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Ocular Drug Delivery System

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ABSTRACT:—

The administration of medications through the eyes is a well-established method. The mechanism of the eye is such that it aids in the removal of different foreign substances, such as invasive germs, that may block the normal physiological function. For a more effective therapeutic effect, a proper medication delivery must release the medicine in a regulated and sustained manner. Traditional drug delivery methods like eye drops, solutions, and emulsions supply the right amount of medication, but barriers like lacrimal drainage and tear flow, among others, cause the medication to drain from the ocular surface others.This led to the introduction of novel approaches to medication administration to the eye.To improve both, methods like liposomes, niosomes, ocuserts (also known as ocular inserts), nanoparticles, nanosuspensions.

• INTRODUCTION :-

For pharmaceutical chemists, getting a medicine into the eye has remained one of the most difficult tasks. Due to factors such naso-lachrymal drainage, lacrimation, medication dilution with tear fluid, tear turnover, and conjunctival absorption, the intraocular bioavailability of the medicine by standard eye drops is relatively low.Drug loss through the precorneal parallel elimination loss route is also influenced by drug binding to proteins. As a result, only a tiny fraction of the medicine (1-3%) really reaches the intraocular tissue via penetrating the cornea.Sincere attempts to extend the time that an ophthalmic medicine is in contact with the cornea can boost its effectiveness. This can be achieved by adding a viscosity-enhancing ingredient to eye drops or by employing an ointment base that is water insoluble in ophthalmic formulations.There are numerous benefits over traditional dosage forms, including extended ocular residency, prolonged release, precise dosing, and decreased dose frequency.

•History :-

In the nineteenth century, squares of dry filter paper were impregnated with dry solutions (such as atropine sulphate and pilocarpine hydrochloride) to create the first solid medication (forerunners of the current insoluble inserts). Small pieces were cut and placed beneath the eyelid. Lamellae, the forerunners of the current soluble inserts, were later created. They were made of glycerinated gelatin that included several ophthalmic medications. Up to the early part of the 20th century, official compendia contained 'lamellae' of glycerinated gelatin. Lamellae were used, but their use was discontinued when stricter guidelines for the sterility of ophthalmic preparations were implemented. Ophthalmic inserts are currently seeing an increase in attention.

• Physiology of eye :-

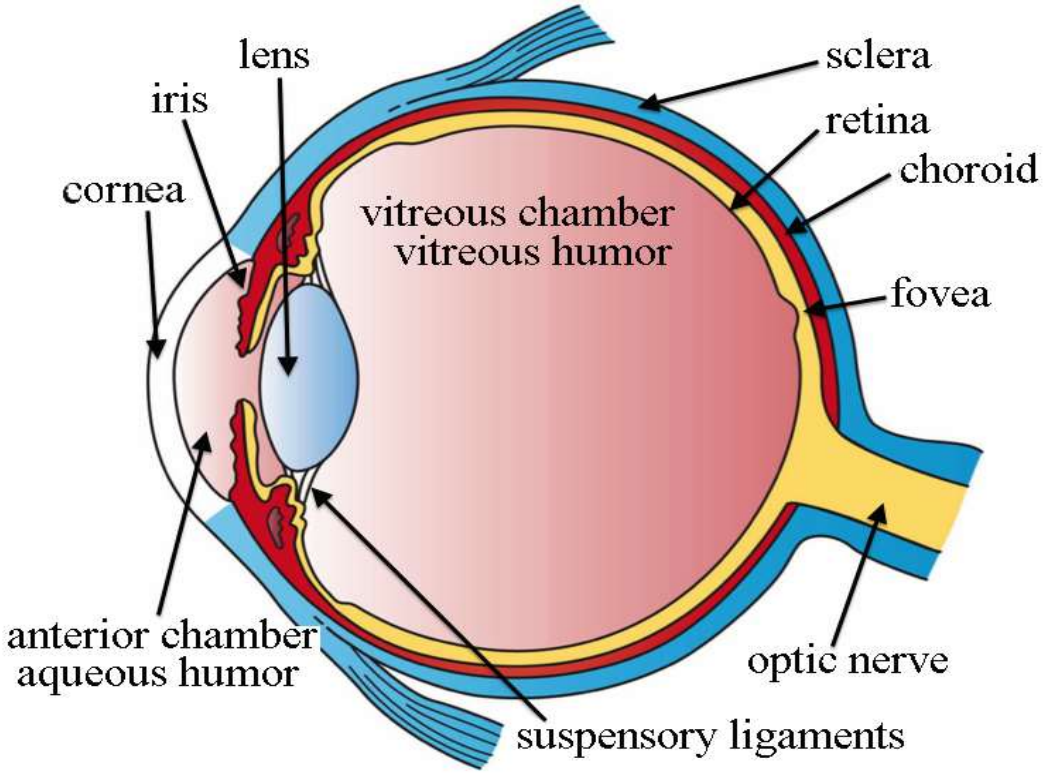

Figure :- physiology of eye

The vitreous body, which lacks blood vessels, the cornea, which is transparent, and the lens make up the eye. Aqueous humour, which has a high oxygen content and the same osmotic pressure as blood, transports nutrients and oxygen to this non-vascular tissue. Humans have 300 l of aqueous humour, which fills the anterior chamber of the eye, which is where the lens is located. At the corneasclerotic junction, the conjunctiva and a thin epithelial layer that covers the cornea are joined. Collagen fibres cross each other to form the cornea's main bulk, which is bordered on the front and back by elastic lamina. A layer of endothelium is present on its posterior surface. Free nerve terminals are abundantly present throughout the cornea. Eye consists of four structure :-

a. Lacrimal glands

b. lacrimal canals

c. lacrimal sac

d. nasolacrimal duct.

At a rate of 16% per minute, the lacrimal fluid secreted by the lacrimal glands is discharged onto the conjunctiva of the upper eyelid. The motion of the eyelids blinking sweeps it across the eyeball and away. The lacrimal sac is compressed by muscles connected to blinking reflux; when these muscles relax, the sac expands and drawslacrimal fluid from the edges of the eyelids along the lacrimal canals into the lacrimal sacs. Human lacrimal fluid has a volume of 7 l and a pH 7.4 isotonic aqueous solution of sodium chloride and bicarbonate. It is used to wash foreign objects out of the conjunctival sac or to dilute irritants. It has lysozyme, which has bactericidal properties.

• Conventional Delivery System :-

Greater corneal penetration with longer drug cornea contact time are necessary for effective ocular drug administration with eye drops. Improvementsin precorneal residence duration and corneal penetration have been made in a number of ways. Iontophoresis, prodrugs, ion-pair forming substances, and cyclodextrins are used to increase corneal permeation[9–13]. There is a large selection of ophthalmic products on the market, and about 70% of prescriptions call for traditional eye drops. High patient acceptability, drug product efficacy, stability, and cost effectiveness may all play a role in the reasoning.

Barriers :-The following barrier factors affect the administration of ocular drugs:-

• Eye and lacrimal fluid separation :-

The corneal epithelium found in the eye can restrict drug absorption from the lacrimal fluid. The penetration of the medication paracellularly is restricted by tight junctions made of corneal epithelial cells. Drugs that are lipophilic have greater corneal permeability than those that are hydrophilic. In other terms, we can state that conjunctiva has leaky epithelium compared to that of the cornea and also has twenty times more surface area than the cornea that allows rapid systemic absorption.

• Blood-ocular partitions :-

Blood-ocular barriers shield the eye from xenobiotics by being present in the bloodstream. Blood-aqueous and blood-retina barriers make up its two components. Endothelial cells in the uvea, or the layer of the eye between the sclera, iris, ciliary body, and choroid, make up the anterior blood-eye barrier. This barrier limits the admission of plasma albumin into the aqueous humour as well as the entry of hydrophilic medicines thatmake up the posterior barrier, which stands between the eye and the plasma stream, form a tight wall junction. Because of the large blood flow and porous walls of the choroid vasculature, medicines are easily accessed.

• Disorder :-

Cataract

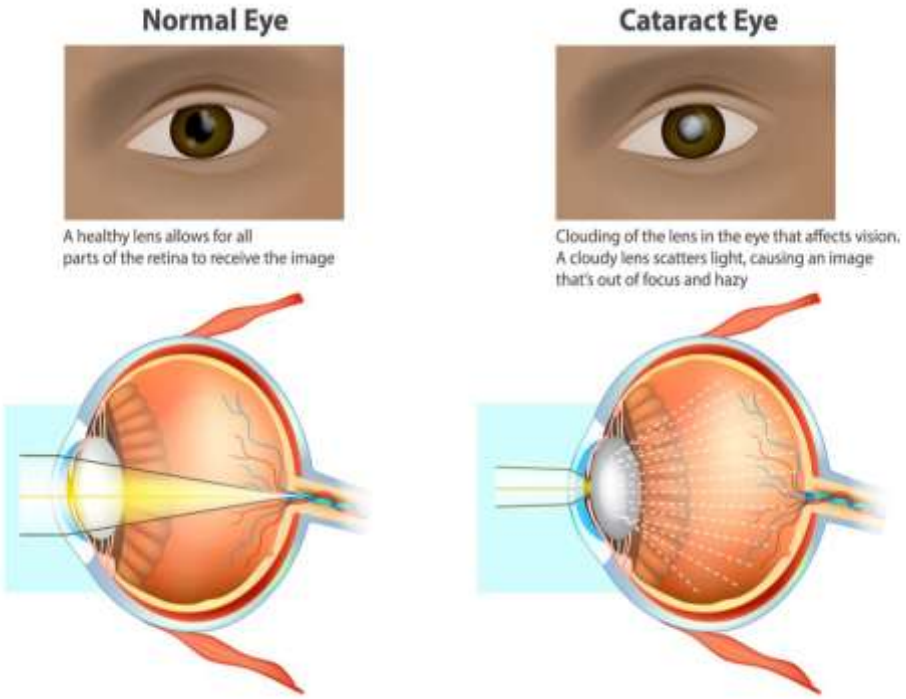

Figure :- Cataract

Any opacity or cloudiness of the ordinarily transparent crystalline lens of the eye is referred to as a cataract. Depending on the size, density, and location of the opacity, a cataract may or may not impair vision. A significant global contributor to curable blindness is severe cataracts.

Conjunctivitis :-

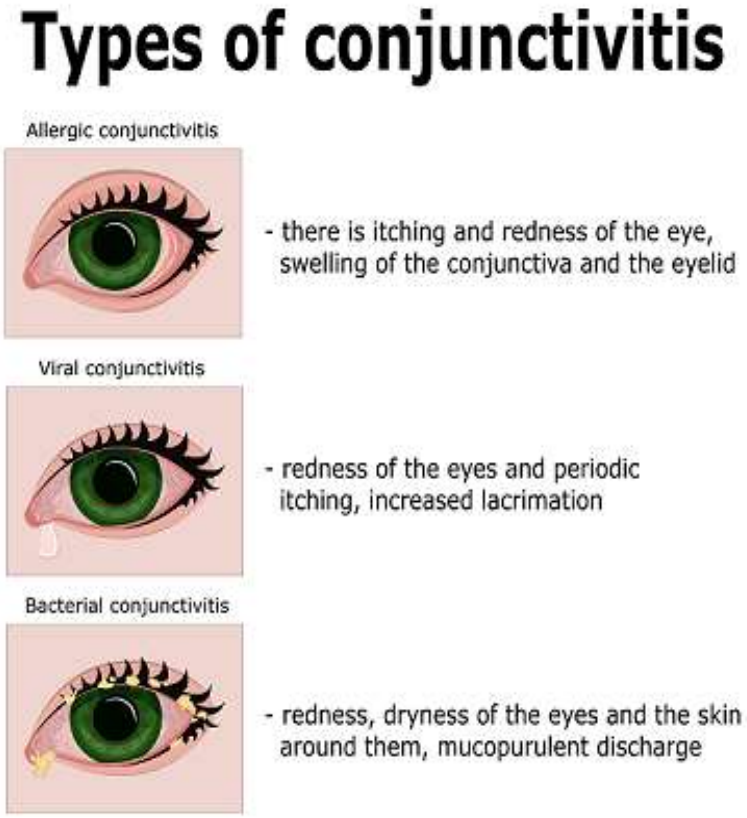

Figure :- Types of Conjunctivitis

An inflammation of the conjunctiva, the clear mucous membrane lining the inside of the eyelids and the white of the eye, is known as conjunctivitis. When the conjunctiva is inflamed, its typically invisible blood vessels become engorged, making the eye seem red. typically, the white, or sclera, is clearly visible through the conjunctiva. Numerous infectious agents, including bacteria or viruses, as well as irritants that are poisonous, chemical, or allergic can all contribute to conjunctivitisconjunctivitis.

Degeneration of the macula :-

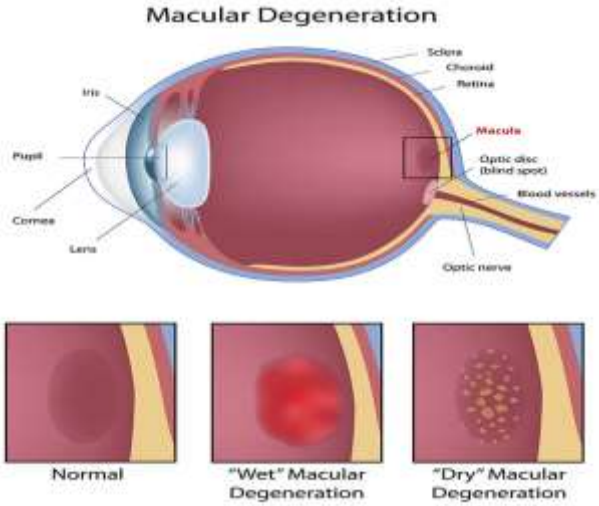

Figure :-Degeneration of the Macula

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Sicca keratoconjunctivitis :-

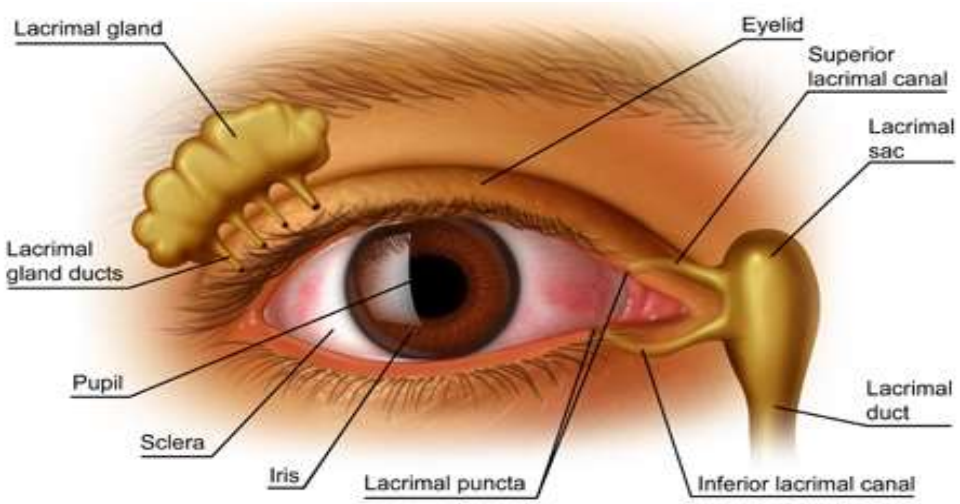

Figure :-Sicca keratoconjunctivitis

Dry eye is a tear film condition brought on by inadequate or excessive tear production. It damages the interpalpebral ocular surface and is accompanied by a number of symptoms that represent ocular discomfort.1 Keratoconjunctivitis sicca (KCS), another name for dry eye syndrome, is a frequent ailment that people who seek ophthalmologic care report. It is characterised by inflammation of the ocular surface and lacrimal glands.

Early identification of a potentially fatal condition may result from the early discovery of dry eye symptoms, which can be an indication of a systemic disease. Additionally, those who have dry eyes are more likely to contract infections that could result in blindness, including bacterial keratitis, and are also more likely to experience complications from routine operations like laser refractive surgery.

Night Blindness :-

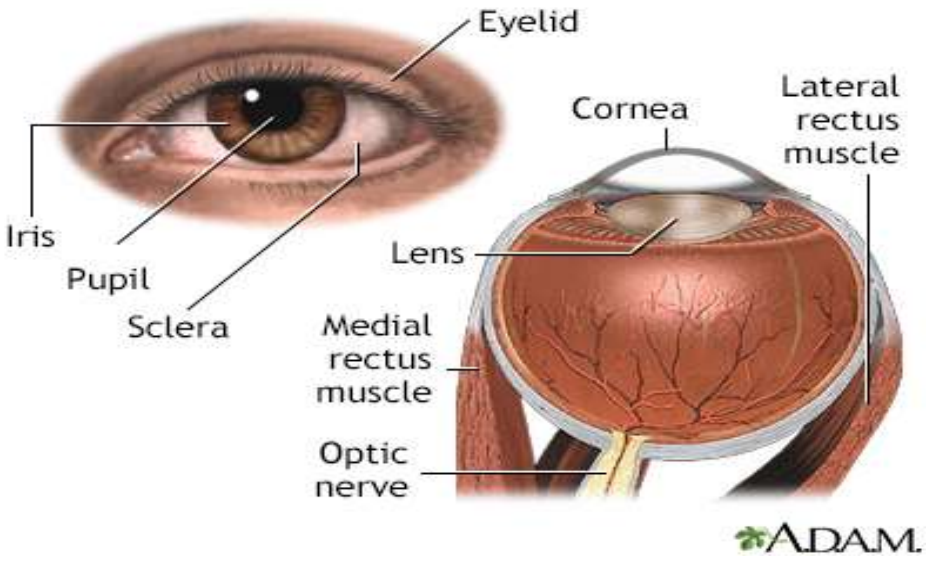

Figure :-Night Blindness

Night blindness, also known as nyctalopia, is the impairment of the eyesight that is typically possible in low light. Given that vitamin A is crucial for maintaining the eye's cells' sensitivity to low light, it might be a warning sign of vitamin A shortage. Other eye conditions including glaucoma and optic nerve disease can also present as night blindness. It is frequently the first sign of retinitis pigmentosa, a chronic and progressive retinal inflammation. Congenital fixed night blindness, one variation of the disorder, is inherited.

• Classification of ocular inserts:-

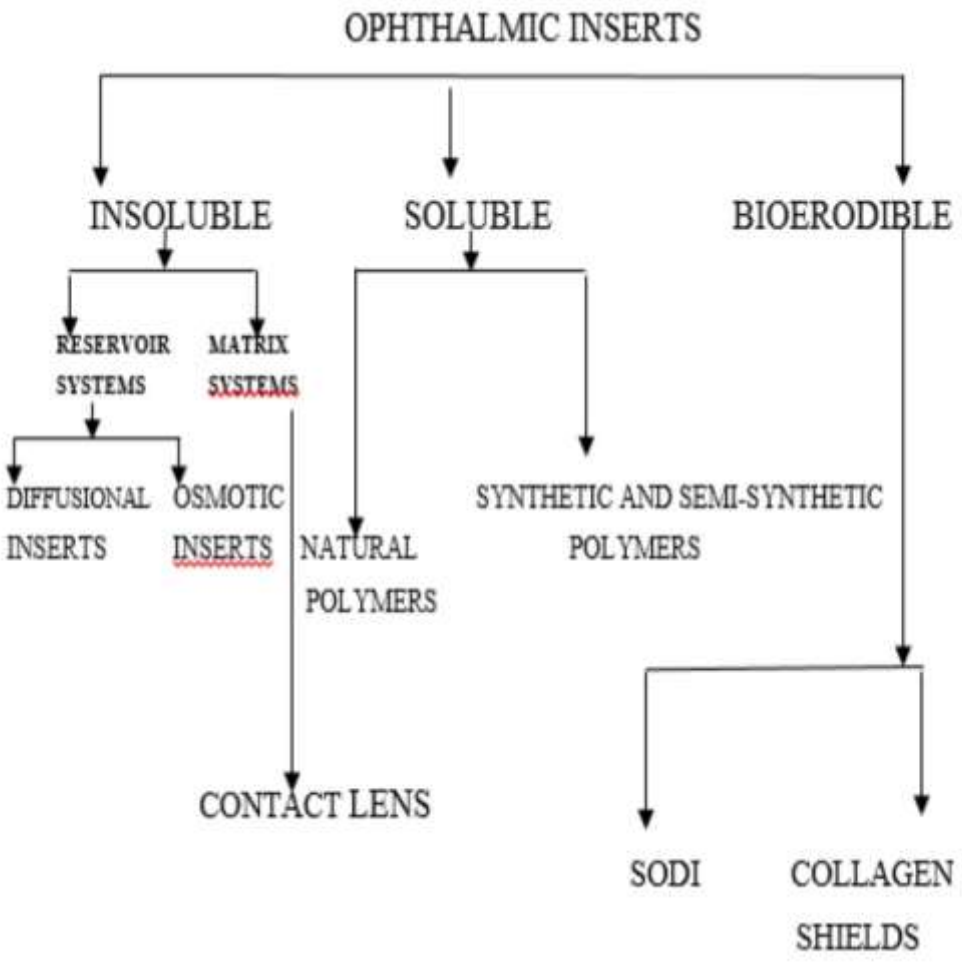

Figure :- Classification of Ocular inserts

Ocular insert are mainly divided in three classes.

1. Insoluble ocular inserts.
2. Soluble ocular inserts
3. Bioerodible ocular inserts.

1.lnsoluble ocular inserts :-

The insoluble inserts have been divided into three groups:

1.hydrophilic contact lenses,

2.osmotic systems,

3.diffusion systems.

In the first and second classes, a reservoir that supplies drugs to the rate controller's inner surface is in touch with it. The reservoir includes a liquid, gel, colloid, semisolid, solid matrix, or a drug carrier that is disseminated or dissolved therein in a homogeneous or heterogeneous manner. Carriers can be constructed of organic, inorganic, synthetic, naturally occurring,hydrophobic, or hydrophilic materials. Contact lenses are included in the third class. The fundamental drawback of these devices is that they are insoluble, necessitating removal after usage.

Diffusion inserts :-

The diffusion systems are comprised of a central reservoir of drug enclosed in semi permeable or micro porous membranes, which allow the drug to diffuse through the reservoir at a precisely determined rate. The drug release from such a system is controlled by The membrane is permeable to lachrymal fluid until enough internal pressure is created to force the drug out of the reservoir. Diffusion through the membrane, which is controllable, regulates the rate at which drugs are delivered.

Osmotic inserts :-

Osmotic inserts are often separated into two categories; the first type has a centre portion that is surrounded by a periphery. A single reservoir or two separate compartments can make up the first central component. The first kind consists of a drug disseminated across a polymeric matrix with or without an extra osmotic solution so that the drug is coated by the polymer as distinct tiny deposits. The second version uses an osmotic pressure sensor and a medication. The drug reservoir is covered by an elastic impermeable membrane, and the osmotic solute reservoir is covered by a semi-permeable membrane. Solutes are deposited in two different compartments. The peripheral section of these osmotic inserts contains in all cases a covering film comprised of an insoluble semi permeable polymer. Through the semi-permeable polymeric membrane, the tear fluid diffuses into peripheral deposits and moistens them to promote their breakdown. The hydrostatic pressure that the solubilized deposits create against the polymer matrix causes the matrix to explod. This is in line with the osmotic portion, which is zero order drug release analysed.

Soft Contact lenses :-

These are structured structures constructed of a covalently bonded hydrophilic or hydrophobic polymer that creates a three-dimensional matrix or network capable of holding onto water, aqueous solution, or solid components.

A hydrophilic contact lens will absorb a drug solution, but it won't administer the medication with the same level of precision as other non-soluble ophthalmic systems. Drug release such a device often starts out quickly and then decreases rapidly over time. Incorporating a homogeneous drug combination during manufacturing or adding a hydrophobic component can both reduce the release rate.

Soluble Ophthalmic Inserts :-

The earliest class of ocular inserts are soluble inserts. They have the significant benefit of being completely soluble, preventing the need to remove them from the application site and restricting treatments to insertion only.

• Types of soluble ophthalmic inserts :-

a) Based on natural polymers e.g. collagen.

b) Based on synthetic or semi synthetic polymers.

Mechanism of Drug release from ocular inserts :-

Diffusion

Through the membrane, the drug is constantly released in this method at a controlled rate. When a medication is in a dispersed form and the insert is made of a solid, non-erodible body with pores, the drug is released by diffusion through the pores. The progressive disintegration of the solid drug in the matrix caused by the inward diffusion of aqueous solutions can sustain controlled drug release. True dissolving in a soluble device mostly happens as a result of polymer swelling. Theactive ingredient in swelling-controlled devices is uniformly disseminated in a glassy polymer. Since glassy polymers are essentially resistant to drugs, there is no diffusion through the dry matrix. Water from the tear fluid leaks out of the eye as the insert is inserted.

Osmosis

transverse impermeable elastic membrane used in the Osmosis mechanism divides the insert's interior into two compartments, first and second. The first compartment is surrounded by a semi-permeable membrane and the elastic membrane, while the second compartment is surrounded by an impermeable material and the elastic membrane. The impermeable membrane of the insert has a medication release hole. The second compartment serves as a reservoir for the drug, which is present in liquid or gel form, while the first compartment contains a solute that cannot flow through the semi-permeable barrier. Water diffuses in the first compartment of the insert when it is inserted into the aqueous environment of the eye, stretching the elastic membrane to expand the first compartment.

Bioerosion

The insert in the bioerosion mechanism is made of a matrix of bioerodible material, and the medicine is disseminated there. By causing the matrix to bioerode, contact of the insert with tear fluid causes a controlled, prolonged release of the medication. The drug is equally distributed throughout the matrix, but it is thought that if the drug is superficially concentrated in the matrix, a more controlled release is obtained. The drug release in fully erodible or E-type devices is regulated by a chemical or enzymatic hydrolytic reaction thatsolubilizes the polymer or breaks it down into smaller, water-soluble molecules. If the devices maintain a stable surface geometry and the medication is present, these polymers can undergo bulk or surface hydrolysis, which exhibits zero order release kinetics.

• Evaluation test for ocular inserts:-

1. Thickness
2. Folding Endurance Test
3. Surface pH
4. Weight uniformity
5. Drug content uniformity
6. Tensile strength
7. In vitro drug release study
8. Ex vivo transcorneal permeability study
9. Drug releasr kinetics
10. Accelerated stability study.

Ointments and Gels:-

Although ophthalmic ointments have the advantage of extending medication contact time with the external ocular surface, their main disadvantages—vision blurring and eyelid mating—can limit their use. For 24 hours, pilopine HS gel with pilocarpine was utilised to give sustained activity. The duration of action and ocular bioavailability of many medications delivered by topical ocular route can be prolonged and improved by using ointments and gels as vehicles, according to a number of workers. A biphasic system made up of two immiscible phases is an emulsion. Ophthalmic emulsions can increase the bioavailability and solubility of previously water-insoluble medications. The categories of pharmaceutical emulsions are numerous.

Objectives with ophthalmic drug delivery methods :-

The creation of a therapeutic system that can deliver an ideal concentration of a drug to the target region and with high therapeutic efficacy is a challenge in ocular drug delivery systems. Due to the cornea's architecture, physiology, and barrier properties, medicines are absorbed quickly; therefore, fast instillations of eye drops are necessary to maintain the therapeutic level in tear film or at specific spots. Consequences of utilising medication solutionsoften include the potential for toxicity at the ocular surface and cellular damage. Due to precorneal loss, which includes solution drainage, lacrimation, tear dynamics, tear dilution, conjunctival absorption, non-productive absorption, and transient residence period, the majority of ocular dose forms have low bioavailability.

The objective in ocular drug delivery systems are categorized as follows:-

• Anterior segment delivery objective :-

Additionally, repeated instillations of eye drops are required to keep a therapeutic drug level the tear film or at the site of action, but doing so with highly concentrated drug solutions runs the risk of damaging the eye's surface cells and causing toxic side effects.

• Posterior segment delivery challenges :-

BRB prevents medications used topically for the eyes from entering the posterior segment of the eye. Poor ocular bioavailability is also caused by some circumstances that prevent drug delivery to the posterior region of the ocular tissue. Both the intravenous route's impact at the posterior site of drug administration and the systemically delivered medication's ability to enter the retina are constrained by the BRB. Because BRB is permeable to more lipophilic molecules, such medications can enter the posterior portion of the eye. Regular administration and high drug concentration systematically generate negative effects [18]. Maintaining the therapeutic concentration of the pharmaceuticals for a longer amount of time while also reducing the number of injections is a significant problem when delivering medications to the posterior portion of the eye. The aqueous humour is the next stop on the anterior route of drug elimination before the humour in the anterior chamber.

• Benefits of ocular inserts :-

Benefits of ocular inserts include the following:-

i. Increased ocular residence, which results in a prolonged drug activity and a higher bioavailability compared to standard vehicles.

ii. Possibility of drug release at a slow, constant rate.

iii. Accurate dosing (in contrast to eye drops, which may be administered incorrectly by the patient and are partially lost after administration, each insert can be made to contain a precise dose which is fully retained.IV. Better patient compliance due to less frequent administration and a lower incidence of visual and systemic side effects.

vi. Longer shelf life.

• Drawbacks of ocular inserts :-

i. Including the fact that patients, who are frequently overly sensitive, see them as an external body in the eye due to their "solidity."

ii. The straightforward removal is occasionally complicated by the insert's unintended migration to the upper fornix.

iii. Their movement around the eye, and the sporadic accidental loss while sleeping or otherwise.

• Conclusion :-

Ocular implants are created to satisfy the growing number of patients who need minimally invasive treatments. Ocuserts require fewer doses to be administered, enhancing patient compliance. Ocular insets have been found to be advantageous because they prevent drug loss and improve patientcompliance while removing the negative effects of pulsed dosing of conventional dosage forms. They also provide controlled and sustained drug delivery with increased bioavailability and corneal contact time. Soluble, insoluble, and biodegradable ocular inserts have all been created so far, and they are further divided into many categories based on their functions. Ocular insets have been found to be advantageous because they prevent drug loss and improve patient compliance while removing the negative effects of pulsed dosing of conventional dosage forms. They also provide controlled and sustained drug delivery with increased bioavailability and corneal contact time.These classes are further divided into different types based on the material and how it behaves when delivering drugs, such as soluble ocular inserts based on natural, synthetic, or semi-synthetic polymer, insoluble ocular inserts including diffusion insert, osmotic insert, and soft contact lenses, and bio-e Ocular inserts and contact lenses, among other non-erodible items, are notable examples of this.

• Reference :-

1) Born, A.J., Tripathi, R.C., Tripathi, B.J.: Wolff's Anatomy ofthe Eye and Orbit, 8th edn. pp. 211–232, 308-334, 454-596.Chapman & Hall Medical, London (1997)

2)Warwick, R., Williams, P.L. (eds.): Gray's Anatomy, 35th Britishedn. pp. 1100–1122. W.B Saunders, Philadelphia (1973

3) Ravindra Reddy K, Ravi Shankar Yadav M, Sabitha Reddy P; Preparation and ealuation of Aceclofenac ophthalmic In situ gels, Journal of Chemical, Biological anhysical Sciences. 2011, 1(2): 289-298.

4) Katariya dhirajkumar champalal, Poddar Sushilkumar S, Current status of ophthalmic insitu forming hydrogel, International Journal of Pharma and Bio Sciences, 2012; 3(3): 372-388.

5)Mueller WH, Deardroff DL, Ophthalmic vehicles: The effect of methyl cellulose on the penetration of Homatropine hydro bromide through the cornea, J Am Pharma Assoc. 56; 45: 334-341.

6)Sultana Y, Jain R, Aqil M, Ali A, Review of Ocular Drug Delivery, Current Drug Delivery. 2006; 3: 207-217.

7)Mishra DN, Gilhotra RM, Design and characterization of bioadhesive in-situ gelling ocular insert of gatifloxacin sesquihydrate, DARU 2008, 16:

8)Meqi SA, Deshpande SG. Ocular drug delivery: Controlled and novel drug delivery. New delhi:CBS Publishers; 2002, p 82- 84

9)Patel PB, Shastri PK, Sehlat PK, Shukla AK. Opthalmic drug delivery systems: challenges and approaches. Systemic Rev Pharm 2010;1:113-20.

10)Peyman GA, Ganiban GJ. Delivery systems for intraocular routes. Adv Drug Delivery Rev 1995;16:107-23.

11)Janoria KG, Gunda S, Boddu SH, Mitra AK. Novel approaches to retinal drug delivery. Expert Opin Drug Delivery 2007;4:371-88

12)Lambert G, Guilatt RL. Current ocular drug delivery challenges. Drug Dev Report Industry.

13)Katz IM. Shaped ophthalmic inserts for treating dry eyes syndrome. aUS Patent 1982;4:343-787.

14) Cohen, E.M., Grim, W.M., Harwood, R.J., and Mehta, G.N., "Solid state ophthalmic medication, U.S. Patent, 1979; 4:179,597.

15). Bawa, R., "Ocular inserts, In: Ophathalmic drug delivery systems, Marcel Dekker, Inc., New York (Mitra.A.K edr), 1993; 58:223.

16)Chien YW.et al, "Ocular drug delivery and delivery systems" In: Novel drug delivery systems. 2 nd ed. New York: Marcel Dekker; 1992.

17)Saettone MF. Solid polymeric inserts/disks as ocular drug delivery systems. In: Edman P, editor. Biopharmaceutics of ocular drug delivery. Boca Raton: CRC Press; 1993. p. 61-79.

18) Khar RK et al, “Targeted and Controlled drug delivery novel carrier systems” 1 st ed. New Delhi; CBS Publishers and Distributors; 2002.

19) Rajput G et al, “A Review on ophthalmic inserts”, International journal of pharma professional research, 2013,4(3):912-920

20)Sowjanya A et al, “Overview of current technologies in ocuserts for the treatment of ophthalmic diseases”, IJRPS, 2012, 3(4):509-516.

21)Tangri et al,“ Basics of Ocular Drug Delivery Systems ”, International Journal of Research in Pharmaceutical and Biomedical Sciences, 2011; 2(4):1541-1552.

22). Sahane NK et al, “Ocular Inserts: A Review”, Drug Invention Today, 2010; 2(1):57-64.

23)Zaffaroni A et al, “Osmotic releasing device having a plurality of release rate patterns”, U.S. Patent: 1977; 4:036, 227.

24)Chien YW. Ocular drug delivery and delivery systems. In: Novel drug delivery systems. 2nd ed. New York: Marcel Dekker; 1992. p. 269-70.

25) Saettone MF, Salminen L. Ocular inserts for topical delivery. Adv Drug Del Rev 1995; 16:95-106.

26)Brahmankar D.M et al, “Biopharmaceutics and Pharmacokinetics a treatise, Vallabh Prakashan, 2010,pp-470-475.

27)Rathore K.S et al, “Review on ocular inserts”, International Journal of Pharm Tech Research. 1:164-169.

28) Bloomfield et al, “Soluble gentamacin ophthalmic inserts as a delivery system”, J.Pharm. Sci., 1987, 76: 583

29) Mitra, A.K. et al, “Ophthalamic drug delivery, In: Drug Delivery Devices, Marcel Dekker, Inc) , New York, 1998;455.

31)Thakur R., Swami G. Promising implication of ocuserts in ocular disease. Journal of 32)Drug Delivery and Therapeutics, 2012; 2(2):18-25 https://doi.org/10.22270/jddt.v2i2.102.

32) Lang JC. Ocular drug delivery conventional ocular formulations. Adv Drug Delivery Rev 33)1995;16:39-43.

33) Robinson JC. Ocular Anatomy and Physiology Relevant to Ocular Drug Delivery. In: Mitra AK, editor. Ophthalmic drug delivery systems. New York: Marcel Dekker; 1993.

34) Himmelstein KJ, Guvenir I, Palton TP. Preliminary Pharmacokinetics model of pilocarpine uptake and distribution in the eye. J Pharm Sci. 1978;67:603–6.[19] Mitra AK. Opthalmic drug delivery. In: Tyle P, editor. Drug Delivery Devices. New York: Marcel Dekker; 1998.

35) Chien YW. Ocular drug delivery and delivery systems. In: Novel drug delivery systems. 2nd ed. New York: Marcel Dekker; 1992. p. 269-70.

36)Saettone MF, Salminen L. Ocular inserts for topical delivery. Adv Drug Del Rev 1995;16:95-106.

37)Khar RK, Vyas SP. Targeted and Controlled drug delivery novel carrier systems. 1st ed. New Delhi; CBS Publishers and Distributors; 2002. p. 384.

38) Korsmeyer RW, Peppas NA. Macromolecular and modeling aspects of swelling-controlled systems. In: Roseman TJ, Mansdorf SZ editor. Controlled Release Delivery Sstems. New York: Marcel Dekker; 1983. Darougar S. Patent literature review of ocular inserts. US Patent 1999; 6: 264-971

39)Di Colo, G., Burgalassi S., Chetoni,P. “Gel forming ocular inserts for ocular controlled delivery”, Int.J.Pharm.,2001Mar 14;215(1-2):101-11. 23. Shell, J.W., and Gale, R.M., “Topical composition containing steroidal in two forms released independently from polymeric carrier”, U.S. Patent. 1984; 4, 432,964.

40) Gurtler, F., and Gurny, R., ‘Patent literature review of ophthalmic inserts”. Drug Dev. Ind. Pharm., 1995; 21(1):1.

41) Bloomfield, S.E., Miyata, T., Dunn, M.W., et al., “Soluble gentamacin ophthalmic inserts as a delivery system “. Arch Opthalmol. 1978; 96:885.