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Ocular Drug Delivery System:- A review

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Abstract:-
Eye diseases are commonly encountered in day to day life, which are cured or prevented through the conventionally used dosage forms like eye drops, ointments. Delivery to the internal parts of the eye still remains troublesome due to the anatomical and protective structure of the eye. To overcome these problems various types of dosage forms such as nanoparticles, liposomes and micro emulsions have been developed. Ocular drug delivery is one of the most challenging tasks faced by Pharmaceutical researchers. Major barriers in ocular medication are the ability to maintain a therapeutic level of the drug at the site of action for a prolonged duration. The anatomy, physiology, and biochemistry of the eye is such that it is impervious to foreign substances, therefore, it is a challenge for the formulator to pass through the protective barriers of the eye without causing any permanent tissue damage. The introduction of new sensitive diagnostic techniques and therapeutic agents necessitates the development of a successful and advanced ocular drug delivery system. Current momentum in the invention of new drug delivery systems hold a promise toward much improved therapies for the treatment of vision, threatening disorders.

I. INTRODUCTION:-

Topical application of drugs to the eye is the well established route of administration for the treatment of various eye diseases like dryness, conjunctiva, eye flu etc. For illness of the eye, topical administration is usually ideal over systemic administration, before reaching the anatomical barrier of the cornea, any drug molecule administered by the ocular route firstly crosses the precorneal barriers. These are the first barriers that slow the penetration of drug into the eye and consist of the tear film and the conjunctiva. The protective mechanisms of the eye such as Blinking, baseline and reflex lacrimation, and drainage decrease the bioavailability of drug and also help to remove rapidly foreign substances like the dust particles bacteria, including drugs, from the surface of the eye. There are most commonly available ophthalmic preparations such as drops and ointments about 70% of the eye dosage formulations in market. But these preparations when instilled into eye they are rapidly drained away from the ocular surface due to blinking tear flow and lachrymal nasal drainage of the eye1. With conventional ophthalmic solution normal dropper used which delivers about 50-75µl per drop and portion of these drops rapidly drain until the eye is back to normal resident volume of 7µl. Due to this drug loss in front of the eye, very small drug is available to enter the cornea and inner tissue of the eye. Actual corneal permeability of the drug is relatively low and very small corneal contact time (about 1-2 min) in humans for instilled solution usually less than 10%. Therefore only small amount of drug actually penetrates the cornea and reaches intraocular tissue. Due to these limitations, newer pharmaceutical ophthalmic formulation such as in-situ gel, nanoparticle, liposome, nanosuspension, microemulsion, iontophoresis and ocular inserts have been developed in last three decades increase the bioavailability of the drug as a sustained and controlled manner. An ideal ophthalmic drug delivery must be able to release the drug in sustained manner and to remain in the area of front of the eye for prolong period of time. As a result it is necessary to optimize ophthalmic drug delivery; the best way towards do so is by adding of polymers of various grades, development of colloidal suspension or using erodible or non erodible insert, development of viscous gel to prolong the precorneal drug retention Micro particle suspension or polymeric solution can be bio adhesive systems

ANATOMY & PHYSIOLOGY OF EYE:-

The eye consists of transparent cornea, lens, and vitreous body without blood vessels. The oxygen and nutrients are transported to this non-vascular tissue by aqueous humor which is having high oxygen and same osmotic pressure as blood. The aqueous humor in human is having volume of 300 µl that fills the anterior chamber of the eye which is in front of lens. The cornea is covered by a thin epithelial layer continuous with the conjunctiva at the cornea-sclerotic junction. The main bulk of cornea is formed of crisscrossing layers of collagen and is bounded by elastic lamina on both front and back. Its posterior surface is covered by a layer of endothelium. The cornea is richly supplied with free nerve endings. The transparent cornea is continued posteriorly into the opaque white sclera which consists of tough fibrous tissue. Both cornea and sclera withstand

the intra ocular tension constantly maintained in the eye. The eye is constantly cleansed and lubricated by the lacrimal apparatus which consists of four structures.

1. lacrimal glands
2. lacrimal canals
3. lacrimal sac
4. nasolacrimal duct.

The lacrimal fluid secreted by lacrimal glands is emptied on the surface of the conjunctiva of the upper eye lid at a turnover rate of 16% per min. It washes over the eye ball and is swept up by the blinking action of eye lids. Muscles associated with the blinking reflux compress the lacrimal sac, when these muscles relax; the sac expands, pulling the lacrimal fluid from the edges of the eye lids along the lacrimal canals, into the lacrimal sacs. The lacrimal fluid volume in humans is 7 µl and is an isotonic aqueous solution of bicarbonate and sodium chloride of pH 7.4. It serves to dilute irritants or to wash the foreign bodies out of the conjuctival sac. It contains lysozyme, whose bactericidal activity reduces the bacterial count in the conjuctival sac. The physiological barriers to diffusion and productive absorption of topically applied drug exist in the precorneal and corneal spaces. The precorneal constraints that are responsible for poor bioavailability of conventional ophthalmic dosage forms are solution drainage, lacrimation, tear dilution, tear turn over and conjuctival absorption.

Barriers to Restrict Intraocular Drug Transport:-

Tear- One of the precorneal barriers is tear film which reduces the effective concentration of the administrated drugs due to dilution by the tear turnover (approximately 1 µL/min), accelerated clearance, and binding of the drug molecule to the tear proteins.In addition the dosing volume of instillation is usually 20–50 µL whereas the size of cul-de-sac is only 7–10 µL. The excess volume may spill out on the cheek or exit through the nasolacrimal duct.[6] Cornea - The cornea consists of three layers; epithelium, stroma and endothelium, and a mechanical barrier to inhibit transport of exogenous substances into the eye. Each layer possesses a different polarity and a rate-limiting structure for drug permeation. The corneal epithelium is of a lipophilic nature, and tight junctions among cells are formed to restrict paracellular drug permeation from the tear film. The stroma is composed of an extracellular matrix of a lamellar arrangement of collagen fibrils. The highly hydrated structure of the stroma acts as a barrier to permeation of lipophilic drug molecules. Corneal endothelium is the innermost monolayer of hexagonal-shaped cells, and acts as a separating barrier between the stroma and aqueous humor. The endothelial junctions are leaky and facilitate the passage of macromolecules between the aqueous humor and stroma

Conjunctiva- of the eyelids and globe is a thin and transparent membrane, which is involved in the formation and maintenance of the tear film. In addition, conjunctiva or episclera has a rich supply of capillaries and lymphatics therefore, administrated drugs in the conjunctival or episcleral space may be cleared through blood and lymph. The conjunctival blood vessels do not form a tight junction barrier, which means drug molecules can enter into the blood circulation by pinocytosis and/or convective transport through paracellular pores in the vascular endothelial layer. The conjunctival lymphatics act as an efflux system for the efficient elimination from the conjunctival space. Recently, it has been reported that at least 10% of a small molecular weight hydrophilic model compound (sodium fluorescein), administered in the subconjunctival space, and is eliminated via the lymphatics within the first hour in rat eyes. Therefore, drugs transported by lymphatics in conjunction with the elimination by blood circulation can contribute to systemic exposure, since the interstitial fluid is returned to the systemic circulation after filtration through lymph nodes.

Sclera - The sclera mainly consists of collagen fibers and proteoglycans embedded in an extracellular matrix. Scleral permeability has been shown to have a strong dependence on the molecular radius; Scleral permeability decreases roughly exponentially with molecular radius additionally, the posterior sclera is composed of a looser weave of collagen fibers than the anterior sclera and the human sclera is relatively thick near the limbus (0.53 ± 0.14 mm), thin at the equator (0.39 ± 0.17 mm).[7Choroid/Bruch's Membrane - Choroid is one of the most highly vascularised tissues he body to supply the blood to the retina. Its blood flow per unit tissue weight is ten-fold higher than in the brain. In addition the choroidal capillary endothelial cells are fenestrated and, in humans, are relatively large in diameter (20–40 µm). Retina -The drugs in the vitreous are eliminated by two main routes from anterior and posterior segments. All drugs are able to eliminate via the anterior route. This means drugs can diffuse across the vitreous to the posterior chamber and, thereafter, eliminate via aqueous turnover and veal blood flow. Elimination via the posterior route takes place by permeation across the retina. One of the barriers restricting drug penetration from the vitreous to the retina is the internal limiting membrane (ILM). The ILM separates the retina and the vitreous, and is composed of 10 distinct extracellular matrix proteins. Although a previous study using primates has suggested that molecules exceeding 100 kDa cannot cross the retinal layers

into the subretinal space,[14] it has been confirmed by immunohistochemical analysis, a full-length, humanized, anti- vascular endothelial growth factor (VEGF) monoclonal antibody, composed of 214 amino acids with a molecular weight of 149 kDa, injected into the vitreous cavity, can penetrate through the sensory retina into retinal pigment epitheliums (RPE), subretinal and choroidal space, in monkey and rabbit. In addition, nanometer-sized particles whose mean diameter is below 200 nm can penetrate across the sensory retina into RPE after intravitreal injection in rabbit. In intact retina, theoretically, the drugs in the subretinal fluid could either be absorbed by the sensory retinal blood vessels or transported across the RPE, where it may be absorbed into the choroidal vessels or pass through the sclera. Drug transport across the RPE takes place both by transcellular and paracellular routes. The driving forces of outward transport of molecules from the subretinal spaces are hydrostatic and osmotic, and small molecules might transport through the paracellular inter- RPE cellular clefts and by active transport through.

TYPES OF OCULAR DRUG DELIVERY SYSTEAM

Type-I are divided into different types

1. Drug Delivery Systems to Anterior Segment of the Eye – e.g.
   Eye-Drops
   Contact Lens
   Cul-de sac Inserts
   Punctal Plugs

2. Drug Delivery Systems to Posterior Segment of the Eye
   Intravitreal Implants (e.g.-Duraser Technology System, Novadu Technology, I-ratio TA, NT-501)
   Injectable Particulate Systems (RETAAC, Cortiject, Visudyne) Eye-Drops

3. Physical Devices
   - Iontophoresis
   - Micro-Electromechanical Intraocular Drug Delivery Device

Type-II are divided into different type

1.Conventional delivery systems
   Eye Drops
   Ointment and Gels
   Ocuserts and Lacrisert

2. Vesicular system
   Liposomes
   Niosomes and Discomes
   Pharmacosomes

3. Control delivery systems
   Implants
   Iontophoresis
   Dendrimer
   Cyclodextrin
   Contact lenses
   Collagen Shield
   Microemulsion
   Nanosuspensions
   Microneedle

Prodrugs
   Penetration Enhancers
   Mucoadhesive Polymers
   Phase Transition Systems/Insitu gel system

4. Particulates (nanoparticles and microparticles)
5. Advanced delivery system
   Cell Encapsulation
   Gene Therapy

Stem cell Therapy
Protein and Peptide therapy
Scleral Plug therapy
siRNA therapy
Oligonucliotide therapy
Aptamer

Different ocular drug delivery system.

Eye Drops: -

Drugs which are active at eye or eye surface are widely administered in the form of Solutions, Emulsion and Suspension. Generally eye drops are used only for anterior segment disorders as adequate drug concentrations are not reached in the posterior tissues using this drugdelivery method. Various properties of eye drops like hydrogen ion concentration, osmolality, viscosity and instilled volume can influence retention of a solution in the eye. Less than 5 Percent of the dose is absorbed after topical administration into the eye. The dose is mostly absorbed to the systemic blood circulation via the conjunctival and nasal blood vessels. Ocular absorption is limited by the corneal epithelium, and it is only moderately increased by prolonged ocular contact. The reported maximal attainable ocular absorption is only about 10 Percent of the dose. When eye drops is administered in the inferior fornix of the conjunctiva, very small amount of the dose reaches to the intraocular tissues and major fraction of the administered drug get washed away with the lachrymal fluid or absorbed systemically in the nasolacrimal duct and pharyngeal sites.

Ointment and Gels:-

Prolongation of drug contact time with the external ocular surface can be achieved using ophthalmic ointment vehicle but, the major drawback of this dosage form like, blurring of vision and matting of eyelids can limits its use. Pilopine HS gel containing pilocarpine was used to provide sustain action over a period of 24 hours. A number of workers reported that ointments and gels vehicles can prolong the corneal contact time of many drugs administered by topical ocular route, thus prolonging duration of action and enhancing ocular bioavailability of drugs.

Ocuserts and Lacrisert: -

Ocular insert (Ocusert) are sterile preparation that prolong residence time of drug with a controlled release manner and negligible or less affected by nasolacrimal damage.9 Inserts are available in different varieties depending upon their composition and applications. Lacrisert is a sterile rod shaped device for the treatment of dry eye syndrome and keratitis sicca and was introduced by Merck, Sharp and Dohme in 1981. They act by imbibing water from the cornea and conjunctiva and form a hydrophilic film which lubricates the cornea.

Liposomes: -

Liposomes are biocompatible and biodegradable lipid vesicles made up of natural lipids and about 25–10 000 nm in diameter. They are having an intimate contact with the corneal and conjunctival 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 increases 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.

Niosomes and Discomes: -

The major limitations of liposomes are chemical instability, oxidative degradation of phospholipids, cost and purity of natural phospholipids. To avoid this niosomes are developed as they are chemically stable as compared to liposomes and can entrap both hydrophobic and hydrophilic drugs. They are non toxic and do not require special handling techniques. Niosomes are nonionic surfactant vesicles that have potential applications in the delivery of hydrophobic or amphiphilic drugs. Vyas and co workers reported that there was about 2.49 times increase in the ocular bioavailability of timolol maleate encapsulated in niosome as compared to timolol maleate solution. Non-ionic surface active agents based discoidal vesicles known as (discomes) loaded with timolol maleate were formulated and characterized for their in vivo parameters. In vivo studies showed that discomes released the contents in a biphasic profile if the drug was loaded using a pH gradient technique. Discomes may act as potential drug delivery carriers as they released drug in a sustained manner at the ocular site.harmacosomes: -

This term is used for pure drug vesicles formed by the amphiphilic drugs. Any drug possessing a free carboxyl group or an active hydrogen atom can be esterified (with or without a spacer group) to the hydroxyl group of a lipid molecule, thus generating an amphiphilic prodrug. The amphiphilic prodrug is converted to

pharmacosomes on dilution with water. The pharmacosomes show greater shelf stability, facilitated transport across the cornea, and a controlled release profile.

Implants: -

For chronic ocular diseases like cytomegalovirus (CMV) 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.

Methods of Preparation of Nanoparticles:-

- Polymerization in a Continuous Aqueous Phase

In this process monomers are dissolved in the aqueous phase and within emulsifier micelles. Additional monomers may be present as monomer droplets stabilized by emulsifier molecules. Initiation of polymerization takes place in the aqueous phase when the dissolved monomer molecules are hit by a starter molecule or by high-energy radiation. Polymerization and chain growth is maintained by further monomer molecules, which originate from the aqueous phase, the emulsifier micelles, or the monomer droplets. The monomer droplets and the emulsifier micelles therefore act mainly as reservoirs for the monomers or for the emulsifier, which later stabilize the polymer particles after phase separation and prevent coagulation. Also, to prevent excessively rapid polymerization and promote the formation of nanoparticles, emulsion polymerization is carried out at an acidic pH (pH is 1–2). The drugs may be added before, during, or after polymerization and formation of particles.

- Interfacial Polymerization

Interfacial polymerization of the polyalkylcyanoacrylate polymers allows the formation of nanocapsules with a shell-like wall65. This carrier type can encapsulate drugs with lipophilic character, and the rate of encapsulation is generally related to the solubility of the drug in the oily compartment. The technique involves dissolving the polyalkylcyanoacrylate (PACA) monomers and lipophilic drug in an ethanolic solution or oil and slowly injecting this mixture into a well- stirred solution of 0.5% poloxamer 338 in water at pH 6 (may contain nonionic surfactant). At the oil/water interface, nanoparticles with a shell-like wall are formed spontaneously by hydroxyl ion–induced polymerization, and the polymeric colloidal suspension occurs immediately.

- Polymerization by Denaturation or Desolvation of Natural Proteins

Macromol:-ecules such as albumin or gelatin can form nanoparticles through the desolvation and denaturation processes. Desolvation of macromolecules in aqueous solution can be induced by changes in pH, charge, or the addition of desolvating agents such as ethanol. The desolvation process induces the swollen molecules to coil tightly. At this point, the tightly coiled macromolecules can be fixed and hardened by crosslinking with glutaraldehyde to form nanoparticles rather than nanocapsules. Nanoparticles are then purified by gel filtration. The denaturation process involves preparing an emulsion from an aqueous phase containing the drug, magnetite particles, and the macromolecule and cottonseed oil. Polymerization is carried out by heat denaturation at temperatures above 120 C or by chemical crosslinking. Nanoparticles are precipitated out and washed with ether (or in the case of gelatin, acetone) and stored in the dry form.

- Solvent Evaporation Method

Gurny et al. were the first to use this process for the production of polylactic acid nanoparticles containing testosterone. In this method, the polymer of interest is dissolved in an organic solvent, suspended in a suitable water or oil medium, after which the solvent is extracted from the droplets. The particles obtained after solvent evaporation are recovered by filtration, centrifugation, or lyophilization. In general, the diameter of the particles depends on the size of the microdroplets that are formed in the emulsion before evaporation of the solvent. Chiang et al. used the solvent evaporation technique with an oil-in-oil emulsion to prepare polylactide-co- glycolide microspheres of 5-fluorouracil for ocular delivery. Microspheres containing cyclosporin A have been prepared with a mixture of 50 : 50 polylactic and polyglycolic acid polymers using the solvent evaporation process. The polymer and drug mixture was dissolved in a mixture of chloroform and acetone, emulsified in an aqueous solution of polyvinyl alcohol, and stirred for 24 hours to evaporate the organic solvent and yield the microparticle dispersion.

- Ionic Gelation Technique

De Campos et al. developed chitosan nanoparticles using the ionic gelation technique. Nanoparticles were obtained upon the addition of sodium tripolyphosphate aqueous solution to an aqueous polymer solution of chitosan under magnetic stirring at room temperature. The formation of nanoparticles was a result of the interaction between the negative groups of the tripolyphosphate and the positively charged amino groups of

chitosan. In this technique, drug in an acetonitrile-water mixture can be incorporated either into chitosan solution or the tripolyphosphate solution.

- Nano-precipitation

Fessi et al. developed nanoparticles using this method. In this technique a polymer and a specified quantity of drug is dissolved in acetonitrile. The organic phase is then added dropwise to the aqueous phase and stirred magnetically at room temperature until complete evaporation of the organic phase takes place. Drug-free nanoparticles may be prepared using the same procedure by simply omitting the drug.

- Spray-Drying

In this technique, microparticles are prepared by dissolving the polymer of interest in an organic solvent. The drug is added to this solution and spray-dried using a spray-dryer. The process parameters and spray nozzle size are set up as required. The spray-dried product is collected by a cyclone separator.

- Polymers used in the Preparation of Nanoparticles

A successful nanoparticulate system may be one that has a high loading capacity, thus reducing the quantity of carrier required for administration. The drug can be either adsorbed onto the surface of performed particles or incorporated into the nanospheres during the polymerization process. Concerning the loading capacity of nanoparticles, it has been found that both the nature and quantities of the monomer used influences the absorption capacity of the carrier. Generally, the longer the chain length, the higher is the affinity of the drug to the polymer.

Several types of polymeric nanoparticles are used in ophthalmic drug Delivery Polymethylmethacrylate (PMMA), acrylic copolymer Nanoparticles, polystyrene, polyvinyl pyridine, Cellulose acetate phthalate, PACA, poly-e-caprolactone (PECL) nanocapsules, etc.[34]

- Gene Therapy: - Along with tissue engineering, gene therapy approaches stand on the front line of advanced biomedical research to treat blindness arising from corneal diseases, which are second only to cataract as the leading cause of vision loss. Several kinds of viruses including adenovirus, retrovirus, adeno-associated virus, and herpes simplex virus, have been manipulated for use in gene transfer and gene therapy applications. Topical delivery to the eye is the most expedient way of ocular gene delivery. However, the challenge of obtaining substantial gene expression following topical administration has led to the prevalence of invasive ocular administration. 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. The advanced delivery systems that prolong the contact time of the vector with the surface of the eye may enhance transgene expression, thereby facilitate non-invasive administration.

- 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 consists of eliminating the injurious agent or attempting to minimize its effects. The most successful ocular application has been the use of limbal stem 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.

- Protein and Peptide therapy: -

Delivery of therapeutic proteins/ peptides has received a great attention over the last few years. The intravitreous injection of ranibizumab is one such example. The designing of optimized methods for the sustained delivery of proteins and to predict the clinical effects of new compounds to be administered in the eye, the basic knowledge of Protein and Peptide is required. However; several limitations such as membrane permeability, large size, metabolism and solubility restrict their efficient delivery. A number of approaches have been used to overcome these limitations. Poor membrane permeability of hydrophilic peptides may be improved by structurally modifying the compound, thus increasing their membrane permeability. Ocular route is not preferred route for systemic delivery of such large molecules. Immunoglobulin G has been effectively delivered to retina by trans Scleral route with insignificant systemic absorption.

- Scleral Plug therapy: -

Scleral plug can be implanted using a simple procedure at the pars plane 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 vitreoretinopathy, cytomegalovirus retinitis responds to repeated intravitreal injections and for vitreoretinal disorders that require vasectomy.

SiRNA therapy: -

For various angiogenesis-related diseases, the use of siRNA is considered as a promising approach. Feasibility of using siRNA for treatment of choroidal neovascularization has been demonstrated using siRNA directed against vascular endothelial growth factor (VEGF) or VEGF receptor 1 (VEGFR1), and both of these approaches are being tested in clinical trials. Topical delivery of siRNAs directed against VEGF or its receptors has also been shown to suppress corneal neovascularisation. siRNA has become a valuable tool to explore the potential role of various genes in ocular disease processes. It appears that siRNAs may be valuable in the pathogenesis and development of new treatments for several ocular diseases, based on in vivo and in vitro studies. However, its use in vivo remains problematic, largely due to unresolved difficulties in targeting delivery of the siRNA to the tumor cells. Viral gene delivery is very efficient however it currently lacks adequate selectivity for the target cell type. New encapsulated siRNA have been developed using liposomes, coupled-antibodies or others polymer vesicles. Therapeutic approach using siRNA provides a major new class of drugs that will shed light the gap in modern medicine.

- Oligonucliotide therapy: -

Oligonucliotide (ON) therapy is based on the principle of blocking the synthesis of cellular proteins by interfering with either the transcription of DNA to mRNA or the translation of mRNA to determine to contribute to the efficacy of antisense ON. One primary consideration is the length of the ON species. Lengths of 17– 25 bases have been shown to be optimal, as longer ONs have the potential to partially hybridize with nontarget RNA species Biological stability is the major barrier to consider when delivering both DNA and RNA oligonucleotides to cells. Protection from nuclease action has been achieved by modification of phosphate backbones, sugar moiety, and bases.

Aptamer: -

Aptamer are oligonucleotides legends that are used for high-affinity binding to molecular targets. They are isolated from complex libraries of synthetic nucleic acid by an Iterative process of adsorption, recovery, and reamplification. They bind with the target molecules at a very low level with high specificity. One of the earliest aptamers studied structurally was the 15 mer DNA aptamer against thrombin, d (GGTTGGTGTGGTTGG). Pegaptanib sodium is an RNA aptamer directed against VEGFb165, where VEGF isoform primarily responsible for pathological ocular neovascularization and vascular permeability.

- Ribozymes 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 pigmento sum (ADRP) is caused by mutations in genes that produce mutated proteins, leading to the apoptotic death of photoreceptor cells.

CONVENTIONAL OCULAR FORMULATIONS ADVANTAGE AND DISADVANTAG

DOSAGE FORM	ADVANTAGE	DISADVANTAGE
Solution	• Convenience	• Loss of drug drainage • Nonsustained action
Suspension	• Patient compliance • Best for drug with slow dissolution	• Drug properties decide performance
Emulsion	• Prolonged release of drug from vehicle	• Patient non compliance • Blurred vision • Possible oil entrapment
Ointment	• Flexibility of drug choice • Improved drug stability • Increased tissue contact time • Inhibition of dilution by tears. • Poor patient compliance	• Sticking of eyelids • Blurr vision

- No true sustained effect.

Gels
- Comfortable
- Less blurred vision than ointment
- No rate control on diffusion
- Mattered eyelids after use

Erodible inserts
- Sophisticated and effective delivery system
- Flexibility in drug type and dissolution rate
- Need only be introduced into eye and not removed
- Patient discomfort
- Requires patient insertion
- Movement of system around eye can cause abrasion

Non-erodible insert
- Controlled rate of release
- Prolonged delivery
- Flexibility for type of drug selected
- Patient discomfort
- Irritation to eye
- Patient placement and removal
- Tissue fibrosis

OCULAR INSERTS AS AN OCULAR SUSTAINED RELEASE DRUG DELIVERY SYSTEM

- The main objective of the ophthalmic inserts is to increase the contact time between the preparation and the conjunctival tissue, to ensure a sustained release suited for topical or systemic treatment.The advantages of ocular inserts over the traditional ophthalmic preparation can be summarized as follows:
  Increased ocular residence, hence, prolonged drug activity and higher bioavailability with respect to standard vehicles.
- Release of drugs at a slow, constant rate.
- Accurate dosing (insert contains a precise dose, which is fully retained at the administration site).
- Reduction of systemic absorption.
- Better patient compliance, due to reduced frequency of administration and less incidence of visual and systemic side-effects.
- Possibility of targeting internal ocular tissues through non-corneal (conjunctival scleral) routes.
- Increased shelf life with respect to aqueous solutions.
- Exclusion of preservatives, thus reducing the risk of sensitivity reactions.
- Incorporation of various novel chemical / technological approaches, such as pro-drugs, mucoadhesives, permeation enhancers, micro particulates, salts acting as a buffer.

All of the benefits listed above cannot be present in a single, ideal device. Each type of insert is a compromise between the desirable properties inherent to solid dosage forms and negative constraints possessed by the structure and components of the insert, fabrication costs, and physical / physiological constraints of the application site. It also bears some disadvantages, which are as follows:

•disadvantage of ocular inserts resides in their ‘solidity’, that is, they are felt by the (often oversensitive) patients as an extraneous body in the eye. This may constitute a difficult physical and psychological barrier to patient compliance.

- Their movement around the eye, in rare instances, the simple removal is made more difficult by unwanted migration of the insert to the upper fornix.
- The occasional unintentional loss during sleep or while rubbing the eyes.
- Their interference with vision.
- Difficulty in placement of the ocular inserts (and removal, for insoluble types).

CLASSIFICATION OF OCULAR INSERT

The foreign-body sensation leads to discomfort, which causes poor-patient compliance, excessive lachrymation that accompanies irritation, dilutes the drug, and reduces its concentration.[1 properly designed ocular insert will minimize the sensation caused by its insertion.

Classification of ocular inserts

- Ease of handling and insertion.
- Lack of expulsion while wearing it.
- Reproducibility of release kinetics (Zero-order drug delivery).
- Applicable to variety of drugs.
- No interference with vision and oxygen permeability.
- Sterility.
- Stability.

- Ease of manufacturing.

Insoluble Ophthalmic Inserts Diffusion inserts

The diffusion systems are composed of a drug reservoir enclosed in a specially designed semi-permeable or microporous membrane, which allows the drug to diffuse from the reservoir The drug release from such a system is controlled by the lachrymal fluid, which permeates through the membrane. A sufficient internal pressure is achieved to drive the drug out from the reservoir. The drug delivery rate is controlled by diffusion through the membrane.

Osmotic inserts:-

The osmotic inserts are generally divided into two types, in the first case the central part of the insert is surrounded by a peripheral part.[19] The centrapart.The composed of a single reservoir, which is composed of the drug with or without an osmotic solute dispersed through a polymeric matrix, so that the drug is surrounded by the polymer as discrete small deposits. IN the second, drug and the osmotic solutes are placed in two separate compartments, the drug reservoir is surrounded by an elastic impermeable membrane and the osmotic solute reservoir surrounded by a semi-permeable membrane. The peripheral part of these osmotic inserts are comprised of a film covering made of an insoluble semi-permeable polymer.[21] The tear fluid dies into the peripheral deposits through the semi-permeable polymeric membrane, wets them, and induces their dissolution. The solubilized deposits create a hydrostatic pressure against the polymer matrix, and cause its rupture in the form of apertures. Rge drug is then released through these apertures from the deposits near the surface of the device.[22] The release of drug through the osmotic insert follows the zero-order drug release profile.

Soft contact lenses:-

These structure are m:-adeup of a covalently cross-linked hydrophilic or hydrophobic polymer that forms a three-dimensional matrix capable of retaining water, aqueous solution or solid components .When a hydrophilic co.When is soaked in a drug solution, it absorbs the drug, but does not deliver the drug as precisely as that provided by other non-soluble ophthalmic systems. The drug release from the system is generally very rapid at the beginning and then declines exponentially with time. The release rate can be decreased by adding the drug homogeneously during the manufacture or by adding a hydrophobic component.Contact lenses have prospects as ocular drug delivery systems.

Soluble OphthalmicInserts:-

Soluble inserts correspond to the oldest class of ocular inserts, which offer the advantage of being wholly soluble, so they need not be removed from the site of application, thus, limiting the interventions to insertion only.They are further category:

Based on natural polymers, for example, collagen. Based on synthetic or semi-synthetic polymers.

The therapeutic agent is absorbed by soaking the insert in a solution containing the drug, and drying and rehydrating it before use in the eye. The amount of drug contained will depend upon the capacity of the binding agent, concentration of the drug solution into which the insert is soaked, and the duration of soaking The soluble ophthalmic inserts are easily processed by

conventional methods – slow erating extrusion, compression or injection molding. The release of the drug takes place when tears penetrate into the insert. This induces drug release by diffusion and forms a layer of gel around the core of the insert. This gelification causes further release of the drug, but it is still controlled by diffusion. The release rate, J, is derived f
rom Fick's law, which yields the following expression.

J= Adkcs/ L

A – do not Surface area of membrane k – Diffusion coefficient of the drug
L – Membrane thickness

CS – Drug solubility in water

d – Diffusion coefficient of the Ocuserts membrane

As all the terms on the right hand side of the above equation are constant, the release rate of the device is also constant.

Bioerodible Ophthalmic Inserts

The bioerodible inserts are composed of homogeneous dispersion of a drug which can be included in or not included in the hydrophobic coat made of bioerodible polymers, which is impermeable to the drug.

MECHANISM OF DRUG RELEASE FROM OCULAR INSERT

Diffusion

In this mechanism, the drug is released continuously at a controlled rate through the membrane into the tear fluid. If the insert is formed of a solid non-erodible body having pores and drug is in a dispersed form, the drug release takes place via diffusion through the pores. Controlled release of the drug can be maintained by a gradual dissolution of the solid dispersed drug in the matrix, as a result of the inward diffusion of aqueous solutions. In a soluble device, true dissolution occurs mainly through polymer swelling. In swelling-controlled devices, the active agent is homogeneously dispersed in a glassy polymer. As glassy polymers are essentially drug- impermeable, no diffusion occurs through the dry matrix. When the insert is placed in the eye, water from the tear fluid begins to penetrate the matrix, swelling occurs, and consequently polymer chain relaxation occurs and drug diffusion takes place. The dissolution of the matrix, followed by the swelling process depends on the polymer structure. A linear amorphous polymer dissolves at a faster rate than a cross-linked or partially crystalline polymer.

Osmosis

In the Osmosis mechanism, the insert is made of a transverse impermeable elastic membrane, which divides the interior of the insert into two compartments, first and second; the first compartment is surrounded by a semi-permeable membrane and the impermeable elastic membrane, and the second compartment is surrounded by an impermeable material and the elastic membrane. There is a drug release orifice in the impermeable membrane of the insert. The first compartment contains a solute that cannot pass through the semi-permeable membrane and the second compartment provides a reservoir for the drug, which is in liquid or gel form. When the insert is placed in the aqueous environment of the eye, water diffuses in the first compartment, which stretches the elastic membrane to expand the first compartment and contract the second compartment so that the drug is forced to come out through the drug release orifices

Bioerosion:-

In the bioerosion mechanism, the insert is comprised of a matrix of bioerodible material in which the drug is dispersed. Contact of the insert with the tear fluid results in controlled sustained release of the drug by bioerosion of the matrix. The drug is dispersed uniformly throughout the matrix, but it is believed that a more controlled release is obtained if the drug is superficially concentrated in the matrix. In truly erodible or E-type devices, the drug release is controlled by a chemical or enzymatic hydrolytic reaction that leads to polymer solubilization, or degrades to smaller, water-soluble molecules. These polymers may undergo bulk or surface hydrolysis, which displays zero-order release kinetics; provided the devices maintain a constant surface geometry and the drug is poorly water-soluble.

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