®) is a useful implantable drug delivery system with a constant drug delivery rate with a pumping duration of up to 2 weeks. Another drug delivery pumping system is the Infusaid®, which is an implantable infusion system (Infusaid Corporation, USA). The device permitted long-term infusion, via refilling, in animals. The pumping force is generated by an expanding fluid (a flurocarbon in liquid-gas equibillirium) at body temperature.

3.4 Other Delivery Devices:-

3.4.1 Ocufit® and Lacrisert®

The Ocufit® is a sustained release, rod shaped device made up of silicone elastomer (U.S. Patent, 1992). The device currently developed by Escalon Ophthalmic Inc. (Skillman, NJ). It was designed to fit the shape and size of the human conjunctival fornix. Its diameter is 1.9 mm and length is 25-30 mm. Lacrisert® (Merk & Co., Inc.) is another cylindrical device, which is made of cellulose and used to treat dry-eye patients.These devices have long retention (2 weeks or more) and sustained release features. Diseases like bacterial, allergic and adenoviral conjunctivitis, trachoma, episcleritis, corneal ulcers do not affect the ocular retention of insert.

3.4.2 Minidisk Ocular Therapeutic Systems

Minidisk ocular therapeutic system (OTS) is a monolithic polymeric device, shaped like miniature (diameter 4-5 mm) contact lens, with a convex and a concave face and described by Bawa et al. The device can easily be placed under the upper or lower eyelid without compromising comfort, vision, or oxygen permeability because of its particular size and shape. It

also requires less time and less manual dexterity for insertion, when compared with Lacrisert.® Different versions of the device have been evaluated, such as nonerodible hydrophilic, nonerodible hydrophobic and erodible.

3.4.3 The 'New ophthalmic delivery system' (NODS®)

The 'New ophthalmic delivery system' (NODS®) is a method for delivering precise amounts of drugs to eye within a water soluble, drug-loaded film. The device consists of a medicated flag (4mm × 6mm, thickness 20mm, weight 0.5 g) which is attached to a paper- covered handle by means of a short (0.7mm) and thin (3-4 mm) membrane. All components (flag, membrane and handle) are made of the same grade of water-soluble polyvinyl alcohol (PVA). The devices are individually packaged and sterilized by gamma-irradiations. For use, the flag is touched onto the surface of lower conjunctival sac. The membrane proceeds to dissolve in the lacrimal fluid, delivering the drug when evaluated in humans, the NODS® produced an 8-fold increase in bioavailability for pilocarpine with respect to standard eye drop formulations.

4. Evaluation of ocular drug delivery systems:-

Ocular drug delivery systems are evaluated by various methods. The ocular in-vitro studies include design of specialized apparatus. The ocular in-vivo studies were done in rabbits and include tear pH measurements, pharmacodynamic studies and scintigraphy to assess precorneal residence of formulations.

4.1 In-vitro evaluation methods:

A number of approaches are used by different workers to conduct in-vitro evaluation of controlled ocular drug delivery systems. These include bottle method, modified rotating basket/ paddle method and flow through apparatus.etc.

4.1.1 Bottle method

In this method, dosage forms are placed in the culture bottles containing phosphate buffer at pH 7.4. The culture bottles are shaken in a thermostatic water bath at 37°C. A sample of medium is taken out at appropriate intervals and analyzed for drug contents.

4.1.2 Diffusion method

An appropriate simulator apparatus is used in this method. Drug solution is placed in the donor compartment and buffer medium is placed in the receptor compartment. An artificial membrane or goat cornea is placed in between donor and receptor compartment. Drug diffused in receptor compartment is measured at various time intervals.

4.1.3 Modified rotating basket method

In this method, dosage form is placed in a basket assembly connected to a stirrer. The assembly is lowered into a jacketed beaker containing buffer medium. The temperature of system is maintained at 37°C. A sample of medium is taken out at appropriate time intervals and analyzed for drug content.

4.1.4 Modified rotating paddle apparatus

In this method, diffusion cells (those that are used for analysis of semi-solid formulations) are placed in the flask of rotating paddle apparatus. The buffer medium is placed in the flask and

paddle is rotated at 50 rpm. The entire unit is maintained at 37±0.5° C. Aliquots of samples are removed at appropriate time intervals and analyzed for drug content.

4.1.5 Flow through devices

There are obvious and insurmountable limitations to the official dissolution testing apparatus concerning maintenance of sink condition for drugs that saturate rapidly in large volumes of medium. The in-homogeneity of the solution in the rotating basket and poor reproducibility led to enhanced use of flow through devices. A constant fluid circulation apparatus is used as a flow through device. The apparatus consist of a glass dissolution cell, a continuous duty oscillating pump, a water bath and a reservoir. The dosage form is placed in the reservoir of the dissolution medium. The whole assembly is maintained at the temperature of 37°C. The dissolution medium is circulated through the apparatus. Sampling of medium is done at various time intervals and analyzed for drug content.

Ali and Sharma had fabricated flow through cell for the determination of in- vitro release of drug from ocular inserts [20]. Sultana et al modified the same apparatus by introducing jacketed flask and eye [21].

4.2 In – vivo evaluation methods

The controlled ocular drug delivery systems can be evaluated for its pharmacokinetic and pharmacodynamic profiles. The main objective of the pharmacokinetic studies is to determine the drug release from the dosage form to the eye. Rabbit is used as an experimental animal because of a number of anatomical and physiological ocular similarities and also due to larger size of the eye. Pharmacokinetic studies are performed by measuring drug concentration in various eye tissues eg. Lens, cornea, iris, ciliary body, retina sclera, aqueous and vitreous humor in rabbits. The intraocular pressure of the eye is measured with a tonometer. Ocular pharmacokinetic studies can also be carried out by tear fluid sampling, which is a non-invasive technique. Usually, disposible glass capillaries of 1ml capacity are used for sampling. The samples are collected from the marginal tear strip of the rabbits. The capillary force fills the tube rapidly and the small volume collected does not interfere with the ocular pharmacokinetics. Extreme care must be taken to avoid any corneal contact and possible induced lacrimation. To withdraw aqueous humour, rabbits are anaesthetized with ketamine and aqueous humour about 200ml is withdrawn from the anterior chamber using 1ml syringe with 26 guage needle. Vitreous samples are also obtained with 20 gauge needle. The entire cornea, lens, and iris-ciliary body are also removed and analyzed for the drug content [22].

CONCLUSION

All approaches presented in the present review lead us to conclude that all system present some interest in ocular drug delivery. They improve ocular drug bioavailibity by increasing ocular drug residence time, diminishes side effect due to systemic absorption and diminishing the necessary therapeutic amount of drug for therapeutic response in anterior chamber. However, all systems have disadvantages associated with them. Hence there is a need for polymer pattern in which drug could be trapped physically to prolong drug residence time from corneal surface and preserve visual activity. Such systems should probably be more hydrophilic than the materials

currently employed and would have to exhibits pseudoplastic behavior to minimize interference with blinking.

REFERENCES

[1] Shell JW, *Drug Dev. Res*., **1985**, 6, 245- 261.
[2] Shell JW, *J. Toxicol. Cut. & Ocular Toxicol*, **1982**, 1(1), 49-63.
[3] Patton TF, and Robinson JR, *J. Pharm. Sci.*, **1976**, 65, 1295-1301.
[4] Wood RW, Lee VHE, Kreutzer J and Robinson JR, *Int. J. Pharm*, **1985**, 23, 175-183.
[5] Prajapati PA, Poddar SS, Patel MM, *Der Pharmacia Lettre*, **2010**, 2 (1) 467-474.
[6] Patton TF, Robinson JR, *J. Pharm. Sci.*, **1975**, 65, 1312-1315.
[7] Hui HW and Robinson JR, *Int. J. Pharm*., **1985**, 26, 203-213
[8] Park H and Robinson JR, *Pharm. Res.*, **1987**, 4, 457-464.
[9] Saettone MF, Monti D, Torracca MT, Chetoni P, Giannaccini B, *Drug Dev. Ind. Pharm.*, **1989**, 15, 2475-2489.
[10] Lin GS, Trope GE and Basu PR, *Curr. Eye. Res*., **1989**, 8(7), 637-648.
[11] Krishna N, Brown F. *Am. J. Ophthalmol*, 1964, 57, 99.
[12] Lerman S, Davis P, Jackson W B. *Can. J. Ophthalmol*. **1973**, 8, 114-118.
[13] Vasantha R, Sehgal P K, Rao P. *Int. J. Pharm*. **1988**, 47, 95 - 102.
[14] Kyyronen K, Hume L, Benedetti L, Urtti A., Topp E, Stella V. *Int. J. Pharm*. **1992**, 80, 161 - 169.
[15] Peyman, GA and Ganiban, GJ *Adv. Drug Deliv. Rev*., **1995,** 16, 107–123
[16] Lee VHL and Robinson, JR *J. Ocul. Pharmacol. Ther*.,**1986**, 2, 67–108
[17] Urtti, A. and Salminen, L. Surv. *Ophthalmol*.**1993**, 37, 435–456
[18] Remington, the science and practice of pharmacy. **2005**, 1, 861-862.
[19] Vyas SP, Roop K. Khar, Controlled drug delivery concepts and advances, **2005**, 1 edition,
[20] Ali A, Sharma SN *Ind. J.Hosp.Pharm*. **1991**, 28, 165-169.
[21] Lee VKL, Robinson JR, *J. Pharm. Sci*. **1979**, 68, 673.
[22] Mitra AK, Mikkelson TJ, *Int. J. Pharm*. **1982**, 10, 219 - 229