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OCULAR DRUG DELIVERY SYSTEM : A NOVEL APPROACH

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Abstract:

Ocular drug delivery is one of the most challenging tasks faced by Pharmaceutical researchers.The ophthalmic preparations are available as sterile, buffered, isotonic solution. Several types of dosage forms are applied as the delivery system for the ocular delivery of drugs. The most prescribed dosage form is the eye drop solution as drops are easier to administer. Characteristics of ophthalmic preparations should be non-irritating to the ocular tissue, homogenous, relatively non-greasy, should not cause blurred vision. Prolonged drug release can be achieved using ophthalmic inserts, solid devices placed in the eye, but the inserts must then be removed when they are no longer needed.

Ocuserts are the new drug delivery systems which are designed in such a way that they release the drug at predetermined and predictable rates thus eliminating the frequent administration of the drug. The systems generally include controlled, delayed and or sustained release bio-erodible implantable elements having multiple layers of different materials and/or different concentrations of materials. The elements generally include an inner layer, or core, including a therapeutic agent, and one or more outer layers made of polymeric materials.

Keywords: Ocular Inserts, Bioerodible Implantable Elements, Homogenous, and Predetermined rate.

1. Introduction:

Ocular drug delivery has stayed as a standout amongst the most difficult charge for pharmaceutical researchers. In developing a drug delivery approach, issues of absorption, distribution, metabolism, elimination (ADME) must be considered. [1]Ocular disposition and elimination of a therapeutic agent is

dependent upon its physicochemical properties as well as the relevant ocular anatomy and physiology. The improvement of more up to date, more delicate demonstrative procedures and helpful operators renders direness to the advancement of greatest fruitful and advanced ocular drug delivery systems. Eye, as an entryway for medication conveyance is by and large utilised for the neighbourhood treatment as against systemic treatment with a specific end goal to maintain a strategic distance from the danger of eye harm from high blood groupings of medication which are not planned for eye.

The conventional ocular dosage forms are eye drops, eye ointments, eye gels, eye solutions, eye injections, eye irritation solutions, eye suspensions, sol to gel systems. The most widely used are eye drops, eye ointments and gels, which constitute 80% of the total ophthalmic preparations. Successful treatment of visual ailments is a ghastly test for researchers in the field, particularly as a result of the way of infections and nearness of the visual boundaries particularly in back visual portions. In order to remove the constraints placed by these

conventional ocular therapies. A newer approach for ocular drug delivery systems are being explored to develop extended duration and controlled units release strategy.[2]

The therapeutic efficacy of an ocular drug can be improved by increasing its contact time with the corneal surface.

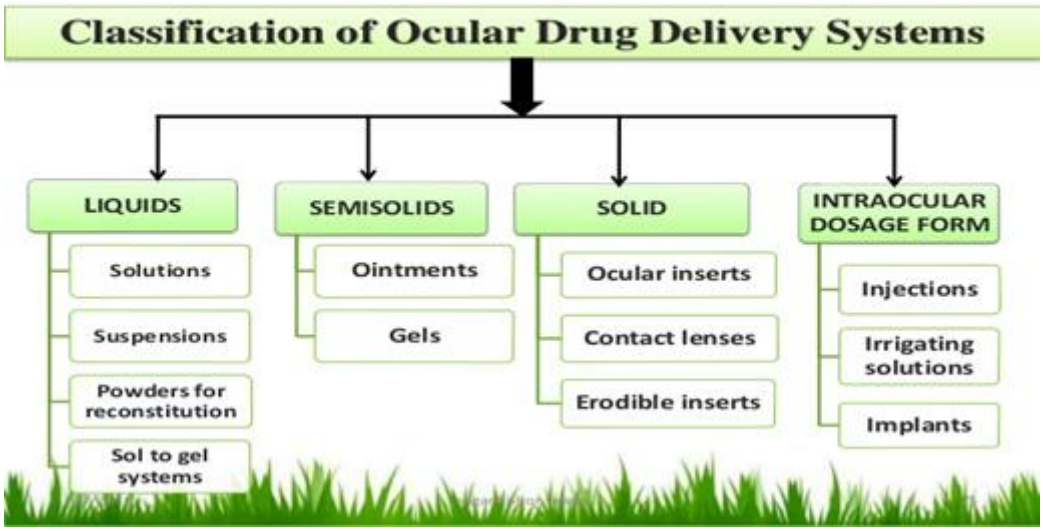
For increasing the contact time viscosity-enhancers are added in preparations or the drug is formulated in a water-insoluble ointment formulation, to sustain the duration of drug-eye contact.[3]

The development of newer, more sensitive diagnostic techniques and therapeutic agents renders urgency to the development of maximum successful and advanced ocular drug delivery systems.[4,5]

The following characteristics are required to optimise ocular drug delivery systems:

- A good corneal penetration.
- A prolonged contact time of drug with corneal tissue..
- Simplicity of installation and removal for the patient.
- A non-irritative and at ease form (the viscoussolution should not irritate lachrymation andreflex flashing).
- Appropriate rheological properties andconcentration of viscolyzer.[6,7]

2. Classification of Ocular Drug Delivery Systems:[8]



3. Ocular Inserts:

Definition: Ocular inserts are the sterile preparations with a thin, multilayered, drug- impregnated solid or a semisolid consistency, and whose size and shape are especially designed for ophthalmic application.[9]The inserts are placed in the lower fornix and less frequently, in the upper fornix or on the Cornea.

They are usually composed of a polymeric vehicle containing the drug. Ocuserts increases corneal contact time, prolongs duration of action, improves bioavailability, reduces the frequency of administration and thus achieves better patient compliance. Generally, all types of ocuserts consists of three components namely, a central drug reservoir in which the drug is incorporated in a polymer, rate controlling membrane which ensures the controlled release of medicament from the drug reservoir and an outer annular ring meant for easy handling and proper insertion shown in figure-6.[10]

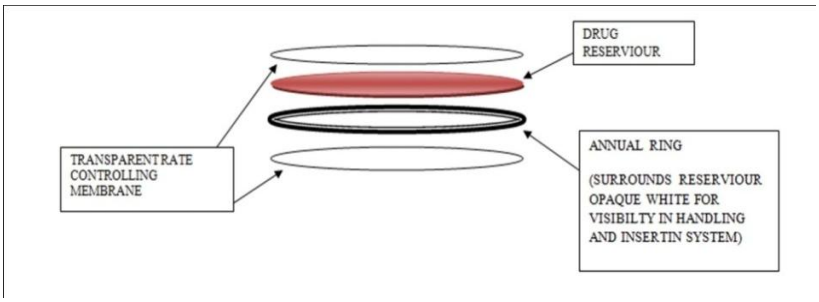


Fig: 2 Schematic diagram of ocular insert.

Ocular inserts can overcome the disadvantages reported with traditional ophthalmic systems like eye drops, suspensions and ointments. Utilization of the principles of controlled release as embodied by ocular inserts offers an attractive approach to the problem of prolonging precorneal drug residence times. Ocular inserts also offer the potential advantage of improving patient compliance by reducing the dosing frequency.

Main Objective: Themain objective of the ophthalmic inserts is to increase the contact time between the preparation and the conjunctival tissue to ensure a sustained release suited to topical or systemic treatment. They are composed of polymeric support with or without drugs, the latter being incorporated as dispersion or a solution in the polymeric support.[11,12,13]

4. Classification of Ocular Inserts:[11,12,13]

Based upon their solubility behaviour:

1. Insoluble inserts:

A. Reservoir systems - Diffusional insert , Osmotic insert

B. Matrix systems – Contact lenses

2. Soluble:

a) Based on Natural polymers - (eg. collagen),

b) Based on synthetic or semi synthetic polymers - (eg. cellulose derivatives)

3. Bioerodible

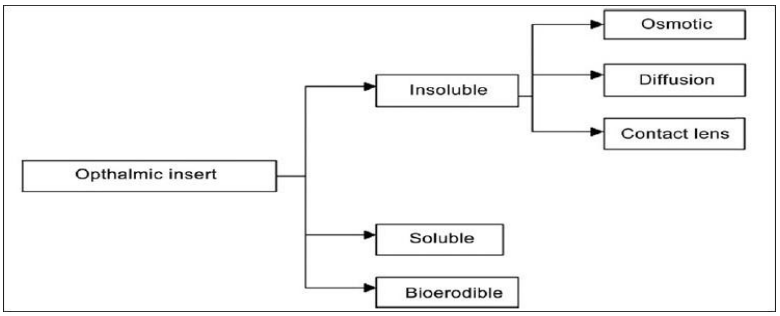


Fig:3 Classification of Ocular inserts.

1. Insoluble Ocular Inserts:

Inserts made up of insoluble polymer can be classified into two categories:

A. Reservoir systems; B. Matrix systems.

A. Reservoir systems:

Each class of inserts shows different drug release profiles. The reservoir systems can release drug either by diffusion or by an osmotic process. It contains, respectively, a liquid, a gel,a colloid, a semisolid, a solid matrix, or a carrier containing drug. Carriers are made of hydrophobic, hydrophilic, organic, natural or synthetic polymers.

They have been sub-classified into:

1. Diffusional inserts, e.g., 'Ocuserts'

2. Osmotic inserts.

1. Diffusional Inserts/Ocuserts:[54]

In diffusion inserts, the release of drug is based on diffusion mechanism.The diffusion systems are compared with a central reservoir of drug enclosed in specially designed semipermeable or microporous membranes, which allow the drug to diffuse from the reservoir at a predetermined rate. The drug release from such a system is controlled by the lachrymal fluid permeating through the membrane and when sufficient internal pressure was developed, then only drug comes out of the reservoir. The drug delivery rate is controlled by diffusion through the membrane, which can be adjusted as per requirement.

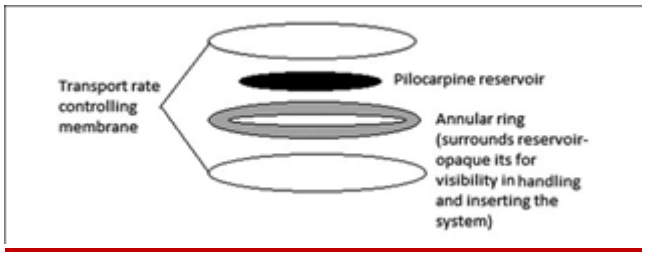


Fig: 4 Diffusional insert.

Occusert therapeutic system is a flat, flexible,ellipticaldevice designed to be placed in the inferior *cul- de-sac* or conjuctival sac between the sclera and the eyelid and to release pilocarpine continuously at a steady state.

Fig:5 Placement of Ocusert into eye.

Two types of Ocusert are available:

a) the Pilo-20 and

b) Pilo- 40.

Theformer delivers the drug at a rate of **20µg/h for 7 days**, andthe latter at a rate of **40µg/h for 7 days.**

This device, Briefly, consists of

1) A reservoir containing pilocarpine alginate enclosed above and below by thin EVA (ethylene-vinyl acetate) membranes.
2) The insert is encircled by a retaining ring of the same material, impregnated with titanium dioxide. The dimensions of the elliptical device are (for the 20 μg/h system): major axis-13.4 mm, minor axis-5.7 mm, thickness-0.3 mm. The membranes are the same in both systems, but to obtain a higher release rate, the reservoir of the 40 μg/h system contains about 90 mg of di (2-ethylhexyl) phthalate as a flux enhancer.

2. Osmotic Inserts:[15]

The osmotic inserts are generally composed of a central part surrounded by a peripheral part and are of two types:

Type 1: The central part is composed of a single reservoir of a drug with or without an additional osmotic solute dispersed throughout a polymeric matrix, so that the drug is surrounded by the polymer as discrete small deposits. The second peripheral part of these inserts comprise a covering film made of an insoluble semi-permeable polymer. The osmotic pressure against the polymer matrix causes its rupture in the form of apertures. Drug is then released through these apertures from the deposits near the surface of the device.

Type 2: The central part is composed of two distinct compartments. The drug and the osmotic solutes are placed in two separate compartments, the drug reservoir being surrounded by an elastic impermeable membrane and the osmotic solute reservoir by a semi-permeable membrane. The second peripheral part is similar to that of type 1. The tear diffuse into the osmotic compartments inducing an osmotic pressure that stretches the elastic membrane and contracts the compartments including the drug, so that the active component is forced through the single drug release aperture.

B. Matrix systems:[11,12,13]

The second category, matrix system, is a particular group of insoluble ophthalmic devices mainly represented by contact lenses. It comprises of covalently cross-linked hydrophilic or hydrophobic polymer that forms a three dimensional network or matrix capable of retaining water, aqueous drug solution or solid components. The hydrophilic or hydrophobic polymer swells by absorbing water. The swelling caused by

the osmotic pressure of the polymer segments is opposed by the elastic retroactive forces arising along the chains or crosslinks are stretched until a final swelling (equilibrium) is reached.

Contact lenses:[11,12,13]

Contact lenses are shaped structures and initially used for vision correction. Their use has been extended as potential drug delivery devices by presoaking them in drug solutions. The main advantage of this system is the possibility of correcting vision and releasing drug simultaneously. Refojo has proposed a subdivision of contact lenses into 5 groups.

a) Rigid

b) Semi-rigid

c) Elastomeric

d) Softhydrophilic

e) Bio-polymeric

When contact lenses soaked in drug solutions it absorbs water-soluble drugs. Contact lenses are used to provide extended release of drugs into the eye. In ophthalmic drug delivery systems, Contact lenses have certainly good prospects. Rigid contact lenses have the disadvantage of being composed of polymers (e.g., polymethylmethacrylic acid) hardly permeable to moisture and oxygen, a problem which has been overcome by using gas permeable polymers such as cellulose acetate butyrate.However, these systems are not suitablefor prolonged delivery of drugs to the eye and their rigidity makes them them very uncomfortable to wear.

Fig:6 Contact lens.

2. Soluble Ocular Inserts:[11,12,13]

Soluble ocular inserts are divided into two types-

a) Based on Natural polymer:

The first type of soluble inserts is based on natural polymer. Natural polymer used to produce soluble ophthalmic inserts is preferably collagen. The amount of drug loaded will depend on the amount of binding agent present, the concentration of the drug solution into which the composite is soaked as well as the duration of the soaking.

b) Based on Synthetic and semi-synthetic polymer:

The second type of soluble insert is usually based on synthetic or semisynthetic polymers (e.g., cellulose derivatives) or on synthetic polymers such as polyvinyl alcohol. A decrease of release rate can be obtained by using Eudragit, a polymer normally used for enteric coating,

as a coating agent of the insert. Ethyl cellulose, a hydrophobic polymer, can be used to decrease the deformation of the insert and thus to prevent blurred vision.

3. Bioerodible Ocular Insert:[11,12,13]

Thebioerodible inserts are composed of metrical homogeneous dispersion of a drug included or not into a hydrophobic coating which is substantially impermeable to the drug. These inserts are formed by bio-erodible polymers (e.g., cross-linked gelatin derivatives, polyester derivatives) which undergo hydrolysis of chemical bonds and hence dissolution. The drug release from such a type of system is due to the contact of the device with the tear fluid, inducing a superficial bio erosion of the matrix.

- Some important ocular inserts are discussed which are available commercially (SODI) or in the advanced states of development (Lacrisert, and minidisc).

❖ **SODI (Soluble Ocular Delivery Inserts): [16,17,18,19]**

- Small water-soluble developed for cosmonauts by soviet scientists who could not us their eye drop in weightless conditions.
- **Composition**: Acryl amide, Vinyl Pyrolidone, Ethylacrylate.
- **Weight-** 15-16 mg.
- In 10-15 sec Softens; in 10-15 min. turns in viscous Liquids; after 30-60min becomes Polymeric Solution.
- **Advantages**: Single SODI applicationreplaces 4-12 eye drops Instillation or 3-6 application of Ointments.

- Once a day in treatment of Glaucoma and Trachoma.
- Active ingredients employed in the course of research on SODI include neomycin, kanamycin, atropine, pilocarpine, dexamethasone, sulfapyridine and Tetracaine.

❖ **LACRISERT:**[58]

- Lacrisertis non-sedated, sterile, pole moulded erodible embed which is produced using hydroxypropyl cellulose. It iswithout any preservative usedfor the treatment of dry eye syndromes.
- It weighs 5 mg and measures 12.7 mm in diameter with a length of 3.5 mm.
- Lacisert is useful in the treatment of keratitis whose symptoms are difficult to treat with artificial tear alone.
- It is inserted into the inferior fornix where it imbibes water from the conjunctiva and cornea, forms a hydrophilic film which stabilizes the tear film and hydrates and lubricates the cornea. It dissolves in 24 hours.
- It is set in the sub-par fornix, where it gets hydrated to from a hydrophilic film, which thus hydrates the cornea.
- Lacrisert is indicated for patients with decreased corneal sensitivity and recurrentcorneal erosions.

Fig:7 Placement of Lacrisert.

❖ **MINIDISC:** [16,17,18,19]

- Minidiscs is a profiled, convex outside, concave from the side of contact with eye surface, dosage form similar to a contact lens with 4-5mm diameter.
- It is made up of counter disc with convex front and concave back surface in contact with eye ball.
- **Composition**: Silicon based pre polymer.
- Hydrophilic or Hydrophobic.
- Drug release for 170 hr.

- Further increase in gentamycin sulphate to320 hrs.
- They were reported to be very comfortable when placed behind the top or bottom of the eyelid.
- Active ingredients employed in research on minidiscs were, among others, sulfisoxazole and gentamicin sulfate.

Fig:8 Minidisc.

5. MECHANISM OF CONTROL DRUG RELEASE FROM OCULAR INSERTS INTO THE EYE:[59]

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

A.Diffusion

B.Osmosis

C.Bio – erosion

A. DIFFUSION:

In the Diffusion 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 with pores and dispersed drug. The release of drug can take place via diffusion through the pores. Controlled release can be further regulated by gradual dissolution of solid dispersed drug within this matrix as a result of 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. Since glassy polymers are essentially drug- impermeable, no diffusion through the dry matrix occurs. When the insert is placed in the eye, water from the tear fluid begins to penetrate the matrix, then 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 cross-linked or partially crystalline polymers. Release from these devices follows in general Fickian 'square root of time' kinetics; in some instances, however, known as case II transport,, zero order kinetics has been observed.

B. OSMOSIS:

In the Osmosis mechanism, the insert comprises a transverse impermeable elastic membrane dividing the interior of the insert into a first compartment and a second compartment; the first compartment is bounded by a semi-permeable membrane and the impermeable elastic membrane, and the second compartment is bounded by an impermeable material and the elastic membrane. There is a drug release aperture in the impermeable wall of the insert. The first compartment contains a solute which cannot pass through the semi-permeable membrane and the second compartment provides a reservoir for the drug which again is in liquid or gel form.When the insert is placed in the aqueous environment of the eye, water diffuses into the first compartment and stretches the elastic membrane to expand the first compartment andcontract the second compartment so that the drug is forced through the drug release aperture.

C. BIO – EROSION:

In the Bioerosion mechanism, the configuration of the body of the insert is constituted from a matrix of bioerodible material in which the drug is dispersed. Contact of the insert with tear fluid results in controlled sustained release of the drug by bioerosion of the matrix. The drug may be dispersed uniformly throughout the matrix but it is believed a more controlled release is obtained if the drug is superficially concentrated in the matrix.In truly erodible or E-type devices, the rate of drug release is controlled by a chemical or enzymatic hydrolytic reaction that leads to polymer solubilization, or degradation to smaller, water-soluble molecules. These polymers, as specified by Heller, may undergo bulk or surface hydrolysis. Erodible inserts undergoing surface hydrolysis can display zero order release kinetics; provided that the devices maintain a constant surface geometry and that the drug is poorly water-soluble.

6. Preparation Methods of Ocular Inserts:

1. Solvent casting method:[22]

In this method using different ratio of drug and polymer and prepare no. of batches are prepared. Firstly, in distilled water the polymer is dissolved. In stirring condition a plasticizer is added to this solution. The weighed amount of drug was added to this solution and stirred to get a uniform dispersion. After mixing the casting solution was poured in petridish and covered withan inverted funnel to allow slow and uniform evaporation at room temperature for 48 h. The dried films thus obtained were then cut by cork borer into circular pieces of definite size containing drug. The ocular inserts were stored in desiccators (air tight container) under ambient condition.

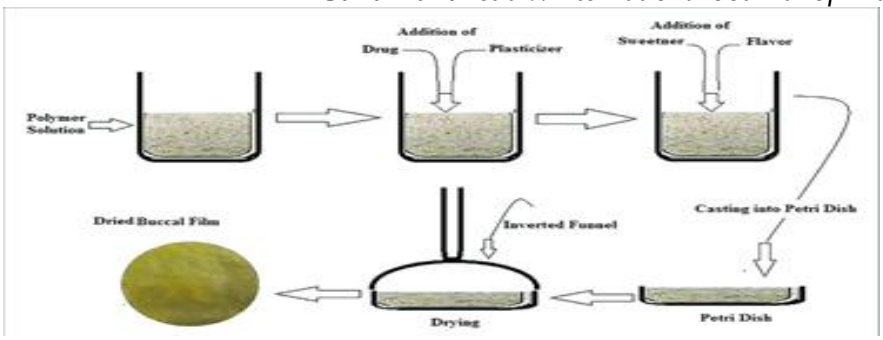


Fig:9 Glass substrate technique

2. Glass Substrate Technique:[23]

Drug reservoir film: 1% w/w polymer for example chitosan was soaked in 1%v/v Acetic acid solution for 24hrs, to get a clear solution of chitosan in acetic acid solution. The solution was filtered through a muslin cloth to remove undissolved portion of the polymer (chitin). Required quantity of drug-β CD complex was added and vortexed for 15minutes to dissolve the complex in chitosan solution. 1%w/v propylene glycol (plasticizer) was added to it and mixed well with stirrer. The viscous solution was kept aside for 30 minutes for complete expulsion of air bubbles. The rate controlling films were prepared. The films were casted by pouring solution into the centre of levelled glass mould and allowing it to dry at room temperature for 24hrs. After drying, films were cut into ocuserts of desired size so that each contains equal quantity of the drug. Then, the matrix was sandwiched between the rate controlling membranes using non-toxic, non- irritating, water insoluble gum. They were wrapped in aluminium foil separately and stored in a desiccator.

3. Melt extrusion technique: [23]

Drug for ex. acyclovir and the polymer were sieved through 60#, weighed and blended geometrically. The plasticizer was added and blended. The blend was then charged to the barrel of Melt Flow Rate apparatus and extruded. The extrudate was cut into appropriate size and packed in polyethylene lined Al foil, heat sealed and sterilized by gamma radiation.

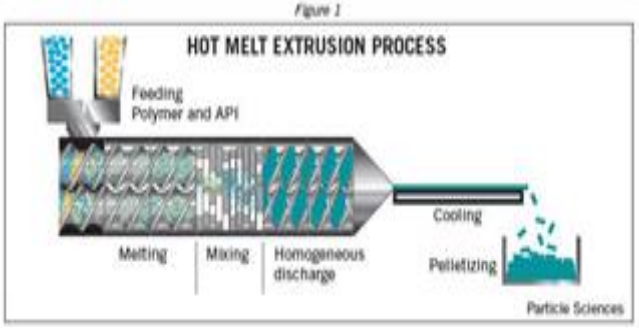


Fig:10 Melt extrusion technique.

4. Gelfoam disc:[24]

A gelfoam disc which diameter is ≈4 mm and 0.5 mm thickness was punched from a slab of gelfoam sponge with a common hole punch and phenylephrine HCL 1.7 mg and tropicamide 0.6 mg were dissolved in a solution (25 µl) of 50% (v/v) ethanol in water. The solution was placed on the Gelfoam disc. Under vacuum for at least 72 h, the wet matrics were dried. By this method placebo devices were also prepared but without drug. The dose of phenylephrine and tropicamide are equal to two drops each of Mydriacyl.

5. Mould Preparation:[25]

Using appropriate amounts of polymer, drug and exicipients we prepare, polymethylsiloxane rod- shaped silicone inserts. Into the aluminium moulds (diameter 0.9 mm, length 22.0 mm), the mixtures were injected, and were allowed to cure at 45°C for 24 h. The resulting rubbery cylinders (diameter 0.9 mm, length 22.0 mm) were appropriately cut to give a drug content of specific amount. The final lengths and weights were in the range 4-12 mm and 2.7-8.0 mg, depending on insert type. The rod shaped silicon inserts were used, as such and after polyacrylic acid or polymethacrylic acid coating, for hydration tests and for in vitro/in vivo drug release studies.

7. Evaluation of Ocuserts:

1. Physical appearance:[25]

The ocuserts are observed visually for their physical appearance such as color and transparency.

2. Uniformity of thickness: [25]

The thickness of the insert was determined using a vernier caliper at five separate points of each insert. For each formulation, five randomly selected inserts were tested for their thickness.

3. Sterility study:[25]

The inserts were sterilized using gamma radiation before carrying out the eye irritancy and in vivo drug release study. No microbial or fungal growth was seen in any of the formulations, which indicate that the films were sterilized completely.

4. Surface pH determination:[26,27,28]

The pH of solutions, drops, suspensions, and in situ gels is most often determined using a potentiometric method. In this method, the pH value is determined by measuring potential difference between electrodes

placed in examined and reference solutions of known pH or between measurement electrode and reference (calomel or silver chloride) electrode, both placed in examined preparation.

5. Clarity examination:[29,30,31]

Clarity examination involves the visual assessment of formulation in suitable lighting on white and black background. It is performed for liquid forms, with the exception of suspensions. This examination applies to eye drops and in situ gels before and after gelling.

Another method of clarity examination involves transmittance measurement using a UV-Vis spectrophotometer. This method can be employed in research on contact lenses filled with active ingredients. The lenses are hydrated in physiological saline and placed on the surface of quartz cuvette. The transmittance is measured afterwards from 200 to 1000 nm wavelength.

6. Examination of size and morphology of particles:[32]

Forexamination of particles' size multiple methods are employed: optical microscopy (microscopic particle count test), light obscuration particle count test, dynamic imaging analysis, laser diffraction particle analyzers, electron microscopy, dynamic light scattering, coulter counter test and nanoparticle tracking analysis.

7. % Swelling Index:[33]

Three ocuserts were weighed and placed separately in beakers containing 4ml of distilled water. At regular intervals of time the films were removed and excess of water on the surface was removed by using a filter paper and then again weighed.

The procedure was continued till there is no increase in weight. The percentage swelling index was calculated using the formula-

% Swelling index = weight of swollen insert - original weight of insert × 100/Original weight of insert

8. Uniformity of weight: [52]

Theweight variation test is done by weighing three patches cut from different places of the same formulation and their individual weights are determined by using the digital balance. Next, their mean value is calculated.

The standard deviation of weight variation is computed from the mean value.

9. Percentage moisture absorption:[23]

The percentage moisture absorption is checked by the physical stability or integrity of the ocular inserts. The inserts are weighed and then placed in desiccators containing 100 ml of saturated solution of aluminum chloride and 79.5% humidity is maintained.

After three days the ocular inserts are taken out and reweighed. The percentage moisture absorbed is calculated using the formula-

% **MA = [(final weight– initial weight) / initial weight] x100 Where, %MA = percentage moisture absorption**

10. Percentage moisture loss: [23,34]

Thepercentage moisture loss is done to check out the integrity of the film in dry conditions. The ocular inserts are weighed and kept in desiccators containing anhydrous calcium chloride. After three days, the ocular inserts are taken out and reweighed; the percentage of moisture loss is then calculated by using the formula-

% ML = [(initial weight– final weight) / final weight] x100

Where, % ML = percentage moisture loss

11. In vitro Drug Release Studies:[35]

The in vitro drug release from the different ocusert was studied using the classical standard

cylindrical tube fabricated in the laboratory (bi-chambered donor receptor compartment model).

Fig:11 Bi-Chambered donor receptor compartment model.

A simple modification of glass tube of 15 mm internal diameter and 100 mm height. The diffusion cell membrane (Prehydrated cellophane) was tied to one end of open cylinder, which acted as a donor compartment and ocusert was placed inside this compartment was shown in figure. The diffusion cell membrane acted as a corneal epithelium. The entire surface of the membrane was in contact with the receptor compartment comprising of STF pH 7.4 in a 100 ml beaker. The content of receptor compartment

was stirred continuously using a magnetic stirrer and temperature was maintained at 37±0.5°C. At specific intervals of time, 1 ml aliquot of solution was withdrawn from the receptor compartment and replaced with fresh buffer solution. The aliquot was analyzed for the drug content using UV spectrophotometer at 292 nm after appropriate dilutions against reference using STF pH 7.4 as blank.

12. In-Vivo Examinations:

Eye Irritancy Test (Draize Eye Test):[36,37,38]

There are many modifications of eye toxicity/irritancy test (Draize eye test) performed for dosage forms, that is, solutions, emulsions, ointments, solids, for example, inserts, and so forth. Examinations are usually carried out on rabbits, whose vision organ anatomy and physiology are well described in literature. Moreover, rabbits' eyes are usually more susceptible to irritating compounds than those of humans. For the test, usually from 3 to 6 rabbits are used, which, on one hand, enables obtaining reliable results, and, on the other hand, is an answer to claims for applying toxic substances to as little animals as possible. The most often used animal subspecies are albino (e.g., New Zealand) rabbits, which are examined and weighed before the test and then placed in specifically adapted cages, designed so as to avoid accidental injuries. The examined preparations are introduced to conjunctival sac or applied directly on the cornea.

At first, about 0.1 mL of analyzed drug was being applied on the eyeball, but many later examinations pointed to reducing the amount, for example, to 0.01 mL, which more reflects real situations. In the test, one eyeball, usually the left one, is used as a control.

After introducing a drug form on the eyeball, the eyelids are usually kept closed for a few seconds, although it is not required. Sometimes sterile solutions are additionally used for rinsing the eyeball surface. An assessment of eyeball condition before and after introducing the formulation is done by observation of the eyeball in suitable light, often using magnifying glass or a slit lamp, which ensures more precise evaluation. Auxiliary procedures which simplify visualization of changes include dyeing with fluorescein and taking photos of eyeball.

Moreover, the discomfort level after application may be indicated by the number of blinkings or rubbings of the eye. The evaluation takes place usually after 1 h, 24 h, 48 h, and 72 h from introducing a drug form on the eyeball and, if essential, also after 7 or 21 days. Duration of examination, as well as its scheme, is individually adapted to the analyzed formulation.

Ocular changes are assessed using a scoring system, in which every change in the area of eyelid, conjunctiva, cornea, and iris is scored. While in literature many scoring systems were proposed, the modified Friedenwald and Draize methods are still widely employed.

Bottle method: [39,40]

In this strategy, dose structures are put in the way of life jugs containing phosphate cradle at pH 7.4. The way of life jugs are shaken in a thermostatic water shower at 37°C. A specimen of medium is taken out at fitting interims and broke down for medication substance.

Diffusion method:[39,40]

A suitable test system device is utilized as a part of this technique. Tranquilize arrangement is set in the contributor compartment and cradle medium is put in the receptor compartment. A fake layer or goat cornea is put in the middle of benefactor and receptor compartment. Medicate diffused in receptor compartment is measured at different time interims.

Modified rotating basket method: [39,40]

In this technique, measurement frame is put in a wicker bin get together associated with a stirrer. The get together is brought down into a jacketed measuring glass containing support medium. The temperature of framework is kept up at 37°C. An example of medium is taken out at suitable time interims and broke down for medication content.

Conclusion

The ocular insert represents a significant advancement in the therapy of eye disease. Ocular inserts are characterized as clean, thin, multilayered, medicate impregnated, strong or semisolid consistency gadgets set into the cul-de-sac or conjuctival sac, whose size and shape are particularly intended for ophthalmic application. They are made out of a polymeric bolster that might possibly contain a medication. Expanding contact time and along these lines enhancing bioavailability. Conceivable diminishment of systemic absorption and in this manner lessened systemic antagonistic impacts. Lessened recurrence of organizations and therefore better patient consistence with lower occurrence of visual side effects. In this survey, we have focused on the advanced approaches in ocular drug delivery system.Advantages with ocuserts such as, Accurate dosing Capacity to provide at constant rate and prolong drug release thus a better efficacy. Increasing contact time and thus improving bioavailability. Possible reduction of systemic absorption and

thus reduced systemic adverse effects.Reduced frequency of administrations and thus better patient compliance with lower incidence of visual side effects.Advantage of inserts as dosage form Ease of handling and insertion Lack of expulsion during wear.Reproducibility of release kinetics Applicability to variety of drugs Non-interference with vision and oxygen permeability. Sterility. Stability. Ease of manufacture.

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