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Review Article

Ocular Inserts: A Novel Approach in Ocular Drug Delivery

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ABSTRACT

Among the ocular dosage forms, the physiological and anatomical constraints put forth by the eye is a significant challenge to the pharmaceutical scientists and researchers to target drugs to the posterior segment of the eye, prolong their contact time with the ocular surface and sustained release. Hence novel drug delivery strategies and formulations are to be developed and explored which will overcome the ocular constraints and provide better patient compliance. At present, various novel and controlled drug delivery systems are being developed in order to attain better ocular bioavailability, sustained action of ocular drugs as well as good patient compliance. Ocular insert is an example of such delivery system. These are sterile preparations, with a thin, multilayered, drug-impregnated, solid or semisolid consistency devices placed into cul-de-sac or conjunctiva sac of the eye. Ocular inserts are an alternative approach to overcome the problems associated with conventional ocular dosage forms like solutions, suspensions, ointments, etc. The article hereunder gives a detailed idea about the classification, mechanism of action, formulation, pros and cons; evaluation and future trends of ocular inserts.

Keywords: Ocular inserts, Sustained release, Ocular constraints, Patient compliance, Ocular bioavailability, Novel drug delivery**Article Info:** Received 17 May 2019; Review Completed 26 June 2019; Accepted 07 July 2019; Available online 15 July 2019**Cite this article as:**Khan A, Raza SN, Itoo A, Sirjohn B, Wani TU, Khan NA. Ocular Inserts: A Novel Approach in Ocular Drug Delivery, Journal of Drug Delivery and Therapeutics. 2019; 9(4):693-703 <http://dx.doi.org/10.22270/jddt.v9i4.3207>***Address for Correspondence:**

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INTRODUCTION:

Ocular drug delivery is one of the most fascinating and challenging tasks faced by the Pharmaceutical researchers. But to obtain and maintain a therapeutic level at the site of action for prolonged period of time is one of the major barriers of ocular medication. The anatomy, physiology and biochemistry of the eye render this organ exquisitely impervious to foreign substances. The challenge to the formulator is to circumvent the protective barriers of the eye without causing permanent tissue damage. The development of newer, more sensitive diagnostic techniques and therapeutic agents render urgency to the development of maximum successful and advanced ocular drug delivery systems¹. One of the new classes of drug delivery systems, polymeric film ocular drug delivery systems/ocular inserts, which are gaining worldwide accolade, release drugs at a pre-programmed rate for a longer period by increasing the pre-corneal residence time².

Ocular inserts are defined as sterile preparations, with a thin, multilayered, drug-impregnated, solid or semisolid consistency devices placed into cul-de-sac or sac of conjunctiva and whose size and shape are especially designed for ophthalmic application. These inserts are

placed in lower fornix and less frequently, in upper fornix or on the cornea. They are usually made up of polymeric vehicle containing drug and are mainly used for topical therapy^{2,3}. They are composed of a polymeric support containing or not drug(s), the latter being incorporated as dispersion or a solution in the polymeric support⁴.

Ocular inserts offer an attractive alternative approach to the difficult problem of limited pre-corneal drug residence time. Disposition and elimination of a therapeutic agent depends on the physicochemical properties as well as the relevant ocular anatomy and physiology. The successful design of a drug delivery system, therefore, requires a complete knowledge of the drug moiety and the constraints to delivery offered by the ocular route of administration. The main objective of the ophthalmic inserts is to increase the contact time between the preparation and the conjunctival tissue, to ensure a sustained release suited for topical or systemic treatment^{4,5,6,7,8}.

BACKGROUND:

The history of ocular inserts dates back to the 19th century when solid medications which consisted of squares of dry filter paper, previously impregnated with dry solutions (e.g.,

atropine sulphate, pilocarpine hydrochloride) were used as ocular inserts. Small sections were cut and applied under the eyelid. Later, the precursors of the present soluble inserts called lamellae were developed which consisted of glycerinated gelatin containing different ophthalmic drugs. Glycerinated gelatin 'lamellae' were present until the first half of the present century in official compendia. However, the use of lamellae ended when more stringent requirements for sterility of ophthalmic preparations were enforced. Nowadays, growing interest is observed for ophthalmic inserts as demonstrated by the increasing number of publications in this field in the recent years².

DESIRED FEATURES OF OCULAR INSERTS⁹:

- ✓ Should be bio stable & biocompatible with the tissues of the eye.
- ✓ Should be nontoxic & non carcinogenic.
- ✓ Should be retrievable & should release the drug at a constant rate.
- ✓ Should be non-immunogenic as well as non-mutagenic.
- ✓ Should possess a good mechanical strength.
- ✓ Should be free from drug leakage.
- ✓ Should be easily sterilizable.
- ✓ Should be easy and inexpensive to manufacture.
- ✓ Should be applicable for a good variety of drugs.
- ✓ Should not interfere with the vision and oxygen permeability.

MECHANISM OF DRUG RELEASE FROM OCULAR INSERTS:

The drug release from the ocular inserts takes place by follows mechanisms:

- 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 through the pores via diffusion. 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^{10,11}.

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; however, in some instances, case II transport, zero order kinetics has been observed¹².

B. Osmosis: In the osmosis mechanism, the insert comprises a transverse impermeable elastic membrane dividing the interior of the insert into two compartments; the first

compartment is bounded by a semipermeable 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 and contract the second compartment, so that the drug is forced through the drug release aperture¹¹.

Bio-erosion: In the Bio-erosion mechanism, the configuration of the body of the insert is constituted from a matrix of bio-erodible material in which the drug is dispersed. Contact of the insert with tear fluid results in controlled sustained release of the drug by bio-erosion of the matrix. The drug may be dispersed uniformly throughout the matrix but it is believed that a more controlled release is obtained if the drug is superficially concentrated in the matrix. In truly erodible 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 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 soluble¹³.

ADVANTAGES OF OCULAR INSERTS^{2, 10, 14, 15}:

Ocular inserts offer several advantages, which can be summarized as follows:

- Increase in ocular residence, hence a prolonged drug activity and a higher bioavailability with respect to standard vehicles;
- Possibility of drug release at a slow, constant rate;
- Accurate dosing (contrary to eye drops that can be improperly instilled by the patient and are partially lost after administration, each insert can be made to contain a precise dose which is fully retained at the administration site);
- Reduction of systemic absorption (which occurs freely mainly with eye drops via the naso-lacrimal duct and nasal mucosa);
- Better patient compliance, resulting from a reduced frequency of administration and a lower incidence of visual and systemic side-effects;
- Possibility of targeting internal ocular tissues through non-corneal (conjunctival scleral) routes;
- Increased shelf life with respect to aqueous solutions;
- Exclusion of preservatives, thus reducing the risk of sensitivity reactions;
- Possibility of incorporating various novel chemical/ technological approaches like pro-drugs, muco-adhesives, permeation enhancers, micro-particulates, salts acting as buffers, etc;
- Reproducibility of release kinetics;
- Sterility.

DISADVANTAGES OF OCULAR INSERTS^{2,14}:

The disadvantages of ocular inserts are as follows:

- A capital disadvantage of ocular inserts resides in their 'solidity', i.e., in the fact that they are felt by the (often oversensitive) patients as an extraneous body in the eye. This may constitute a formidable physical and psychological barrier to user acceptance and compliance;
- 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 unintentional loss during sleep or while rubbing the eyes;
- Their interference with vision, and
- Difficult placement of the ocular inserts (and removal, for insoluble types).

CLASSIFICATION OF OCULAR INSERTS:

On the basis of their physico-chemical behavior, the inserts have been classified, as soluble (S) or insoluble (I). 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 (S) inserts, also generally defined by some authors¹⁶ as erodible (E), 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 Saettone¹⁷, 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 process¹⁸.

Hence, ocular inserts are classified as given below:

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

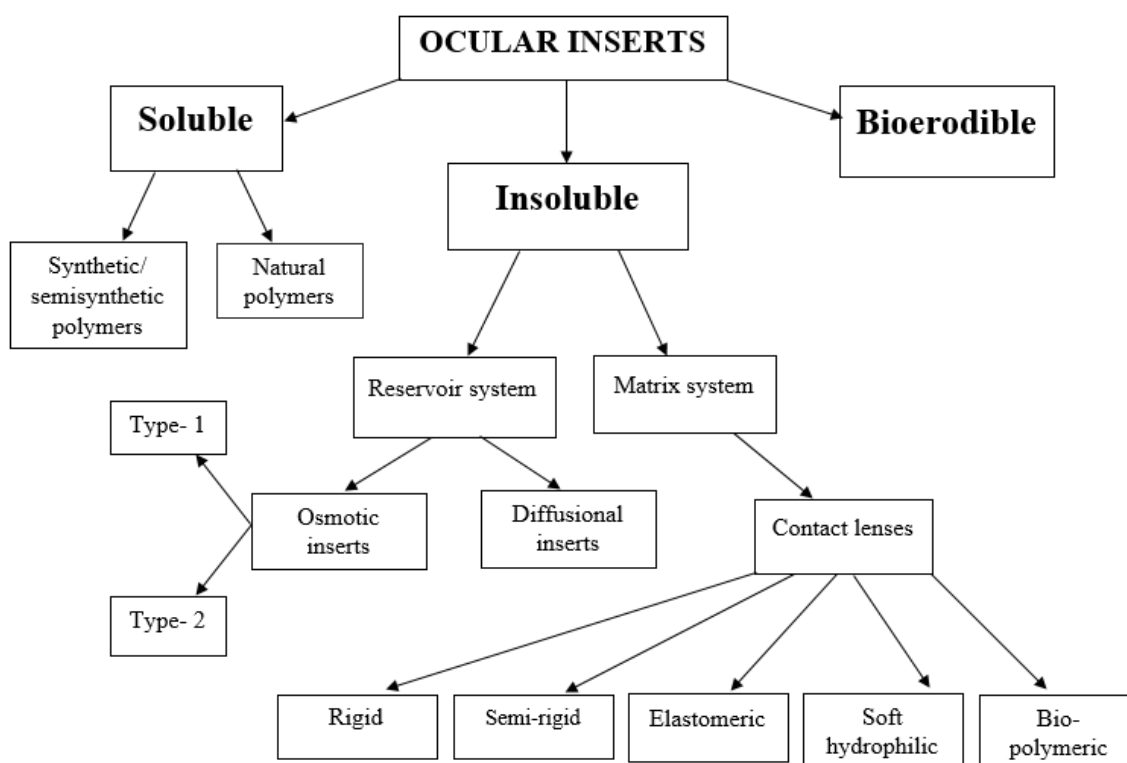


FIG. 1: Classification of Ocular Inserts.

I. SOLUBLE OCULAR INSERTS:

Soluble inserts resemble to the oldest class of ocular inserts, which offer the advantage of being wholly soluble, so they need not be removed from the site of application, thus, limiting the interventions to insertion only^{19,20}. They are further categorized:

- Based on natural polymers, for example, collagen.
- Based on synthetic or semi-synthetic polymers²⁰.

A. Natural polymers:

The first type of soluble inserts based on natural polymer which is used to produce soluble ophthalmic inserts is

preferably collagen²⁰. The therapeutic agent is absorbed by soaking the insert in a solution containing the drug, and drying and rehydrating it before use in the eye. The amount of drug contained will depend upon the capacity of the binding agent, concentration of the drug solution into which the insert is soaked, and the duration of soaking¹⁹. As the collagen dissolves, the drug is gradually released from the interstices between the collagen molecules². The soluble ophthalmic inserts are easily processed by conventional methods viz slow evaporating extrusion, compression or injection molding. The release of the drug takes place when tears penetrate into the insert. This induces drug release by means of diffusion and forms a layer of gel around the core of the insert. This gelification causes further release of the drug,

but it is still controlled by diffusion. The release rate, J , is derived from Fick's law, which yields the following expression²¹:

$$J = \frac{ADKCs}{L}$$

When A - Surface area of the membrane.

K - Diffusion coefficient of the drug

L - Membrane thickness

C_s - Drug solubility in water

D - Diffusion coefficient of the Ocusert membrane.

Since all the terms on the right hand side of the above equation are constant, so is the release rate of the device²².

B. Synthetic and semi-synthetic polymer: This type of soluble insert is usually based on synthetic polymers like

polyvinyl alcohol or on semi-synthetic polymers (e.g., cellulose derivatives). 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 *et al*²³ have observed in rabbits that Eudragit coated inserts containing pilocarpine induced a miotic effect of a longer duration, compared to the corresponding uncoated ones. However, the inherent problems encountered with these soluble inserts are the rapid penetration of the lachrymal fluid into the device, the blurred vision caused by the solubilization of insert components and the risk of expulsion due to the initial dry and glassy consistency of the device²⁴. In order to decrease the deformation of the insert and thus to prevent blurred vision Ethyl cellulose, a hydrophobic polymer, can be used. As for the risk of expulsion, several authors have incorporated carbomer, a strong but well tolerated bio-adhesive polymer.

Table 1: Components of Soluble Inserts Containing Synthetic Polymers^{20,25}

Soluble synthetic polymers	Cellulose derivatives - Hydroxypropyl cellulose, methylcellulose, and hydroxyethyl cellulose Divers - Polyvinyl alcohol, ethylene vinyl acetate copolymer.
Additives	Plasticizer - Polyethylene glycol, glycerin, propylene glycol Enteric coated polymer - Cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate. Complexing agent - Polyvinylpyrrolidone. Bioadhesives - Polyacrylic acids

I. Insoluble Ocular Inserts: Inserts made up of insoluble polymer can be classified into two categories:

A. Reservoir systems; B. Matrix systems².

A. Reservoir Systems: Each class of inserts shows different drug release profiles. The reservoir systems can release drug either by means of 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 organic, hydrophilic, hydrophobic, natural or synthetic polymers. They have been sub-classified into:

1. Diffusional inserts, e.g., 'Ocuserts';
2. Osmotic inserts.

1. Diffusional insert or Ocuserts: Ocusert system, a novel ocular drug delivery system is based on porous membrane. The release of drug from diffusional inserts/Ocusert is based on a diffusional release mechanism. It consists of a central reservoir of drug enclosed in specially designed microporous membrane allowing the drug to diffuse from the reservoir at a precisely determined rate².

As pointed out by Urquhart,²⁶ the Ocusert pilocarpine ocular therapeutic system, developed by Alza Corporation, is notable for several reasons. This product was the first rate-

controlled, rate specified pharmaceutical for which the strength is indicated on the label by the rate(s) of drug delivery *in vivo*, rather than by the amount of contained drug. It provides predictable, time-independent concentrations of drug in the target tissues, which is otherwise impossible to achieve with conventional, quantity-specified, pulse entry ophthalmic medications. The near-constant drug concentration in ocular tissues markedly improves the selectivity of action of pilocarpine. A major advantage is that reduction of intraocular pressure (IOP) in glaucoma patients is fully maintained while two disturbing side effects of the drug, miosis and myopia, are significantly reduced.

Pilo-20 and Pilo-40 are the two types of Ocusert are available. The former delivers the drug at a rate of 20 $\mu\text{g}/\text{h}$ for 7 days, and the latter at a rate of 40 $\mu\text{g}/\text{h}$ for 7 days. Briefly, it consists of a reservoir containing pilocarpine alginate enclosed above and below by thin EVA (ethylene-vinyl acetate) membranes. 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 $\mu\text{g}/\text{h}$ 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 $\mu\text{g}/\text{h}$ system contains about 90mg of di (2-ethylhexyl) phthalate as a flux enhancer²⁷.

Table 2: Components of Diffusional Inserts^{20,25}

Central reservoir	Glycerin, ethylene glycol, propylene glycol, water, methyl cellulose mixed with water, sodium alginate, poly (vinyl pyrrolidone), poly or ethylene stearate.
Micropores membrane	Polycarbonates, polyvinyl chloride, polysulfones, cellulose esters, crosslinked poly (ethyl oxide), cross-linked polyvinylpyrrolidone, and cross-linked polyvinyl alcohol.

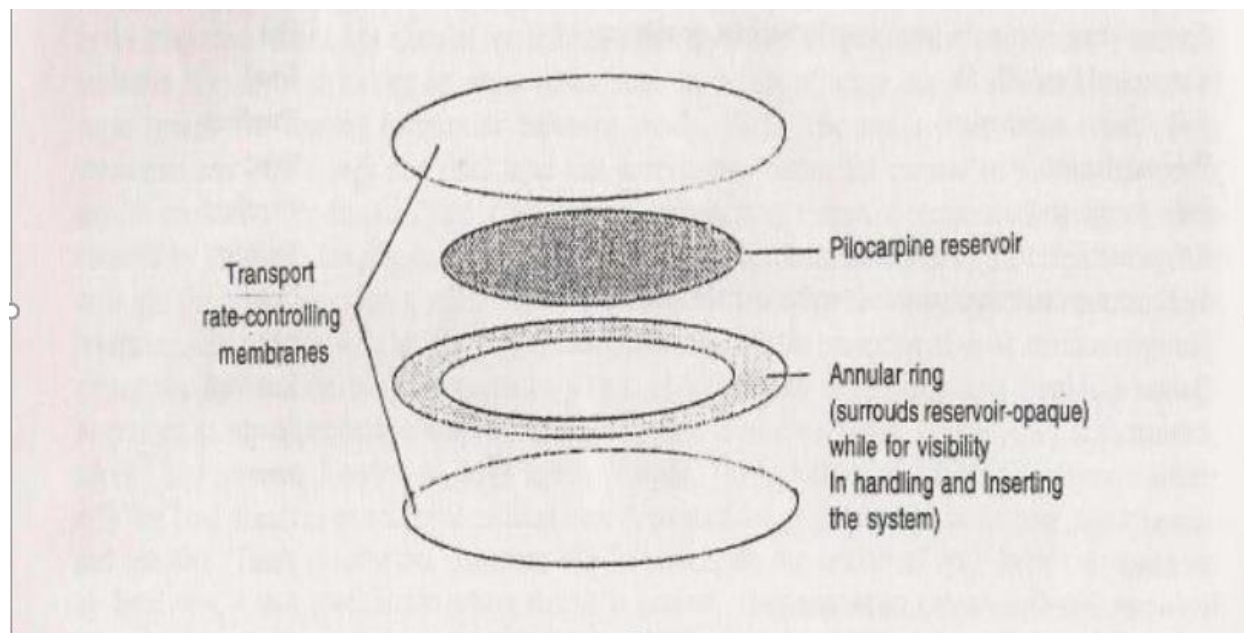


FIG. 2: Diffusional Inserts²⁷

2. Osmotic inserts: 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 comprises 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, through which drug is released 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 diffuses into the osmotic compartment inducing an osmotic pressure that stretches the elastic membrane and contracts the compartment including the drug, so that the active component is forced through the single drug release aperture²⁸.

Table 3: Components of Osmotic Inserts^{20,25}

Water permeable matrix	Ethylene - vinyl esters copolymers, Divers- plasticized polyvinyl chloride (PVC), polyethylene, cross-linked polyvinylpyrrolidone(PVP)
Semi permeable membrane	Cellulose acetate derivatives, Divers - Ethyl vinyl acetate (EVA), polyesters of acrylic and methacrylic acids (Eudragit ®).
Osmotic agents	Inorganic – magnesium sulfate, sodium chloride, potassium phosphate dibasic sodium carbonate and sodium sulfate. Organic- calcium lactate, magnesium succinate and tartaric acid. Carbohydrates – Sorbitol, mannitol, glucose and sucrose.

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 cross links are stretched until a final swelling (equilibrium) is reached ².

Contact Lenses: Contact lenses are shaped structures, 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. Contact lenses coated with drugs can absorb on its surface water-soluble substances, released after applying the drug over the eyeball for a longer period of time. The first and most widely used polymer in the production of lenses was the cross-linked poly (2-hydroxyethyl methacrylate) with small amount of ethylene glycol dimethylacrylic acid (EGDM) or poly (vinyl pyrrolidone) ^{29,30}. Poly (vinyl pyrrolidone) is used for

increasing water of hydration, while EGDM is used to decrease the water of hydration². In recent years, research has been conducted on employing silicon-based lenses³¹⁻³⁴. Interest in contact lenses still grows, which is confirmed by increase in the number of articles on its use published in recent years. Examples of drugs whose pharmaceutical availability from lenses was researched include timolol³¹, ciprofloxacin³², dexamethasone³³, and cyclosporine³⁴.

Peng and Chauhan developed a new delivery system for Cyclosporin- A delivery for the purpose of Dry eye syndrome (DES) treatment using Vitamin- E-loaded silicone-hydrogel contact lenses. ACUVUE OASYS lenses were selected due to the drug release profiles and loaded with Vitamin E. The results showed that Vitamin-E-loaded lenses can provide Cyclosporin- A release within the therapeutic window for a period of about a month. It is a promising delivery system though that *in vivo* release and toxicity studies are required³⁵.

Types of Contact Lenses:

Refojo³⁶ has proposed a subdivision of contact lenses into 5 groups.

a) Rigid

b) Semi-rigid

c) Elastomeric

d) Soft hydrophilic

e) Bio-polymeric

Rigid contact lenses have the disadvantage of being composed of polymers (e.g., poly methyl methacrylic 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 suitable for prolonged delivery of drugs to the eye and their rigidity makes them very uncomfortable to wear. For this reason, soft hydrophilic contact lenses were developed for prolonged release of drugs. The soft hydrophilic contact lenses are very popular because they are easy to fit and are tolerated better. The drug incorporation into contact lenses depends on whether their structure is hydrophilic or hydrophobic. When contact lens (including 35 to 80% water) is soaked in solution, it absorbs the drug. Drug release depends markedly on the amount of drug, the soaking time of the contact lens and the drug concentration in the soaking solution^{2,28}.

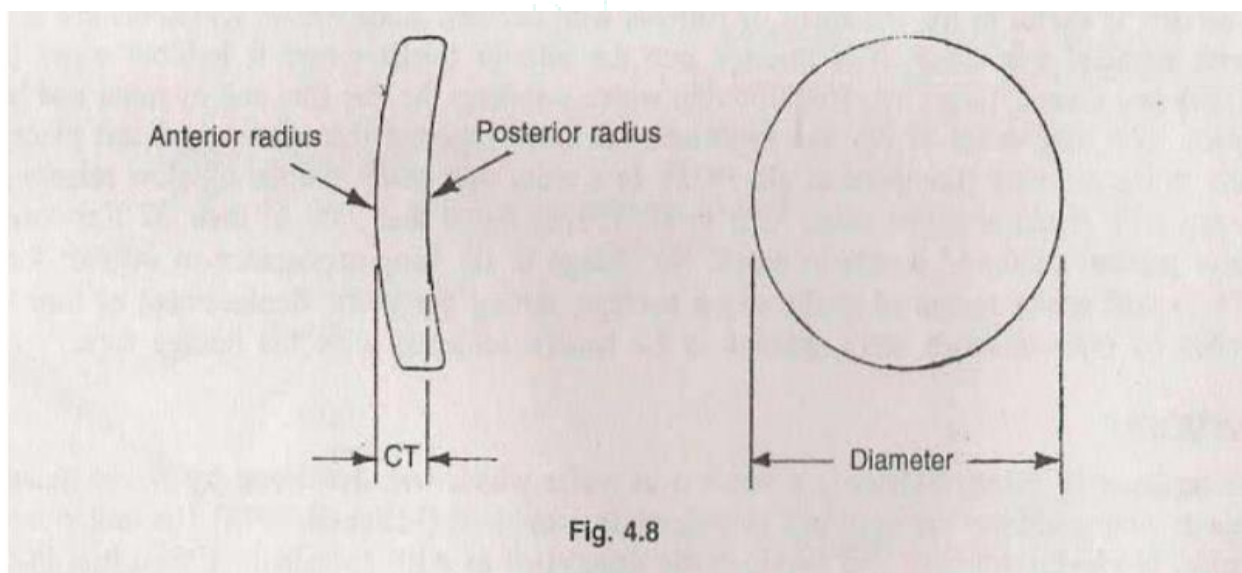


Fig. 4.8

FIG. 3: Ocular Lens²⁷

III. Bioerodible Ophthalmic Inserts: They are formed by bio-erodible polymers (e.g., polyester derivatives, cross-linked gelatin 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 gelatin insert was used to increase bioavailability of dexamethasone in the rabbit eye. The dexamethasone levels were found to be four-fold greater in the aqueous humor compared to a dexamethasone suspension. However, erodible systems can have significantly variable erosion rates based on individual patient physiology and lachrymation patterns, while degradation products and residual solvents used during the polymer preparation can cause inflammatory reaction. Some important ocular inserts which are available commercially

are soluble ophthalmic drug inserts (SODI) while others are in the advanced stages of development like collagen shield, ocufit, new ophthalmic delivery system (NODS) and minidisc¹².

POLYMERIC SYSTEMS EMPLOYED IN THE FORMULATION OF OCULAR INSERTS:

Polymers used in ocular inserts can be of natural, synthetic or semi synthetic in nature. Further, they can be either water soluble polymers with linear chains or water insoluble polymers joined by cross linking agents. Most commonly used polymer groups include nonionic polymer like hydroxypropyl methyl cellulose (HPMC); polycationics like chitosan, DEAE-dextran and polyanionics like polyacrylic acid (PAA) derivatives e.g. carbopols, polycarbophils, carboxy-methylcellulose. Some of the polymers used in ocular inserts are given in Table 4.

Table 4: Commonly Used Polymers in Ocular Inserts⁹

Cellulose polymers	Cellulosic polymers such as methyl cellulose; hydroxyethylcellulose (HEC); hydroxypropylmethylcellulose (HPMC); hydroxypropylcellulose (HPC) were introduced as viscolizers into artificial tear preparations to retard canalicular drainage and improve contact time. All cellulose-ethers impart viscosity to the solution, have wetting properties and increase the contact time by virtue of film forming properties. Drug release was found to be better in terms of extent and amount. Controlled release has been observed with various beta-blockers from HPM inserts with improved ocular bioavailability and reduced toxicity and dosing frequency. HPC, HPMC, PVP and PVA were also used in different ratios to prepare the ocular films with the objective to reduce the frequency of drug administration, patient compliance, controlled drug release and greater therapeutic efficacy for ocular infections such as conjunctivitis, keratitis, kerato-conjunctivitis and corneal ulcers.
Polyvinyl Alcohol (PVA)	PVA was introduced into ophthalmic preparations and reported to have a superior corneal contact time. PVA lowers the surface tension of water reducing interfacial tension at an oil/water interface and enhances tear film stability. This film-forming property together with ease of sterilization, compatibility with a range of ophthalmic drugs and an apparent lack of epithelial toxicity lead to use of PVA as a drug delivery vehicle and artificial tear preparation. Polyvinyl alcohol (PVA) has been used as a carrier to formulate polymeric inserts and were found to enhance bio-availability in comparison to solutions.
Poly (ethylene oxide) [PEO]	Poly Ethylene Oxide (PEO) exhibits good compressibility and thus is easy for the manufacturing of matrix tablets. In contact with an aqueous medium, poly (ethylene oxide) hydrates and gels superficially, the polyether chains of PEO forming strong hydrogen bonds with water. Drug release from poly (ethylene oxide) matrices is controlled by polymer swelling and erosion, or drug diffusion through the gel, or by both processes. Various release patterns can be achieved depending on the poly (ethylene oxide) molecular mass and physicochemical properties of the drug. Good mucoadhesive properties and lack of irritancy to the rabbit eye has been reported. It points that this polymer can be an interesting candidate material for controlled release erodible ocular inserts.
Pluronics, Poloxamer F127	Sustained drug delivery can also be achieved by use of a polymer that changes from solution to gel at the temperature of the eye (33 to 34o C). An example of this type of polymer is poloxamer F127, which consists of linked polyoxyethylene and polyoxypropylene units. At room temperature, the poloxamer remains as a solution. When the solution is instilled onto the eye surface, the elevated temperature causes the solution to become a gel, thereby prolonging its contact time with the ocular surface.
Collagen	Collagen is widely used for biomedical applications. It accounts for about 25 % of the total body protein in mammals and is the major protein of connective tissue, cartilage and bone. Importantly, the secondary and tertiary structures of human, porcine, and bovine collagen are very similar, making it possible to use animal-sourced collagen in the human body. Collagen shields are designed to be sterile, disposable, temporary bandage lenses that conform to the shape of the eye and protect the cornea. Their dissolution time on cornea ranges from 12-17 hours and is controlled by varying degree of cross-link of the polymer.
Eudragit	The polymer system avoids of any irritant effect on cornea, iris and conjunctiva up to 24 hours after application and seems to be a suitable inert carrier for ophthalmic drug. Similarly, In another study, Eudragit RL100 polymer nanoparticle system loaded with cloricromene polymer matrix was prepared and characterized on the basis of physicochemical properties, stability and drug release features by topical administration in the rabbit eye and was compared with an aqueous solution of the same drug.
Poly (Lactic Acid) / Poly (Glycolic Acid)	Polymers such as poly (lactic acid) or poly (glycolic acid) undergo hydrolytic degradation in the body and become monomers of lactic acid or glycolic acid. These monomers can be metabolized and eliminated from the tissues. It is possible to incorporate drugs in the matrix of these polymers. The polymer containing the drug releases the drug for a sustained period and undergoes degradation simultaneously. These polymers have been used as materials of absorbable surgical sutures for many years and proved to be safe and biocompatible. Feasibility of delivering drugs to the retina and vitreous as well as the subconjunctival space using the microspheres of biodegradable polymers has been reported.
Alginate and derivatives	Alginate is a linear co-polysaccharide isolated from brown seaweeds and certain bacteria. Chemically it is a (1-4)-linked block copolymer of α -D-mannuronate (M) and its C-5 epimer R-L-guluronate (G), with residues arranged in homopolymeric sequences of both types and in regions which approximate to the disaccharide repeating structure (MG). Commercially, alginate is widely used as a gelling agent not only in foods but also in other industries such as pharmaceutical, biomedical, and personal care). As it is easy to prepare alginate ionotropic gels at mild conditions, it is possible to entrap drugs and living cells in alginate gels, which allow a wide application of alginate as scaffolds for tissue engineering, drug delivery systems, and cell encapsulation and transplantation. Drug release from such matrices may be controlled by polymer swelling or erosion or drug diffusion in hydrated gel or by these processes all together. All these properties and applications are ultimately dependent on the molecular architecture and gelling mechanism. Recently alginate-chitosan ocular inserts has been studied as an efficient means of delivering antibiotics (gatifloxacin).

OCULAR INSERT DEVICES:

The various types of inserts available or in development are presented in Table 5.

Table 5: Ocular Insert Devices ^{2,12,37}

Name	Reported By	Description
Soluble ocular drug Insert (SODI)	Khromow <i>et al.</i>	Small oval wafer, composed of soluble copolymers consisting of actylamide, N-venyl pyrrolidone and ethyl acetate, softens on insertion.
New ophthalmic drug delivery system	Lloyd <i>et al.</i>	Medicated solid polyvinyl alcohol flag that is attached to a paper- covered with handle. On application, the flag detaches and gradually dissolves, releasing the drugs.
Collagen shields	Bloomfield <i>et al.</i>	Erodible disc consisting of cross-linked porcine scleral collagen, used as tear substitue and for the delivery of gentamicin.
Ocusert	Quigley <i>et al.</i>	Flat, flexible elliptical insoluble device consisting of two layers, enclosing a reservior, used commercially to deliver Pilocarpine for 7 days.
Minidisc ocular therapeutic system	Bewa <i>et al.</i>	This monolytic polymeric device, originally described by Bawa <i>et al.</i> (Bausch and Lomb, Rochester, New York) and referred to as Minidisc ocular therapeutic system (OTS), is shaped like a miniature (diameter 4-5 mm) contact lens, with a convex and a concave face, the latter conforming substantially to the sclera of the eye. The particular size and shape reportedly allow an easy placement of the device under the upper or lower lid without compromising comfort, vision or oxygen permeability.
Lacrisert	Lamberts <i>et al.</i>	Rod-shaped device made from Hydroxy propyl cellulose used for the treatment of dry eye syndrome as an alternative to tears.
One-side-coated ocular insert	Sasaki <i>et al.</i>	Prepared by attaching a polypropylene tape on the one side of the polymer disc of poly (2-hydroxypropylmethacrylate) (HPM) containing Tilisolol as a model ophthalmic drug.
Bioadhesive ophthalmic drug insets (BODI)	Gurtler <i>et al.</i>	Adhesive rods based on a mixture of Hydroxy propyl cellulose, ethyl cellulose, Poly acrylic acid and cellulose acetate phthalate
Silicone rubber/ hydrogel composite ophthalmic inserts	Chetoni <i>et al.</i>	A cylindrical device containing mixtures of silicone elastomer and sodium chloride as a release modifier with a stable polyacrylic acid (PAA) or polymethylacrylic acid (PMA) interpenetrating polymer network grafted on to the surface.
Dry drops	Diestelhorst <i>et al.</i>	A preservative free of hydrophilic polymer solution that is freeze dried on the tip of a soft hydrophobic carrier strip, immediately hydrate in tear strip
Molecularly imprinted soft contact lenses	Hiratani <i>et al.</i>	Soft contact lenses consisted of <i>N,N</i> -diethylacrylamide, methacrylic acid and ethylene glycol dimethacrylate. Timolol was used as a model drug.
Gelfoam	Simamora <i>et al.</i>	Slabs of Gelfoam impregnated with a mixture of drug and cetyl ester wax in chloroform.
New ophthalmic mydriatic insert	Stephane <i>et al.</i>	New insoluble-matrix retropalpebral ophthalmic insert containing phenylephrine and tropicamide. Potential alternative as drug delivery system prior to cataract surgery.
OphthaCoil	Pijls <i>et al.</i>	The ocular insert consists of a pradoß oxacin -loaded adherent hydrogel on a thin wire, which is coiled. The inner lumen of the coil was P lled with a polymer rod made from a poly (2-hydroxyethyl methacrylate) hydrogel and loaded with the same drug.
Gelatin hydrogels and lyophilisates with potential applications as ocular inserts	Madalina <i>et al.</i>	Hydrogels and lyophilisates were obtained by chemical and lyophilisates crosslinking of gelatin using <i>N</i> -hydroxysuccinimide and <i>N,N</i> -(3-dimethylaminopropyl)- <i>N'</i> -ethylcarbodiimide hydrochloride. Pilocarpine hydrochloride was used as a model drug.
Mucoadhesive ocular insert	Hornof <i>et al.</i>	The inserts tested were based either on unmodified or thiolated poly (acrylic acid) for the controlled delivery of ophthalmic drugs and to evaluate its efficacy <i>in vivo</i> .

EVALUATION OF OCULAR INSERTS:

A. Universal Tests for Ophthalmic Pharmaceuticals:

1. Description: The test often called appearance on a specification is a qualitative description of the ophthalmic pharmaceuticals. For example, the description of ophthalmic preparations on a specification may read: transparent/opaque preparation, proper labeling, imprinted with "Rx"³⁸

2. Identification: The purpose of this test is to verify the identity of the active pharmaceutical ingredient (API) in the ophthalmic pharmaceuticals. This test should be able to discriminate between compounds of closely related structures that are likely to be present³⁸.

3. Assay: This test determines the strength or content of the API in the ophthalmic pharmaceuticals and is sometimes called a content test³⁸.

4. Impurities: This test determines the presence of any component that is not the API or an excipient of ophthalmic pharmaceuticals. The most common type of impurities that are measured is related substances, which are processed impurities from the new drug substance synthesis, degradation products of the API, or both³⁸.

B. Quality Control Test Procedures for Ocular Inserts as Per IP, BP and USP:

1. Uniformity of dosage units: Dosage units are defined as dosage forms containing a single dose or part of a dose of an active substance in each dosage unit. To ensure the consistency of dosage unit, each unit in a batch should have active substance content within a narrow range around the label claim. Unless otherwise stated, the uniformity of dosage unit specification is not intended to apply to suspensions, emulsions or gels in single dose containers intended for cutaneous administration. The term 'uniformity of dosage unit' is defined as the degree of uniformity in the amount of the active substance among dosage units. The test of mass variation is applicable for the following dosage forms:

TESTS	I.P	B.P	U.S.P
Uniformity of dosage units	Not specified	specified	Not specified
Content uniformity	Not specified	specified	Not specified

OTHER TESTS:

Swelling Index: Different swelling degree is exhibited by Hydrophilic polymers of different structures, depending on relative resistance of matrix network structure to water particles' movement. Polymer chains exhibiting low ability to form hydrogen bonds may not be able to form strong network structure, resistant to fast water penetration. The bigger the strength and number of hydrogen bonds between polymer chains are, the slower the water particles diffuse into the hydrated matrix. Swelling of the polymer is vital to activation of bio-adhesive abilities, which activate just after swelling begins. With the growth of polymer hydration, the adhesion grows until the moment when excessive hydration leads to sudden fall of adhesion strength, which is an effect of the untangling of outer polymer layer. The degree and speed of insert hydration, as well as swelling, affect drug release from a dosage form. Therefore, this parameter is of greatest significance for drug release prediction and bio-adhesive matrix potential. Swelling examination is performed to measure bulk hydrophilicity and polymer hydration. In the

- ✓ Solutions enclosed in single dose containers and in soft capsules
- ✓ Solids (including powders, granules and sterile solids) that are packed in single-dose containers and contain no added active or inactive substances³⁹.

2. Content uniformity: Select not less than 30 units, and proceed as follows for the dosage form designated. For solid dosage forms like powders assay 10 units individually using an appropriate analytical method. Calculate the acceptance value (AV) using the equation 1;

$$|M-X| + ks \dots \dots \dots (1)$$

Where,

X = mean of individual contents(x₁, x₂,.....x_n) expressed as a percentage of the label claim.

M= reference value

k = acceptability constant

s = sample standard deviation

Single-dose powders for eye drops and eye lotions comply with the test or, where justified and authorized, with the tests for uniformity of content and/or uniformity of mass. Herbal drugs and herbal drug preparations present in the dosage form are not subject to the provisions of this paragraph³⁹.

3. Uniformity of content: The test for uniformity of content of single dose preparation is based on the assay of the individual contents of active substance of a number of single dose units to determine whether the individual contents are within the limits set with reference to the average contents of the sample. Using the suitable analytical method, determine the individual contents of the active substances of 10 dosage units taken at random³⁹.

procedure, a specified number of inserts are chosen, weighed, and put separately in beakers containing a solution simulating tear fluid, physiological saline buffered with phosphates, or distilled water at fixed temperature, for example, 32°C ± 0.5°C. In specified time intervals, inserts are taken out, dried with filter paper, and weighed once more. The procedure is repeated until the moment when mass growth is not observed anymore⁴⁰.

The degree, to which the liquid is taken up, called the swelling index, is calculated from the formula⁴⁰:

$$\text{Swelling index} = \left[\frac{(W_t - W_o)}{W_o} \right] \times 100$$

Where, W_o is the initial sample weight and W_t is the sample weight at t time.

Examinations of Moisture Absorption and Loss: These examinations are performed in order to assess physical stability and integrity of inserts' polymer matrix in dry conditions and at raised moisture. For moisture absorption

examination, a specified number of inserts are chosen and placed in desiccator, in which high moisture level, for example, 75 ± 5% RH, is maintained. After a specified time period, inserts are taken out and weighed again, and the percentage moisture absorption is calculated from the formula⁴⁰:

$$\% \text{ Moisture Absorption} = \frac{(\text{Final weight} - \text{Initial Weight})}{\text{Initial weight}} \times 100$$

In moisture loss examination, a chosen number of inserts are put in desiccator containing anhydrous calcium chloride, which ensures dry conditions inside the container. After a suitable time period, inserts are taken out and weighed again, and the percentage moisture loss is calculated from the formula⁴⁰:

$$\% \text{ Moisture Loss} = \frac{(\text{Initial Weight} - \text{Final weight})}{\text{Initial weight}} \times 100$$

Thickness of film: Film thickness is measured by using the Dial caliper at different points of the formulation and the mean value is calculated²⁷.

Accelerated stability studies: The accelerated stability studies are carried out to predict the degradation that occurs over prolonged periods of storage, at normal conditions. The films of the insert are taken in a separate petri dish and are kept at three different temperatures 400°C, 500°C, and 600°C, and the time taken for degradation of the ocular inserts is checked^{41,42}.

Test for sterility: It is done for detecting the presence of viable forms of microorganisms in the preparation. The working conditions should be monitored regularly by taking the samples of air and surface of the working area, and there should not be any cross contamination. The test is based on the principle that if the nutrient media is provided to the microorganisms and they are kept in a favorable condition of temperature, the microorganisms will grow and their presence is indicated by the turbidity in medium. The batch size taken for sterility testing in case of ophthalmic and other non-injectable preparations is given in Table 6.

Table 6: Consistent with USP, JP and BP, Minimum Number of Articles to be Tested in Relation to the Number of Articles in the Batch^{38,43}

Not more than 200 containers	5% or two containers, whichever is greater.
More than 200 containers	10 containers.
Not more than 100 containers*	10% or 4 containers, whichever is greater.
More than 100 but not more than 500 containers**	10 containers.
More than 500 containers***	2% or 20 containers, whichever is less.
*** If the product is presented in the form of single-dose containers.	
*** If the batch is not known, use the maximum number of items prescribed.	
**** If the contents of one container are enough to inoculate the 2 media, this column gives the number of containers needed for both the media together.	

CONCLUSION:

The main efforts in ocular drug delivery during the last few years has been on the design of systems which will prolong the residence time of topically applied drugs in the conjunctival sac and will improve patient compliance. Various newer approaches like ocular inserts as discussed in this article have been found promising. However, further research is needed in this field in order to overcome the drawbacks still associated with these types of drug delivery systems.

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Authors have declared that no competing interests exist.

REFERENCES:

- Katz IM: Shaped ophthalmic inserts for treating dry eyes syndrome, US Patent 1982; 4:343-787.
- Deivasigamani K, Mithun B, Pandey VP, Nandhakumar J, Sengottuvelu S, Sonkar S and Sivakumar T: The concept of ocular inserts as drug delivery systems- An overview, Asian Journal of Pharmaceutics 2008; 2:192-199.
- Jennifer S, Wentworth, Paterson CA, Wells JT, Tilki N, Gray RS and McCartney, Collagen shields exacerbate ulceration of alkali-burned rabbit corneas. Archives of Ophthalmology 1993; 111:389-392
- Mitra AK, Ophthalmic Drug Delivery Systems. Marcel Dekker, New York, Vol. 58, 1993: 29-57.
- Chatterjee CC, Human Physiology. Medical allied Agency, Calcutta, Edition 10, Vol. 2, 1994: 2.
- Neeffe CW, Contact lens for ocular drug delivery. US Patent 1974; 3:786-812.
- Gibaldi M, Perrier D, Pharmacokinetics. Marcel Dekker, Second Edition 1993.
- Chien YW, Novel drug delivery systems. Marcel Dekker, Second Edition 1992.
- Madhuri B, Vikas G and Mahesh B, Ocular Inserts: A Rate Controlled Drug Delivery System - A Review, International Journal of Pharmaceutical Erudition 2012; 2:49-63.
- Roseman TJ, Mansdorf SZ, Controlled Release Delivery Systems. Marcel Dekker, New York, 1983: 77-90.
- Darougar S, Patent literature review of ocular inserts. US Patent 1999; 6:264-971.
- Dabhi V, Yogi J, Bhimani B, Patel U and Patel G, Ocular inserts as controlled drug delivery systems, International Journal of Pharmaceutical Research and Bio-Science 2014; 3:468-480.
- Heller J, Controlled release of biologically active compounds from bioerodible polymers, Biomaterials 1980; 1:51-57.
- Saettone MF and Salminen L, Ocular inserts for topical delivery, Advanced Drug Delivery Reviews 1995; 16:95-106.
- Mitra AK, Ophthalmic Drug Delivery Systems. Marcel Dekker, New York, Vol. 58, 1993: 1-27.
- Mitra AK, Ophthalmic Drug Delivery Systems. Marcel Dekker, New York 1993: 223-259.

17. Edman P, Biopharmaceutics of ocular drug delivery. CRC Press, Boca Raton, 1993: 61-79.
18. Saettone MF, Bucci G, Speiser P, Ophthalmic Drug Delivery, Biopharmaceutical, Technological and Clinical Aspects. Liviana Press, Fidia Research Series, Vol. 11, 1987: 179-189.
19. Patton TF and Robinson JR, Quantitative precorneal disposition of topically applied pilocarpine nitrate in rabbit eyes, Journal of Pharmaceutical Sciences 1976; 65:1295-1301.
20. Rajput G, Sharma S, Chaudhury S and Banshraj, Review on ophthalmic inserts, International journal of pharma professional's research 2013; 4:912-920.
21. Mitra A, Ophthalmic drug delivery. In: Tyle P, editor. Drug Delivery Devices. New York: Marcel Dekker; 1998.
22. Mitra AK, Ophthalmic Drug Delivery Systems. Marcel Dekker, New York, Vol. 58, 1993: 83-103.
23. Saettone MF, Chetoni P, Torraca MT, Giannaccini B, Naber L, Conte U, *et al*: Application of the compression technique to the manufacture of Pilocarpine inserts, Acta Pharm Technol 1990; 36:15-19.
24. Gurtler F and Gurny R, Patent literature review of ophthalmic inserts, Drug Development and Industrial Pharmacy 1995; 21:1-18.
25. Rathore KS and Nema RK, Review on ocular inserts, International Journal of Pharm Tech Research 2009; 1:164-169.
26. Robinson JR, Ophthalmic Drug Delivery Systems, American Pharmaceutical Association, Washington DC, 1980: 105-116.
27. Sahane NK, Banarjee SK, Gaikwad DD, Jadhav SL and Thorat RM, Ocular inserts: a review, International Journal of Current Research and Review 2010; 2:57-64.
28. Rastogi SK, Vaya N and Mishra B, Ophthalmic inserts: An overview, The Eastern Pharmacist; 1996: 41-44.
29. Rajasekaran A, Arul Kumaran KSG, Padma Preetha J, and Karthika K, A comparative review on conventional and advanced ocular drug delivery formulations, International Journal of Pharm Tech Research 2010; 2:668-674.
30. Tangri P and Khurana S, Basics of ocular drug delivery systems, International Journal of Research in Pharmaceutical and Biomedical Sciences 2011; 2:1541-1552.
31. Jung HJ, Abou-Jaoude M, Carbia BE, Plummer C, and Chauhan A, Glaucoma therapy by extended release of timolol from nanoparticle loaded silicone-hydrogel contact lenses, Journal of Controlled Release 2013; 165:82-89.
32. Hui A, Boone A, and Jones L, Uptake and release of ciprofloxacin-HCl from conventional and silicone hydrogel contact lens materials. Eye & Contact Lens 2008; 34:266-271.
33. Boone A, Hui A, and Jones L, Uptake and release of dexamethasone phosphate from silicone hydrogel and group I, II, and IV hydrogel contact lenses. Eye and Contact Lens 2009; 35:260-267.
34. Peng CC and Chauhan A, Extended cyclosporine delivery by silicone-hydrogel contact lenses, Journal of Controlled Release 2011; 154:267-274.
35. Yavuz B, Pehlivan SB, and Unlu N, An Overview on Dry Eye Treatment: Approaches for Cyclosporin A Delivery. The Scientific World Journal 2012; Article ID 194848.
36. Refojo M, Polymers in contact lenses: An overview, Current Eye Research 1985; 4:719-723.
37. Patel GM and Patel MM: Recent advances and challenges in ocular drug delivery system. Pharma Times 2007; 39:21-25.
38. Sahab Uddin Md, Abdullah Al Mamun, Tanvir Kabir Md, Jinnat Ruksana Setu, Sonia Zaman, Yesmin Begum and Shah Amran Md, Quality Control Tests for Ophthalmic Pharmaceuticals: Pharmacopoeial Standards and Specifications, Journal of Advances in Medical and Pharmaceutical Sciences 2017; 14:1-17.
39. Vishal Gupta N and Viswanatha Reddy G, A Comparative study of quality control tests for eye preparations as per IP, BP and USP, International Journal of Drug Development & Research 2015; 7:61-68.
40. Baranowski P, Karolewicz B, Gajda M, and Pluta J, Ophthalmic Drug Dosage Forms: Characterization and Research Methods. The Scientific World Journal 2014; Article ID 861904.
41. Lee VH, Li SY, Sasaki H, Saettone MF and Chetoni P, Influence of drug release rate on systemic timolol absorption from polymeric ocular inserts in the pigmented rabbit, Journal of Ocular Pharmacology and Therapeutics 1994; 10:421-429.
42. Grass GM, Cobby J and Makoid MC, Ocular Delivery of pilocarpine from erodible matrices, Journal of Pharmaceutical Sciences 1984; 73:618-21.
43. Ministry of health and family welfare, Government of India: Indian Pharmacopoeia. India Controller of Publication, First Edition 1996.

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