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Ocular insert delivery at target tissue

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ABSTRACT

Ocular inserts are solid dosage forms and can overcome the disadvantage reported with traditional ophthalmic systems like aqueous solutions, suspensions and ointments. The ocular inserts maintain an effective drug concentration in the target tissues.

Ocular inserts are sterile preparations, with a thin, multilayered, drug impregnated, solid or semisolid consistency devices placed into cul-de-sac or conjunctiva sac. They are usually made up of polymeric vehicle containing drug. Ocular drug delivery is one of the most fascinating and challenging tasks being faced by the Pharmaceutical researchers. One of the major barriers of ocular medication is to obtain and maintain a therapeutic level at the site of action for prolonged period of time. The therapeutic efficacy of an ocular drug can be greatly improved by prolonging its contact with the corneal surface. Newer ocular drug delivery systems are being explored to develop extended duration and controlled release strategy. Some of the newer, sensitive and successful Ocular delivery systems like inserts, biodegradable polymeric systems, and collagen shields are being developed in order to attain better ocular bioavailability and sustained action of ocular drugs.

KEYWORDS

Drug delivery,ocusert,ocular insert,target delivery

INTRODUCTION:

Ocular drug delivery is one of the most fascinating and challenging tasks being faced by the Pharmaceutical researchers. One of the major barriers of ocular medication is to obtain and maintain a therapeutic level at the site of action for prolonged period of time. The challenges to the formulator are to circumvent the protective barriers of the eye without causing permanent tissue damage. The development of newer, more sensitive diagnostic techniques and therapeutics agents renders urgency to the development of maximum successful and advanced ocular drug delivery systems. The therapeutic efficacy of an ocular drug can be greatly improved by prolonging its contact with the corneal surface. For achieving this purpose, viscosity enhancing agents are added to eye drop preparations or the drug is formulated in a water insoluble ointment formulation to sustain the duration of intimate drug eye contact. Unfortunately, these dosage forms give only marginally maximum sustained drug-eye contact than eye drop solutions and do not yield a constant drug bioavailability 1 . Repeated medications are still required throughout the day. These practical issues have stimulated the search for alternative methods for ocular drug delivery. Much of the work recently devoted to ocular inserts, which serves as the platform for the release of one or

more active substances. To overcome the constraints placed by conventional ocular therapies like short residence time, pulsed dosing of drug, frequent instillation, large drainage factors. Newer ocular drug delivery systems are being explored to develop extended duration and controlled release strategy. Some of the newer, sensitive and successful Ocular delivery systems like inserts, biodegradable polymeric systems, and collagen shields are being developed in order to attain better ocular bioavailability and sustained action of ocular drugs.

Physiology of Eye:

The eye consists of transparent cornea, lens, and vitreous body without blood vessels. The oxygen and nutrients are transported to this nonvascular tissue by aqueous humor which is having high oxygen and same osmotic pressure as blood. The aqueous humor in human is having volume of 300µl 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 4 . The eye is constantly cleansed and lubricated by the lacrimal apparartus which consists of four structures. lacrimal glands, lacrimal canals, lacrimal sac, 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 7µl 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 5 . 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

Advantages of Ocular Inserts:

In comparison with the traditional ophthalmic preparation i.e., eye drops, the solid ophthalmic devices presents some advantages:

1. Increasing contact time and thus improving bioavailability.

2. Possibility of providing a prolong drug release and thus a better efficacy.

3. Reduction of systemic side effects and thus reduced adverse effects.

4. Reduction of the number of administrations and thus better patient compliance.

5. Reduction in systemic absorption.

6. Possibility of targeting inner ocular tissues through non-corneal (conjunctival sclera) routes.

7. Possibility of incorporation of various novel chemicals and technological approaches such as pro-drug, mucoadhesives, permeation enhancers, microparticulate, salts acting as buffers.

Of course not all benefits listed above can present in single, ideal device. Each type of inserts represents compromise between desirable properties inherent by solid dosage forms and negative constraints imposed by structure and components of insert itself, by fabrication cost, as well as by the physical/physiological constrains of application site.

Disadvantages of Ocular Inserts:

1. A capital disadvantage of ocular inserts reside in their 'solidity', i.e., in the fact that they are felt by the (often oversensitive) patients as an extraneous body in the eye .

2. Their movement around the eye, in rare instances, the simple removal is made more difficult by unwanted migration of the inserts to upper fornix.

3. The occasional inadvertent loss during sleep or while rubbing the eyes.

4. Their interference with vision.

5. Difficult placement of the ocular inserts (and removal, for insoluble types).

Classification of occusert:

Non erodible ocular insert – it includes ocusert and contact lenses. • Ocusert – The most widely used ocular insert is ocusert. The technology used in this is an insoluble delicate sandwich technology. In ocusert the drug reservoir is a thin disc of pilocarpine alginate complex sandwiched between two transparent discs of micro porous membrane fabricated from ethylene vinyl acetate copolymer. The micro porous membrane permits the tear fluid to penetrate into the drug reservoir compartment to dissolve drug from the complex.

Contact lenses: When contact lenses are soaked in drug solution it can absorb water soluble drugs. Then these contact lenses loaded with drug are placed in the eye for releasing of drug for prolonged period. The hydrophilic contact lenses can be used to prolong the ocular residence time of the drugs. In humans, the bionite lens which was made from hydrophilic polymer (2-HEMC) has been shown to produce a greater penetration of fluorescein

Corneal shield A non cross linked homogenized, procaine scleral collagen slice is developed. Topically applied antibiotics have been used in conjunction with the shield to promote healing of corneal ulcers. Collagen shields are fabricated with foetal calf skin tissue and originally developed as a corneal bandage. These devices, once softened by tear fluid, form a thin peliable film that confirms exactly to the corneal surface and undergoes dissolution up to 10, 24, & 72 hrs. Collagen film proved as a promising carrier for ophthalmic drug delivery system because of its biological inertness, structural stability and good biocompatibility. ¬

Erodible ophthalmic insert – The erodible ophthalmic inserts included the marketed device such as lacriserts, SODI, and minidisc.

Lacrisert – Lacrisert is a sterile rod shaped device which is made up of hydroxyl propyl cellulose without using any preservatives and used for the treatment of dry eye syndromes. It is 12.7mm in diameter with a length of 3.5mm and weight is 5mg. Lacrisert 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 stabilise the tear film and hydrates and lubricates the cornea, it dissolves in 24 hrs

SODI –Soluble Ocular Drug Insert is a small oval wafer developed for cosmonauts who could not use eye drops in weightless conditions. It is an oval shaped sterile thin film made up of acryl amide, N-vinylpyrrolidone and

ethylacrylate called as ABE. It weighs about 15- 16 mg. It is used to treat glaucoma and trachoma. It is inserted into the inferior cul-de-sac and gets wet and softens in 10-15 seconds. After 10-15 min the film turns into a viscous polymer mass, after 30-60 minutes it turns into polymer solution and deliver the drug for about 24 hrs.

Minidisc - The minidisc consists of a contoured disc with a convex front and concave back surface in the contact with the eyeball. It is like a miniature contact lens with a diameter of 4- 5mm. The minidisc is made up of silicone based prepolymer-α-ψ-bis (4-methacryloxy) butyl polydimethyl siloxane. Minidisc can be hydrophilic or hydrophobic to permit extend release of both water soluble and insoluble drugs.

FORMULATION METHODS OF OCUSERT

Solvent Casting Method: In this method using different ratios of drug and polymer a no. of batches are prepared. The polymer is dissolved in distilled water. A plasticizer is added to this solution under stirring conditions. The weighed amount of drug was added to above solution and stirred to get a uniform dispersion. After proper mixing the casting solution was poured in clean glass Petri dish and covered with an inverted funnel to allow slow and uniform evaporation at room temperature for 48 h. The dried films thus obtained were cut by cork borer into circular pieces of definite size containing drug. The ocular inserts were then stored in an airtight container (desiccator) under ambient condition.

Glass substrate technique: 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 .

Melt extrusion technique: 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 charge the blend was then charged to the barrel of Melt Flow Rate apparatus and extruded. Theextrudate was cut into appropriate size and packed in polyethylene lined Al foil, heat sealed and sterilized by gamma radiation.

Evaluation of Ocular Inserts

1. Film thickness
2. Content uniformity
3. Uniformity of Weight
4. Percentage moisture absorption
5. Percentage moisture loss
6. In-vitro drug release
7. In-vivo drug release
8. Accelerated stability studies.

Thickness of Film: Film thickness is measured by using dial caliper at different points and the mean value was calculated .Reading were taken over an circular film of area of 38.5 mm square. The standard deviation in thickness was computed from the mean value.

Drug Content Uniformity: To check the uniformity of the drug in the To check the uniformity of the drug in the cast film inserts are cut at different places in the cast films and each film is place in vials containing 5 ml of pH 7.4 phosphate buffer and shaken to extract the drug from patch. 1 ml from above resulting solution is taken and dilute. The solution is analyzed by spectrophotometer using pH 7.4 phosphate buffer as blank. The drug content was calculate using the following formula

Mg of drug in one patch=As.Cr/Ar

Where As =Absorbance of sample solution.

Ar =Absorbance of standard solution.

Cr =Concentrat.ion of drug in Standard solution.

Same procedure is adopts for all the batches of cast films in triplicates and mean drug content and standard deviation of variance are calculate.

Uniformity of Weight: The weight variation test is carried out by weighing three patches cut from different places of same formulation and their individual weights are determine by using the digital balance. The mean value is calculated. The standard deviation of weight variation is compute from the mean value.

Percentage moisture absorption: The percentage moisture absorption test is carried out to check physical stability or integrity of ocular inserts. Ocular inserts are weigh and place in a desiccators containing 100 ml of saturated solution of aluminium chloride and 79.5%humidity is maintain. After three days the ocular inserts are taken out and reweigh. The percentage moisture absorption is calculate using the formula.

Percentage moisture absorption =Final weight –Initial weight/initial wt×100

Percentage Moisture Loss: The percentage moisture loss is carries out to check integrity of the film at dry condition. Ocular inserts are weighing and keep in a desiccators containing anhydrous calcium chloride. After 3 days, the ocular inserts are taken out and reweigh, the percentage moisture loss is calculate using the formula

Percentage moisture loss = Initial wt-final wt/initial wt ×100

In-vitro drug Release: To simulate the actual physiological conditions prevailing in the eye an in-vitro dissolution is use in the present work.

In-vitro release studies are carried out using bi-chamber donor-receiver compartment model design using commercial semi-permeable membrane of transparent and regenerated cellulose type (sigma dialysis membrane). It is tie at one end of the open cylinder, which acts as the donor compartment. The ocular insert is place inside the donor compartment. The semi permeable membrane is use to simulate ocular in vivo condition like corneal epithelial barrier in order to simulate the tear volume, 0.7 m1 of distilled water is place and maintain at the same level throughout the study in the donor compartment. The entire surface of the membrane is in contact with reservoir compartment, which contains 25ml of pH 7.4 phosphate buffers and stirs continuously using a magnetic stirrer. Samples of 1ml are withdrawn from the receptor compartment at periodic intervals and replace with equal

volume of distilled water. The drug content is analyze at 246 nm against reference standard using pH 7.4 phosphate buffer as blank on a UV/visible spectrophotometer.

In-vivo Drug Release Rate Study: The inserts are sterilized by using UV radiation before in-vivo study. Inserts are taken in a Petri dish along with 100 mg of pure drug, which are spread to a thin layer. This Petri dish along with polyethylene bags and forceps are place in UV sterilization chamber (hood). The inserts and other materials are exposing to UV radiation for one hour. After sterilization, inserts are transferee into polyethylene bag with the help of forceps inside the sterilization chamber itself. The pure drugs which are sterilized along with inserts are analyzing for potency by UV spectrophotometer after suitable dilution with pH 7.4 phosphate buffer. The male albino rabbits, weigh between 2.5-3.0 kg are require for the experiment. The animals are house on individual cages and customized to laboratory conditions for 1 day. Receive free access to food and water. The ocular inserts containing drug are taken for in-vivo study which are previously sterilize on the day of the experiment and are place into the lower conjunctivas cul-de-sac. The inserts are inserting into 7 eyes at same time and each one eye of seven rabbits is serving as control. Ocular inserts are removing carefully at 2, 4, 6, 8, 10, 12 and 24 hours and analyze for drug content as dilution mention in drug content uniformity. The drug remaining is subtracted from the initial drug content of inserts which will give the amount of drug release in the rabbit eye. Observation for any fall out of the inserts is also recording throughout the experiment. After one week of wash period the experiment is repeating for two times as before.

Accelerated Stability Studies: The accelerated stability studies are carries out to predict the breakdown that may occur over prolong periods of storage at normal shelf condition. The films of the formulation are taken in a separate Petri dish and are keep at three different temperatures 400C, 500C and 600C and the period for break down or degradation of the ocular inserts is check. When ocular inserts show degradation the time in days is note and subject to determine the drug content of each individual film using the drug content uniformity procedure.

Stability of ocular insert: Stability studies were carried out on ocular insert formulations according to ICH guidelines. A sufficient number of ocular inserts (packaged in aluminum foils) were stored in a humidity chamber with a relative humidity of 75 ± 5% and temperatures of 40 ± 2°C and at room temperature. Samples were withdrawn at time 0, 3 weeks, 3 weeks, 6 weeks, 3 months, and 6 months. Ocular inserts were also evaluated for their physical characteristics (color) and also analyzed for drug concentration. The degradation rate constant was determined from the plot of logarithm of the remaining drug vs. time.

Conclusion: The ocular insert (solid drug) releasing drug demonstrated by extensive investigations and clinical tests, have not gained a wide acceptance by ophthalmologists. At this moment, the Ocusert systems are the only medicated inserts marketed in Western countries, and the acceptance of these devices has been, to the present date, far from enthusiastic. According to recent information the NODS project will not be further developed. As said before, the commercial failure of inserts has been attributed to psychological factors, such as the reluctance of ophthalmologists and patients to abandon the traditional liquid and semi-solid medications, to price factors and to occasional therapeutic failures (e.g., unnoticed expulsion from the eye, membrane rupture, etc. Development of noninvasive delivery techniques will revolutionize ocular drug delivery. The potential for the growth of sustained drug delivery systems involving polymeric systems is limitless, and newer polymers would serve the purpose of controlled and sustained delivery for treating vision-threatening diseases. Advances in nanotechnology and noninvasive drug delivery techniques will remain in the forefront of new and novel ophthalmic drug delivery systems.

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