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Review Article

A Review on Occular Inserts and Implants

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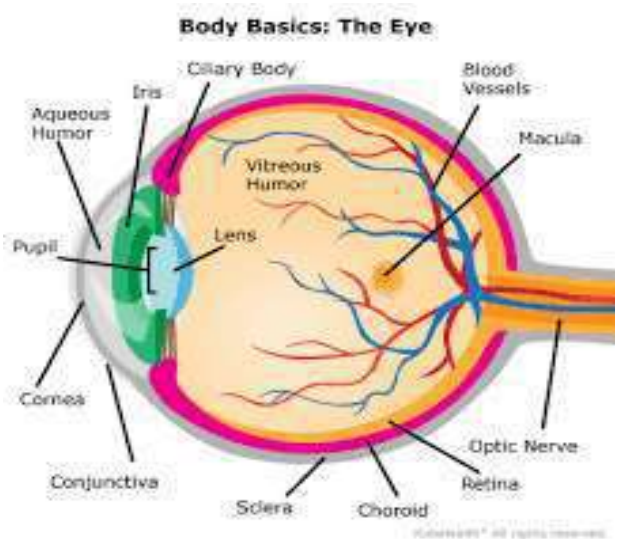
The eye is a sensory organ. Research is difficult from the perspective of drug distribution. Occular inserts are a revolutionary technology for delivering drugs to the eye and a cutting- edge technology in the treatment of eye diseases. Occular diseases require localized administration of drugs to the tissues around the occular cavity. In the present update, the authors discuss the basic concept of ocular inserts as drug delivery system and examine the few inserts, which are available in the market or are being developed by pharmaceutical companies for drug delivery. The non-cross-linked films showed poor mechanical, physicochemical properties, and very little potential of sustaining drug release, however cross-linking the films enhanced tensile strength by 70%, but elasticity decreased by 95%. The cross-linked ocular inserts showed less swelling than non- cross- linked. Formulation AF8[20% gelatin and 70% glycerin, treated by cross-linker for 1h] demonstrated the longest drug release for 24hours.

Keywords: Ocular; Implants; Inserts; Intravitreal: Eye.

INTRODUCTION

The eye is the structure in change of concentrating light and focusing it into photoreceptors, which allows it to convert it into electrical impulses towards the visual cortex where the sensation of vision takes place. The sensation of vision can be divided into the ability to detect light and movement, visual perspective, visual field, depth perception, visual acute, color and shape perception.



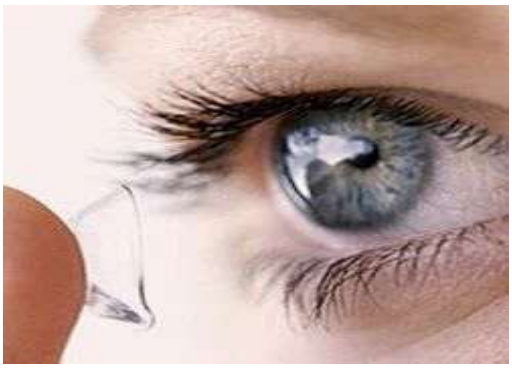
Development of new drug candidates and novel drug delivery technologies for effective treatment of ocular diseases has shown a sharp increase in recent years. Treatment of anterior segment diseases has witnessed significant success owing to advances in prodrug approach and permeability enhancers.

OCCULAR INSERTS:

History of occular inserts:

The first solid medication was used in the 19th century, which consisted of squares of dry filter paper, previously impregnated with dry solutions (e.g. atropine sulphate, hydrochloride). Small sections were cut and applied under eyelid. Later, lamellae, the precursors of the present soluble inserts, were developed. They consisted of glycerinated gelatin containing different ophthalmic drugs. Glycerinated gelatin 'lamellae' were present in official compendia until the first half of the present century. However, the use of lamellae ended when more stringent requirements for sterility of ophthalmic preparations were enforced. Now a days, growing inserts is observed for ophthalmic inserts as demonstrated by the increasing number of publications in this field in recent years.

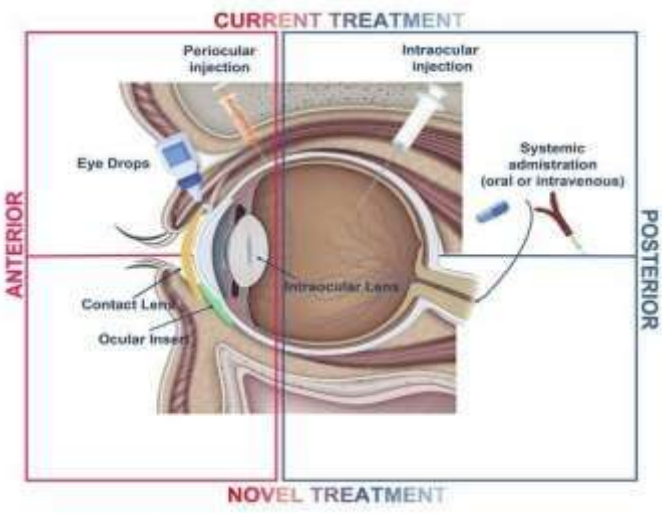
Biodegradable inserts: The hydrophobic coating, made of a bio-corrosion and impermeable polymer, may or may not be present in a homogeneous drug dispersion forming a bio-insertion. This suggests that a bio-corrosive polymer was used to create a gasket. Successfully used Biodegradable material include poly (orthopaedic) and poly (plastic orthocarbonate). This system must be exposed to tear fluid while exhibiting obvious biocorrosion of the substrate before they can be released.



Ocular inserts are sterile, multi-layered, drug-impregned devices placed into the conjunctival sac of the eye for the prolonged release of medication. Eye inserts are classified based on their physiological properties as insoluble, soluble, or bio erodible. Soluble inserts, also are erodible, for example monocytic polymeric devices that undergo gradual dissolution while releasing the drug, and do not need removal.

Nasolacrimal dust system (NDS):

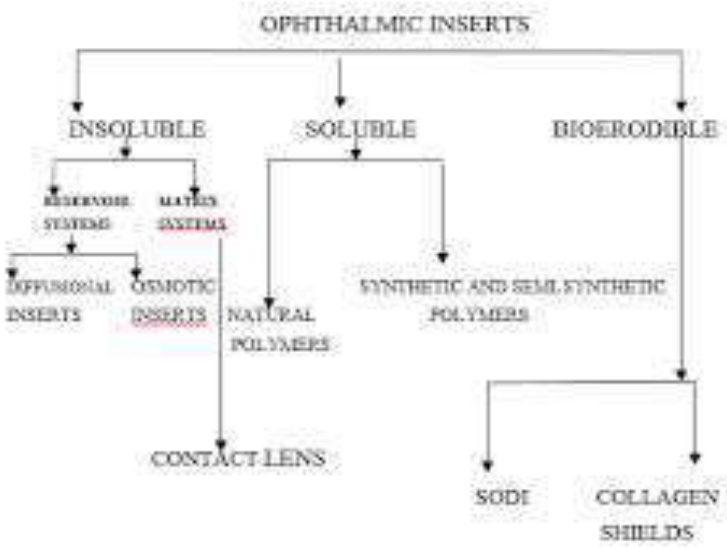
The lacrimal dust system transmits tears from the surface of the eye to the nasal cavity. The NDS consists of a secretory component and an excretory component. Tears enter the dust system at the lacrimal punctate and conduct through canaliculi within the eyelids.



CLASSIFICATION OF OCCULAR INSERTS

The inserts have been classified, on the basis of their physico-chemical behaviour, as soluble or insoluble. Only the latter types can usually deliver drugs by a variety of methods at a controlled, predetermined rate, but need removal from the eye when 'empty'. Soluble inserts, also generally defined by some authors as erodible, are monolytic polymeric devices that undergo gradual dissolution while releasing the drug, and do not need removal. It should be pointed out that, as indicated in the article by Saettone, the terms 'soluble' and 'erodible' are not interchangeable, and correspond to distinct chemical processes, even if a clear-cut distinction between the two mechanisms is sometimes difficult. True dissolution occurs mainly through polymer swelling, while erosion corresponds to a chemical or enzymatic hydrolytic process.

Hence, ocular inserts are classified as given below:



I. Insoluble ocular inserts
II. Soluble ocular inserts
III. Bio-erodible ocular inserts**.**

I. Insoluble occular 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 gela colloid, a semisolid, a solid matrix, or a carrier containing drug. Carriers are made of hydrophobic, hydrophilic, organic, natural or synthetic polymers.

B. **Matrix systems:**

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.

II. Soluble occular inserts:

These soluble inserts offer the advantage of being entirely soluble so that they do not need to be removed from their site of application, thus limiting the intervention to insertion only. They can be broadly divided into two types; the first one being based on natural polymers and the other on synthetic or semi-synthetic polymers.

A. Natural polymers:

The first type of soluble inserts is based on natural polymer. Natural polymer used to produce soluble ophthalmic inserts is preferably collagen. The therapeutic agent is preferably absorbed by soaking the insert in a solution containing the drug, drying, and re-hydrating it before use on the eye.

B. Synthetic and semi-synthetic polymer:

The second type of soluble insert is usually based on semi-synthetic 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. Saettone have observed in rabbits that Eudragit coated inserts containing pilocarpine induced a miotic effect of a longer duration, compared to the corresponding uncoated ones.

III. Bio-erodible occular inserts:

These inserts are formed by bio-erodible polymers (e.g., cross-linked gelatine derivatives, polyester derivatives) which undergo hydrolysis of chemical bonds and hence dissolution. The great advantage of these bio-erodible polymers is the possibility of modulating their erosion rate by modifying their final structure during synthesis and by addition of anionic or cationic surfactants. A cross-linked gelatine insert was used by Attia to increase bioavailability of dexamethasone in the rabbit eye. The dexamethasone levels in the aqueous humour were found to be four-fold greater compared to a dexamethasone suspension.

OCCULAR IMPLANTS:

Currently ocular implants have been extensively used for the treatment of both posterior and anterior and anterior segment eye diseases. In the fabrication of intraocular implants biodegradable and non-biodegradable polymers have been employed. Some of the advantages of these include overcoming of the blood-retina barrier, allowing drug delivery at therapeutic levels directly into the target site; prolonged drug delivery and reduction of the side effects frequently observed with intravitreal injections and systemic administration.

Biodegradable implants:

The implants containing biodegradable polymers can be either matrical or reservoir systems. In the former, the drug can also be released by diffusion through the matrix pores. In reservoir systems, the membrane generally degrades slower than in drug diffusion. A wide variety of natural and synthetic biodegradable polymers have been investigated for the development of implants. Natural polymers, such as bovine serum albumin, human serum albumin, collagen, and gelatin have been studied for drug delivery. However, the use of these polymers is limited due to their higher cost and questionable purity. Synthetic polymers, such as poly(amide), poly (amino acids), poly(esters), poly(urethanes) have been increasingly used to deliver drugs as they are devoid of most of the problems associated with natural polymers.

OTHER OCCULAR IMPLANTS

1. Corneal implants

A keratoprosthesis is an artificial cornea, which is used when conventional keratoplasty does not work well in a given patient. Keratoprosthesis can be broadly categorized as bio-integrated and non-bio-integrated. The bio-integrated design are first implanted in the subcutaneous tissues of molar region to allow them to develop a soft tissue cover which is then used to integrate them with the ocular surface of the affected eye. Patients having healthy posterior segment and visual potential but is bilaterally blind is considered to use keratoprosthesis.

2. Complication

Complications of intracorneal rings include complications during surgery like improper centration, too shallow or too deep insertion, corneal perforation, etc. Postoperative complications are segment displacement, segment exposure and corneal melt, corneal and scarring deposits around the device.

3. Glaucoma valve implant

Medical therapy is the only way for management of glaucoma. Laser is performed as a prophylaxis for angle closure glaucoma and as an adjunct. SLT is performed for primary open angle glaucoma. Surgery is reserved for advanced and complicated glaucoma. To increase success rate of surgery in high-risk cases aqueous shunts are used.

COMMON EYE INFECTIONS:

Bacteria are the causative pathogens for a large number of eye infections. In addition, virus, fungus and protozoans also cause eye infections. As such, eyes are prone to number of diseases but more commonly found are mentioned here.

- Conjunctivitis.
- Blepharitis.
- Keratitis.
- Cataract.
- Iritis (anterior uveitis).
- Glaucoma.

SCOPE:

- The scope of ocular inserts and implants includes sustained drug delivery for treating chronic eye diseases, replacing damaged eye structures (like intraocular lenses after cataract surgery), and providing a controlled, targeted release of medications directly to the eye to improve therapeutic outcomes and patient compliance.
- These devices overcome limitations of traditional eye drops by ensuring prolonged drug contact with the eye, accurate dosing, and reduced systemic absorption, though they can present challenges in placement and patient comfort.

Conventional Occular Drug Delivery Constraints

For the ailments of the eye, topical administration is usually preferred over systemic administration so as to avoid systemic toxicity, to attain rapid onset of action, and for decreasing the required dose. Though topical administration offers many advantages to treat disorders of anterior structures of the eye, it suffers from a serious disadvantage of poor bioavailability due to several biological factors (Fig. 2), which exist to protect the eye and consequently limit the entry of ocular drugs. The constraints in topical delivery of the eye are discussed in the following section.

METHOD OF PREPARATION:

Preparation of Brimonidine Occular Inserts:

Polymeric ocular inserts containing brimonidine were prepared using film-casting method. The present composition (w/w) of the prepared polymeric ocular inserts is listed. PVP K-90 was used as insert-forming polymer and different viscosity grades of HPMC, chitosan, Carbopol, and sodium alginate were employed as bio adhesive materials.

Evaluation:

Drug content Uniformity:

Ocular inserts belonging to each formulation was dissolved in suitable quantity of distilled water and the solution was filtered, suitably diluted and brimonidine content was analyzed spectrophotometrically at 320 nm. This test was done on ten ocular inserts for each formulation.

Development of the Occular Inserts:

Once the polymer mixtures that formed films were selected, the composition of the formulation was determined and working condition were established to standardize the method of preparation. The ophthalmic inserts were made using the solvent evaporation technique.

Swelling (SW):

For the SW test, three samples of each formulation were cut with a diameter of 1cm, which were weighed in an analytical balance, then immersed in 5 ml of SLF PH 7.4 0.1, and placed at 37 °C. Each sample was weighed every 10 min as follows: the samples was removed from the DSE by removing the excess of it with Whatman paper to be weighed later. The swelling was determined through the weight variation in the samples; once this ceased to vary, it was indicative of the completion of the test, and finally the formula described below was used.

PH:

The measurement was performed with the potentiometer HANNA H12210, United Kingdom, once the components of the mixture were completely dissolved (10 min) in 3 different points of the mixing vessel (surface, midpoint, and bottom).

In Vivo Tolerance Assay:

An acute tolerance test was performed on New Zealand white albino rabbits of 1.55-1.65 kg weight to determine the ocular tolerance of inserts. All animals were healthy and free of clinically observable abnormalities.

CURRENT MARKETED PRODUCTS:

1.Iluvien:

Iluvien is sustained release fluocinolone acetonide formulation undergone phase 3 clinical trials for treatment of Diabetic Macular Edema (DME). It's an injectable, non-erodible intravitreal implant for the treatment of DME. Iluvien is designed for sustained release of the formulation for over three years. Implant is injected into back-of-the eye using 25G needle creating self-healing hole which is very similar to intravitreal injection. Currently, the only FDA approved method for treating DME involves laser photocoagulation therapy which can leave irreversible blind spot.

2.Retisert:

Retisert is (Fluocinolone Acetonide (FA) intravitreal implant) for treatment of chronic, non-infectious posterior uveitis. Retisert is surgically implanted into vitreous humour by 3-4 mm incision containing 0.59 mg of fluocinolone acetonide which delivers the medicament up to 2.5 years. Retisert implant is composed of a central core consisting of FA compressed into a 1.5 mm diameter. Each FA tablet is enclosed in a silicone elastomer cup containing a release orifice. A semi-permeable layer of PVA coats the tablet inside the cup reservoir near the release orifice, creating a membrane between the tablet and the orifice that serves as an additional barrier for drug release from the cup. A suture tab, made from PVA film, is attached to the silicone cup using silicone adhesive.

3.Durasert:

Durasert technology system uses a drug core with one or more surrounding polymer layers, and delivers drugs for predetermined periods of time ranging from days to years. The drug release is controlled by permeability of the polymer layers.

4.Vitrasert:

Using the Durasert system, an antiviral drug, ganciclovir (GCV)-loaded intravitreal implant (Virasat, Bausch and Lomb Inc., Rochester, NY, USA) has been developed for the treatment of AIDS related cytomegalovirus (CMV) retinitis, that avoids systemic side effects and minimizing frequent intravitreal injections. This approach can significantly delay progression of CMV when compared with conventional ganciclovir intravenous treatment.

5.Cortiject:

Cortiject (Novagali Pharma S.A.) is a preservative-free emulsion composed of oily carrier and phospholipid as surfactant, encapsulating corticosteroid prodrug with activated tissue targeting mechanism. Released dexamethasone (DEX) palmitate is de-esterified by a retina-specific esterase and activated to be DEX. A single intravitreal injection provides sustained release for 6-9 months. Cortiject is under the phase I studies and need to be investigated.

Advantages of occular inserts and implants:

- Increased accuracy of dosing.
- Overcome the side effects of pulsed dosing produced by conventional formulations.
- Provide sustained and controlled drug delivery.
- Improved ocular bioavailability of drug by increasing the corneal contact time.
- Provide targeting within the ocular globe and prevent drug loss to other ocular tissues.
- Circumvent the protective barriers like drainage, lacrimation and conjunctival absorption.
- Provide comfort, better patient compliance and improved therapeutic performance of drug.
- Provide better housing of delivery system.
- Increasing contact time and improving bioavailability.

- Providing a prolong drug release and thus a better efficacy.
- Reduction of adverse effects.
- Increased residence time/ bioavailability.
- Precision dosing with controlled release, avoids pulsate drug delivery.
- Combinational therapeutic approaches.

Disadvantages of occular inserts and implants:

- Physical and psychological obstacles of placing solid objects on the eye, foreign body sensation.
- Potential accidental loss
- Some devices difficult to inserts or remove.
- Movement around the eye could interfere with vision
- Potential burst release upon insertion prior to controlled delivery.
- The occasional inadvertent loss during Sleep or while rubbing the eyes.
- The ocular inserts reside in their 'solidity', that is, they are felt by the (often oversensitive) patients as an extraneous body in the eye.
- Their movement around the eye, in rare instances, the simple removal is made more difficult by unwanted migration of the insert to the upper fornix.
- The occasional inadvertent loss during Sleep or while rubbing the eyes.
- Their interference with vision.
- Difficult placement of the ocular inserts.

Applications:

- Ocular inserts and implants are used in ophthalmology to deliver drugs and support eye function for various conditions.
- particularly those affecting the anterior or posterior segments of the eye.
- Their primary application is in delivering drugs like antibiotics, anti-inflammatories, and agents for glaucoma or diabetic retinopathy.
- **Uveitis**: Controlled delivery of corticosteroids to reduce inflammation.
- Inserts and implants release anti-glaucoma drugs for weeks to months.
- After cataract or refractive surgeries, implants can deliver antibiotics, steroids, or anti-inflammatory drugs.
- Reduces the need for frequent post-op eye drops.
- Ocular inserts can continuously release lubricants or anti-inflammatory drugs.
- Ocular inserts release anti-allergic drugs slowly to prevent itching, redness, and irritation.

CONCLUSION:

Occular inserts and implants are to be developed to accommodate the increasing number of patients requiring long-term progressing treatments. Eventually, multidisciplinary integration of delivery technologies to optimize drug bioavailability is needed. Developments in fields of biomedical engineering, nanotechnology and non-invasive drug delivery could open up the possibilities for drug delivery to the ocular posterior segments in the near future. Summing up, at the moment only 4 OI medicinal products are officially registered on the global pharmaceutical market; diverse clinical studies are being conducted aimed at studying the compliance and effectiveness of the insert as a preferred dosage form over traditional eye drops therapy, increasing the accuracy of API dosing and minimizing cross-contamination. It's evident that drug delivery to the posterior segments of eye presents significant and considerable confrontations. As, systemic administration is not effective prior to high drug doses, toxicity, blood retinal and aqueous barriers novel technologies needs to be primarily designed and to be developed to provide sustained action, enhance bioavailability, improved patient safety and minimal adverse effects.

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