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OCULAR INSERTS: A PROMINENT TECHNIQUE FOR OCULAR DRUG DELIVERY

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ABSTRACT: The eye is a sensitive organ, and the administration of drugs into the ocular cavity is a tedious task. Ocular insert is the prominent technique to overcome problems associated with conventional dosage forms like repeated administration, drug drainage via lacrimal fluids drainage, formation of crystalline deposits on the cornea, pH instability, pulsed dosing of drugs, *etc*. This review focuses on developing a novel technique to treat ailments associated with the eye cavity. The major complications associated with the drug's delivery into the eye are rapid pre-corneal drug loss due to nasolacrimal drainage, tear flow, and dilution of the drug leading to poor bioavailability, inadequate residence time, *etc*. Ocular inserts are thin films meant to be placed in a cul-de-sac, providing prolonged release without irritating the eyes. They are mostly made of polymers that encloses drug within them, which aids in the sustained release of the drug. Newer ocular drug delivery systems are being surveyed, such as Collagen shields, Biodegradable polymers, Inserts, Outfit, Minidisc`s, NODS, *etc*., and are formulated to attain enhanced bioavailability. In forthcoming years, great attention will be paid to developing non-invasive sustained drug release for both anterior and posterior segment eye disorders. The current aim in the invention of a new drug delivery system holds a promise toward many improved therapies for the treatment of vision-threatening disorders.

INTRODUCTION: Introducing a drug into the eye cavity is a unique opportunity and challenge. Ocular drug delivery is one of the most fascinating and perplexing ventures facing pharmaceutical scientists. One of the major barriers to ocular medication is maintaining and obtaining a therapeutic level at the site of action for the desired period. Newer delivery systems are being surveyed to develop prolonged duration and controlled release strategies.

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Some newer, subtle, and successful ocular delivery systems like inserts, biodegradable polymeric inserts, and collagen shields are being developed to accomplish better ocular bioavailability and sustained action of ocular drugs.

The most frequently used dosage forms, *i.e.*, ophthalmic solutions, suspensions, and ointment dosage forms, are no longer sufficient to combat some present virulent diseases; ophthalmic solutions and suspensions are compromised in their effectiveness by several limitations, leading to poor ocular bioavailability. A wide population nowadays suffers from various ocular diseases, many of which lead to visual impairment and ocular blindness. Certain ocular diseases are quite rare, whereas others, such as cataracts, age-related macular degeneration (AMD), and conjunctivitis,

are very common, especially in the aging population. Pharmacotherapeutics aims to attain an effective drug concentration at the intended site of action for a desired period. For local therapy, the eye is generally used as a portal for drug delivery [1, 2, 3].

Barriers to Drug Permeation: The human eye is spherical and has a diameter of 23mm. The eye is divided into three layers; the outermost coat comprises the clear, transparent cornea and the white, opaque sclera.

Ocular Surface Barrier: The superficial layers of the cornea and conjunctiva are the ocular surface and are in contact with the tear film. The corneal surface consists of only 5% of the total ocular surface, and the other 95% is filled with the conjunctiva. The innermost layer of the eye, *i.e.*, the cornea is, consist of five layers:

1. Epithelium
2. Bowman's layer
3. Stroma
4. Descemet's membrane
5. Endothelium [4]

Tear: It is the first protective layer of the cornea and conjunctiva. They are made up of three layers *i.e.*, a lipid layer (outermost layer), a water layer (middle layer), and lastly, the mucous layer (innermost layer). The tear film is the precorneal barrier that decreases active drug concentration. The total volume of dose fixing is 2550µL, but the cul-de-sac size is 7-10µL. The extra tear volume is left *via* a nasolacrimal duct or rush on the skin of the cheeks [5].

Conjunctiva: The topical eye drops absorption route mostly excludes the corneal and non-corneal routes, *i.e.* (conjunctival/ scleral). This barrier is self-possessed from developed epithelial cells that travel from the upper end of the cornea to the center and the extent to the bottom of the cornea. The limits of the drug diffusion among the cells that form the tight junctions in the topmost corneal epithelial cells. Over the conjunctiva and sclera, the drug may enter into the intraocular tissues in the non-keratin trails. The conjunctival space is eradicated with the help of a competent efflux system through the conjunctival lymphatics [6].

BRB (Blood Retinal Barrier): The BRB inhibits the drug passes from the blood into the retina. The Blood Retinal Barrier is divided based on endothelial cells of the tight junction of RPE and retinal capillary, *i.e.* oBRB is used for the outer and iBRB is used for the inner. The purpose of iBRB is maintained by astrocytes and Muller cells. The blood-eye-barrier contains the BAB and the BRB. The leading purpose is to switch the solute and the nutrients into the intraocular tissue [7].

Ideal properties required to optimize ocular drug delivery system:

- Good corneal penetration.
- Prolong contact time with corneal tissue.
- Simplicity of instillation for the patient.
- Should be non-irritative and comfortable form.
- Need appropriate rheological properties and concentrations of the viscid system [8].

Ocular Inserts: Ocular inserts are small, delicate, sterile, stratified solid pieces of a device placed into the conjunctival sac to deliver drugs. Two types of inserts are available 1st is Erodible and 2nd is non-erodible. Ocular inserts are also known as ocuserts. They offer the advantages of increasing the residence time, improving the bioavailability of drugs and reducing the dosing frequency. Within 24 hours, the inserts may dissolve completely. The inserts' erosion majorly depends on the type and concentration of polymers used. The non-erodible inserts are made of either matrix or reservoir that helps sustain the drug release [9, 10].

Requirement for Success of Ocular Inserts:

- Physician acceptance;
- Patient compliance;
- Ease of handling and insertion;
- Comfort;
- Lack of expulsion during wear;

- Lack of toxicity;
- Non-interference with vision and oxygen permeability;
- Reproducibility of release kinetics;
- Applicability to a variety of drugs;
- Sterility;
- Stability:
- Ease of manufacture;
- Availability at a reasonable rate [11].

History of Ocular Inserts: The first solid medication in the 19th century consisted of squares of dry filter paper, previously soaked with dry drug solutions. These squares were cut into thin sections and placed under the eyelid. Later, lamellae, soluble inserts were prepared. They were formulated using glycerinated gelatine consisting of different drugs used in ophthalmic therapy. Glycerinated gelatine 'lamellae' were present in official compendia until the first half of the 20th century. However, the use of lamellae decreased when laws were enforced regarding the sterility of ophthalmic preparations. There is an increase in demand for ocular inserts over conventional formulations [12, 13, 14].

Merits: Compared to traditional dosage forms, ocular Inserts are more promising. Some are listed below:

1. Increases the residing time and thus improves bioavailability.
2. The side effects due to the pulsed dosing of conventional dosage form can be overcome by using an ocular insert.
3. Provide comfort, better patient compliance, and improve the therapeutic performance of the drug.
4. Increased shelf life in comparison to aqueous solutions.
5. Less to no use of preservatives reduces the risk of corneal irritation.
6. Can target intra -ocular tissues via non-corneal routes [15, 16].

Demerits:

1. A prominent disadvantage of ocular inserts is their solid consistency, which patients still treat as foreign material in the eye. This might develop a psychological barrier.
2. Removal of inserts is difficult due to the migration of inserts to the upper fornix.
3. Interference with vision.
4. The occasional loss during sleep or while rubbing the eyes [15, 16].

Introduction to the Anatomy and Physiology of the Eye: The eye is one of the human body's most complex and sensitive organs. In the human eye, three layers can be distinguished. The outer region consists of the cornea and the sclera. The cornea refracts and transmits the light to the lens, and the retina protects the eye against infection and structural damage to the deeper parts. The sclera develops an outer connective coat that protects the eye from various forces and maintains its shape. Both cornea and the sclera are connected at the limbus.

A transparent mucous membrane covers the Conjunctive, the visible part of the sclera. The middle layer consists of the iris, ciliary body, and choroid. Iris controls the light entering the eye and the amount of light reaching the retina; the ciliary body maintains the shape of the lens and is the site of production of aqueous humor, and the choroid is a vascular layer that delivers nutrients and oxygen to the outer retinal layers. The innermost eye layer is the retina, which consists of rods and cons cells. The three transparent structure surrounded by the ocular layers is called the aqueous, the vitreous, and the lens. The oxygen and nutrients are transported to the nonvascular tissue by aqueous humor with a high oxygen and osmotic pressure similar to blood. The aqueous humor in humans has a volume of 300µl that fills the anterior chamber of the eye in front of the lens. The eye is constantly cleansed and lubricated by lacrimal glands, lacrimal canals, lacrimal sac and nasolacrimal duct. The secreted fluid by the lacrimal gland washes the eyeball and is swept away by the blinking movement of the eyelids.

The volume of lacrimal fluid is 7µl and is an isotonic aqueous solution of HCO_3 and NaCl having pH 7.4. It acts by washing the foreign bodies out of the conjunctival sac. The fluid contains lysozyme, whose action is bactericidal; it reduces the bacterial count in the conjunctival sacs [17, 18].

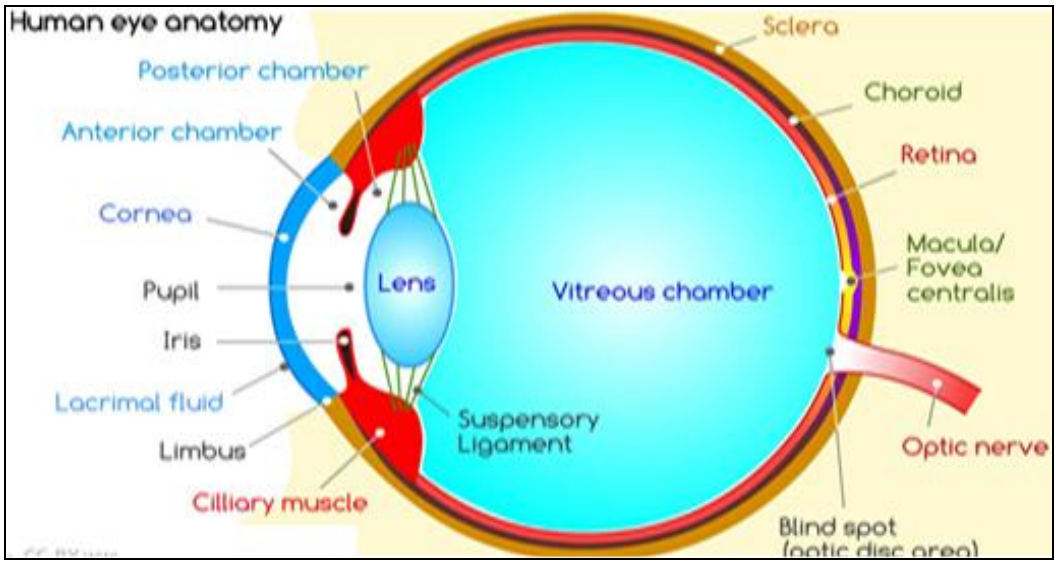

FIG. 1: ANATOMY OF THE EYE

Mechanism of Diffusion: The mechanism of controlled drug release into the eye is as follows:

1. Diffusion,
2. Osmosis,
3. Bio-erosion.

Diffusion: In this Diffusion mechanism, the drug is released constantly at a pulsatile rate via the membrane into the tear fluid. Suppose an insert is made of a solid non-erodible body with pores and dispersed drugs. The release of the drug takes place using diffusion amidst the pores. A controlled release can be maintained by the gradual dissolution of solid dispersed drugs within the matrix due to the inward diffusion of aqueous solutions. In a soluble device, dissolution occurs mainly by polymer swelling. When the insert is placed in the eye, tear fluid begins to penetrate the matrix, swelling, and consequently, polymer chain relaxation and drug diffusion take place. The dissolution of the matrix, which follows the swelling process, depends on polymer structure: linear amorphous polymers dissolve much faster than crosslinked or partially crystalline polymers. Release of drug from ocuserts follows a pattern of Fickian 'square root of time' kinetics; in some instances, however, known as case II transport, zero-order kinetics has been shown [19].

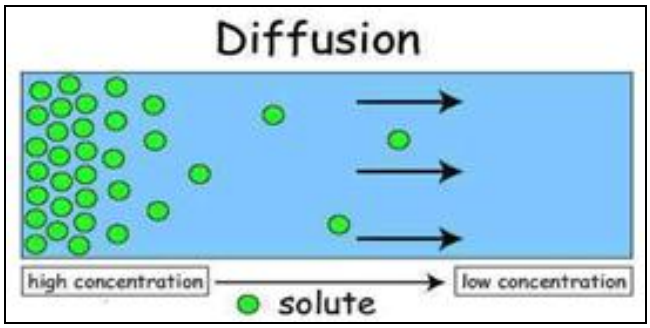

FIG. 2: DIFFUSION MECHANISM

Osmosis: In the Osmosis mechanism, the insert consists of a transverse impermeable elastic membrane dividing the interior of an insert into a first fragment and a second fragment; the first fragment is surrounded by a semi-permeable membrane and an impermeable elastic membrane, and an impermeable material and the elastic membrane surround the second fragment.

The impermeable membrane of the insert contains an orifice that releases the drug. The first fragment contains a solute that could not pass through the semi-permeable membrane, and the second fragment provides a reservoir for the drug, which is still in liquid or gel form [20].

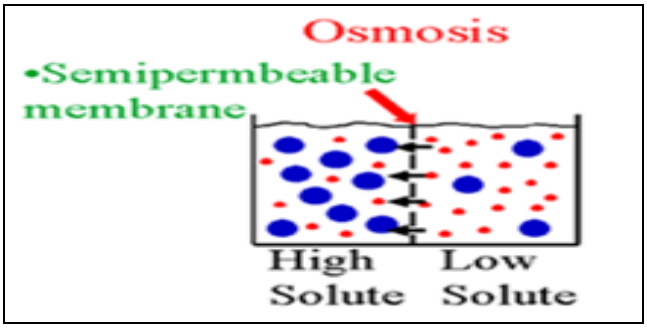

FIG. 3: OSMOSIS MECHANISM

Bio-erosion: In the Bio erosion mechanism, the pattern of the body of the insert is constituted from a matrix of bio-erodible material in which the drug is diffused. Inserts when contact with tear fluid result in controlled release of the drug by bioerosion of the matrix. The drug might be dispersed uniformly within the matrix, but a more prominent controlled release pattern is observed if the drug is superficially concentrated in the matrix.

In truly erodible or E-type devices, the drug release rate is controlled by a chemical or enzymatic hydrolytic reaction that leads to polymer solubilization or degradation to smaller, water-soluble molecules. As specified by Heller, these polymers might undergo bulk or surface hydrolysis. Erodible inserts undergoing surface hydrolysis can exhibit zero order release kinetics; if the devices maintain a constant surface geometry and the drug is poorly water-soluble [21].

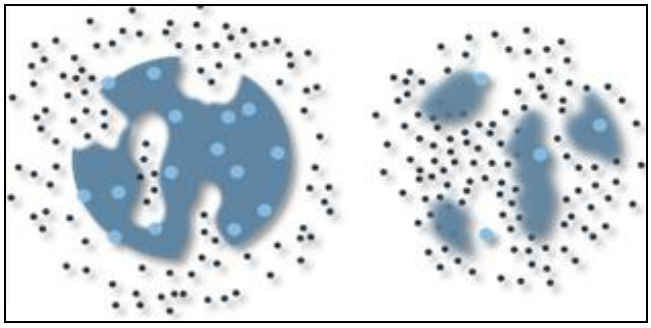

FIG. 4: BIOEROSION MECHANISM OF POLYMER

Classification of Occusert:

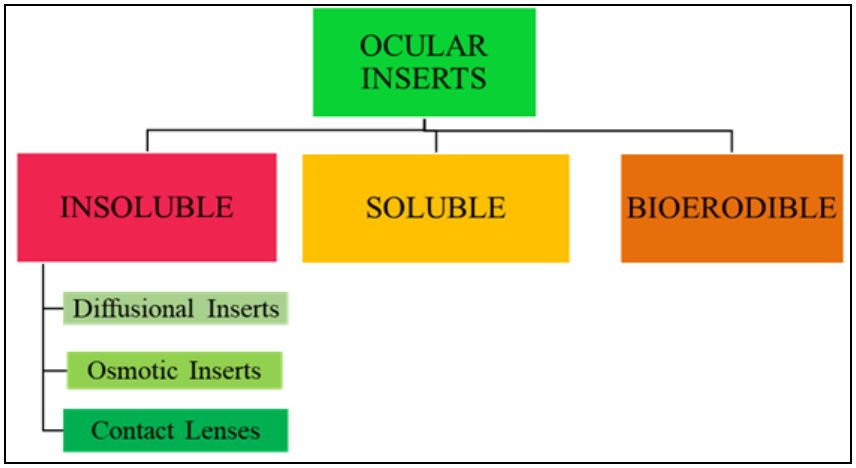

FIG. 5: CLASSIFICATION OF OCUSERTS

They are classified on the basis of their solubility;

a) Insoluble ophthalmic inserts.

b) Soluble ophthalmic inserts.

c) Bio-erodible ophthalmic inserts.

a) Insoluble Ophthalmic Inserts:
Subclassified into:

1. Diffusional Inserts.
2. Osmotic Inserts.
3. Contact Lenses.

Diffusional Inserts: The diffusional inserts are composed of a central reservoir in which the drug is enclosed in a specifically designed semi-permeable membrane, which regulates the rate of drug diffusion from the reservoir at an exclusively determined rate. The drug is not driven out from the reservoir until adequate internal pressure is reached; this happens when the lacrimal fluid permeates the membrane. It follows Fick's diffusion equation:

$$J=-DAdc/dx$$

J = solute flux

D = Diffusion co-efficient for the drug within the ocular membrane,

A = Area of membrane

dc/dx = Concentration gradient within the membrane along the direction of drug flow [22].

Osmotic Inserts: The osmotic inserts are made of two diverse compartments. 1st compartment holds the drug, and the 2nd compartment encloses osmotic solute, jammed between the rate-controlling membranes. The tears diffuse into the osmotic compartment, including an osmotic pressure due to which the drug diffuses [23].

Contact Lenses: Contact lenses are structured covalently crosslinked lipophilic or lipophobic polymer that forms a 3-dimensional network that is capable of retaining water, aqueous drug solution, or solid components. A hydrophilic contact lens absorbs the drug when soaked in a drug solution. Still, it does not give a delivery as precise as that other non-soluble ophthalmic systems provide.

The drug release from such a system is generally very rapid initially and then declines exponentially with time. The release rate can be decreased by incorporating the drug homogeneously during the manufacture or by adding a hydrophobic component [24].

B) Soluble Ophthalmic Inserts: These are entirely soluble inserts, so removing them from their administration site is unnecessary. The release of the drug from this type of insert is due to the penetration of lacrimal fluid into the inserts that promote the drug's release by diffusion and forming a layer of gel around the insert's core.[25]

C) Bioerodible Ophthalmic Inserts: The inserts comprise homogeneous dispersion of a drug that is either present or not into the hydrophobic coating, which is considerably impermeable. The release of the drug from the insert is due to contact of the device with the lacrimal fluid inducing a superficial diversion of the matrix [26].

Formulation Method of Ocuserts:

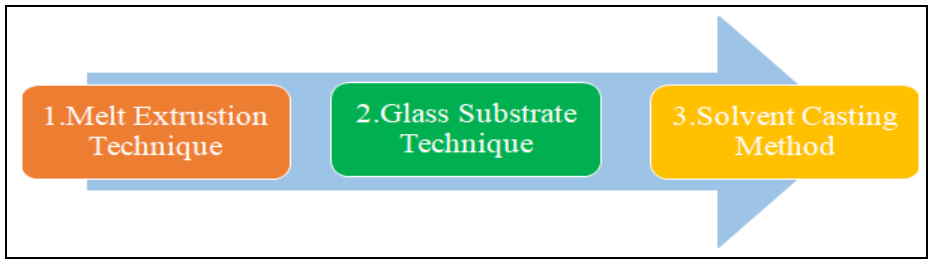

FIG. 6: FORMULATION METHOD OF OCUSERTS

Melt Extrusion Technique: The drug and the polymer are passed through sieve with a mesh size of 60, weighed and blended. Plasticizer is added to the mixture. The blend is discharged in the Melt flow rate apparatus container and extruded. The extrudate was cut into optimum size and packed in polyethylene lined Aluminium foil, they are heat sealed and sterilized using gamma radiation [27].

Glass Substrate Technique: In this method the polymer is soaked in 1%v/v Acetic acid solution for 24hrs, to get a clear solution. The solution is filtered. The required amount of drug is added and vortexed for 15 min to dissolve the complex in a polymer solution. The plasticizer is added to the above solution. The thick solution is obtained and kept apart for thirty minutes until all air bubbles are removed. The rate-controlling films are fashioned. The films are made by pouring the solution into the epicenter of levelled glass mould and are allowed to dry at room temperature for 24 hours. The dried films are cut to form ocular inserts in specified shapes and sizes.

Then, the matrix is incorporated between the rate-controlling membranes using non-toxic, non-irritating gum, and water-insoluble gum. They are wrapped in aluminium foil separately and stored in a desiccator [28].

Solvent Casting Method: In this method, several batches are prepared using different proportions. The polymer is dissolved in a suitable solvent. Into this solution plasticizer is added with continuous

stirring; the accurately weighed amount of drug is added to the above solution and a uniform dispersion is achieved. When the proper blend is formed, the solution is allowed to be cast into the petri dish using an inverted funnel to allow slow and uniform evaporation at room temperature until the film is dried. The obtained dried films are cut into required sizes and shapes using a cork borer. The prepared ocuserts are stored in air-tight containers [28].

Evaluation Parameters of Ocular Inserts: Ocular inserts are evaluated based on various parameters.

Uniformity of Weight: Three patches were weighed and cut at three different sites of the same formulation and the individual weight of every piece determined by using the digital balance [29].

Uniformity of Thickness: Thickness was determined using Vernier-calliper/micro-meter gauze. Thickness was measured at five different points of each insert. The mean value was calculated [30].

Surface pH: In this phenomenon ocular inserts were taken out and kept in a petri dish to swell freely at 270°C for 30 min in zero point one milliter of double-distilled water. The swollen inserts were isolated, and surface pH was evaluated [31].

Percentage Moisture Loss: This checks the film's adherence in dry conditions. The weight of the inserts were checked and kept in a desiccator containing calcium chloride solution and after 3 days, they were reweighed. Moisture loss was calculated by [32]:

% Moisture loss = Initial weight - Final weight x 100 / Initial weight

Percentage Moisture Absorption: This test is performed to check the stability of ocular inserts. They were weighed and placed in desiccators containing a saturated solution of aluminium chloride and humidity maintained at 79.5%.

After 3-days' time period inserts were taken out and reweighed. The percent moisture absorption was calculated [32]:

% moisture absorption = Final weight – Initial weight x 100 / Initial weight

***In-vivo* Drug Release:** 1st sterilization of ocuserts was done by gamma radiation, for the drug release study two groups of healthy rabbits were chosen. Ocular inserts were impregnated in cul- de sac of each rabbit. The inserts are taken out at regular intervals 2, 4, 6, 8, 12 up to 24 hours. The left over drug content was calculated and subtracted from the initial value, which gives the exact amount of drug released inside the eyes [20].

***In-vitro* Drug Release:** This test was performed on the donor-receiver compartment model of transparent regenerated cellulose cells. Insert is tied on an open cylinder which plays the role of donor compartment. The semi-permeable membrane, *i.e.*, corneal epithelial barrier stimulates the tear volume 0.7 ml (distilled water) and is kept in the donor compartment.

The reservoir holds a phosphate buffer of pH-7.4, stirred using a magnetic stirrer. A specified amount of sample was taken out and analyzed at 246nm wavelength using standard phosphate buffer of the same pH as blank by UV-Visible spectro-photometer [20].

Folding Endurance: Folding endurance for ocuserts was evaluated by no. of folds to make the crack, cracks were counted. The folding endurance test was repeated using other sets of ocular inserts [33].

Drug Content Uniformity: Insert films were cut into thin sections and placed in distinct vials containing phosphate buffer, shake vigorously to extract the drug. Then 1ml of the solution is drawn out from the vial and diluted for evaluation of absorbance by spectrophotometer using a pH 7.4 phosphate buffer as blank solution.

Content of the drug in one patch = As x Cr / Ar

Where, As (Absorbance of above solution), Ar (Absorbance of standard solution), Cr (Concentration of drug in standard solution) [33].

Swelling Index: Small film is cut and weighed first and then it is soaked in tear fluid of pH 7.4 for an hour. After 1 hour, the film is reweighed.

Swelling index is determined by the given formula:

Swelling index = $W_1 / W_2 \times 100$

Where, W_1: Initial Weight, W_2: Final Weight.[34]

Accelerated Stability Studies: Accelerated stability studies are carried out to forecast the breakdown that may occur over an extended storage period at normal shelf conditions. The films of the formulation are taken in a separate Petri dish and are kept at three different temperatures 400°C, 500°C and 600°C and the period for break down or degradation of the ocular inserts is checked. When ocuserts show degradation the time in days is noted [25].

Tensile Strength: Tensile strength of the prepared films was calculated according to the following equation:

$$\text{Tensile strength} = \text{N} / \text{mm}^2$$

Where, N: Breaking load. mm^2: Cross-sectional area of the sample mm [35].

Commercial Ocular Inserts: In the following paragraphs, some important ocular inserts are discussed, which are available commercially (SODI) or in the advanced stages of development (Collagen shield, ocufit, NODS and minidisc).

Soluble Ophthalmic Drug Insert (SODI): Soluble ophthalmic drug insert (SODI) is a small, thin film developed by Soviet scientists for astronauts who could not use eye drops in weightless conditions. After film's introduction into the upper conjunctival sac, a SODI softens in l0-15 seconds, adapting to the eyeball's shape. In the next l0-15 min, the film turns into a polymer congeal, which gradually suspends within an hour while releasing the drug. The sensation of an 'extraneous body' in the eye disappears in 5-15 min [36].

Collagen Shields: Collagen is the structural protein of bones, tendons, ligaments, and skin and comprises more than 25% of the total body protein in mammals. This protein is derived from intestinal collagen. Bloomfield *et al.* are credited for first suggesting using collagen inserts as tear substitutes and delivery systems in 1977 -1978. The Collagen shields should be stored in dry condition and hydrated before they are introduced to the eye. Collagen shields were studied on animal and human models and may be used as carriers of anti-inflammatory drugs such as dexamethasone, antibiotics like gentamicin or antiviral drugs. Applying collagen shields leads to higher drug levels in the cornea and the aqueous humor compared to contact lenses and eye drops [37].

Ocufit: The Ocufit is a sustained release, rod-shaped device made of silicone elastomer, patented in 1992 and currently developed by Escalon Ophthalmics Inc. (Skillman, NJ). It was constructed to fit in the shape and size of the inferior conjunctival fornix where it imbibes water from conjunctiva and forms a hydrophilic film that stabilizes tear film, which hydrates and lubricates the cornea.

The diameter should not exceed 1.9 mm and 25-30 mm in length. Smaller sizes are now planned for children and newborn babies. An example of a rod-shaped insert is the Lacrisert (Merck and Co., Inc.), a cellulosic device used to treat dry-eye patients a day; long relief from dry eye syndrome has been reported from a single insert placed in the eye early in the morning. The insoluble Ocufit combines two important features, long retention and sustained drug release [38].

The New Ophthalmic Delivery System (NODS): In 1985, Smith and Nephew Pharmaceuticals Ltd patented NODS, it is a method for delivering precise amounts of drugs in the eye within a water-soluble, drug-loaded film. The device consists of a medicated flag ranging (4 mm x 6 mm, thickness 20 μm, weight 0.5 g) attached to a paper-covered handle using a short and thin membrane ranging 0.7 mm & 3-4μm, respectively. All factors (flag, membrane, and handle) have the same grade of water-soluble polyvinyl alcohol (PVA). The devices are individually enveloped and sterilized by gamma irradiation. For use, the flag is placed into the surface of the lower conjunctival sac [39].

CONCLUSION: The ocular inserts as a system should be non-carcinogenic, retrievable, bio-stable, and bio-compatible, with minimal tissue-insert interaction, stable, non-toxic, and should release the drug at a fixed rate for a predetermined duration of medication. Ocular inserts reduce the frequency of dosing, thus increasing patient compliance it also overcomes major drawbacks of pulsed dosing and provides sustained and controlled release of the drug. Different drugs can be incorporated into the

inserts, like antivirals, antibiotics, anti-glaucoma, lubricants for treating dry eyes, anaesthetics, NSAIDs, *etc*. for treating various drug ailments. Various methods are used to formulate ocular inserts, like solvent casting, melt extrusion, and glass substrate. In forthcoming years, the research in ophthalmic delivery will take a maneuver.

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