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Review on Ocular Inserts

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Abstract: The conventional dosage forms are account for 90% of currently accessible ophthalmic formulations. The major problem encountered is rapid precornel drug loss. To improve ocular drug bioavailability, there are significant efforts directed towards newer drug delivery systems for ophthalmic administration. Newer research in ophthalmic drug delivery systems is directed towards a combination of several drug delivery technologies, that includes to develop systems which is not only prolong the contact time of the vehicle at the ocular surface, but which at the same time slow down the elimination of the drug.

Key Words: Ocular Inserts, Newer Ocular Drug Delivery System, *In-Situ* Gel.

Introduction:

Ocular drug delivery is one of the most fascinating and challenging tasks facing 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 anatomy, physiology and biochemistry of the eye render this organ exquisitely impervious to foreign substances. The challenging 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 therapeutics agents renders urgency to the development of maximum successful and advanced ocular drug delivery systems[1] .

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. Repeated medications are still required throughout the day[2] .

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. It has become clear, however that the development of an ocular insert that reliably combines controlled release with absence of any irritation to the patient, poses a formidable technical challenge [3].

The conventional ocular dosage forms for the delivery of drugs are-

i. Eye drops (solution, suspension)

ii. Ophthalmic Ointments

The eye drop dosage form is easy to install but suffers from the inherent drawback that most of the instilled volume is eliminated from the pre-corneal area[4] resulting in a bioavailability ranging from 1-10% of total administrated dose [5]. The poor bioavailability and rapid pre-corneal elimination of drugs given in eye drops is mainly due to conjunctival absorption, rapid solution drainage by gravity, induced lachrymation, blinking reflex, low corneal permeability and normal tear turnover. Because of poor ocular bioavailability, many ocular drugs are applied in high concentrations. This cause both ocular and systemic side-effects[6], which is often related to high peak drug concentrations in the eye and in systemic circulation. The frequent periodic instillations of eye drops are necessary to maintain a continuous sustained therapeutic drug level. This gives the eye a massive and unpredictable dose of medication[7] .

Suspension types of pharmaceutical dosage forms are formulated with relatively water insoluble drugs to avoid the intolerably high toxicity created by saturated solutions of water-soluble drugs. However, the rate of drug release from the suspension is dependent upon the

rate of dissolution of the drug particles in the medium, which varies, constantly in its composition with the constant inflow and outflow of lachrymal fluid[8].

In order to overcome the constraints placed by these conventional ocular therapies viz.

i. Short residence time
ii. Pulsed dosing of drug.
iii. Frequent instillation
iv. Large drainage factor.

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[6].

The following recent trends are in existence[9]:

a) Membrane-bound ocular inserts (biodegradable and non-biodegradable) e.g. Ocusert®, Alza Corp.
b) Mucoadhesive dosage forms (ocular films or sheath, ophthaCoil, polymer rods, HEMA hydrogel, Dispersion, polysulfone capillary fiber)
c) Collagen shields, cyclodextrine based system, ophthalmic rods (artificial tear inserts e.g. Lacrisert®)
d) Filter paper strips (drug-impregnated filter paper strips for staining agent- sodium fluorescent, lissamine green and rose Bengal)
e) Soft contact lenses, implants, flexible coils and cotton pledgets (Drug presoaked hydrogel type, polymeric gels)
f) Phase Transition systems (*in-situ* gel formation system: ion- activated based, pH changed based, temperature change based) [10] .
g) Nanoparticles (Microspheres, nanosuspension, Amphiphilogels, Niosomes, Liposomes, Dendrimers and Quantom dots) [11,12]
h) Ocular Iontophoresis and pumps
i) Chemical delivery systems vesicular systems[9]

Utilization of the principal of controlled release as embodied by ocular inserts therefore offers an attractive alternative approach to the difficult problem of prolonging pre-corneal drug residence time[13]

Ocular disposition and elimination of a therapeutic agent is dependent upon its physicochemical properties as well as the relevant ocular anatomy and physiology[14]. The successful design of a drug delivery system, therefore, requires an integrated knowledge of the drug entity and the constraints to delivery offered by the ocular route of administration.

Ophthalmic Inserts as Ocular Sustained Release Drug Delivery System:

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

They are composed of a polymeric support containing or not drug (s), the latter being incorporated as dispersion or a solution in the polymeric support. The inserts can be used for topical or therapy[15].

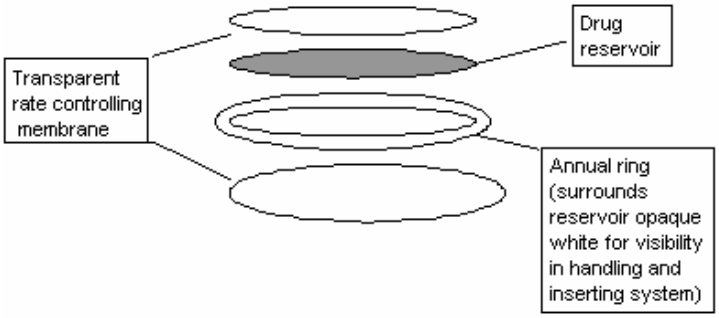

Fig. 1. Schemetic diagram of ophthalmic insert

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 to topical or systemic treatment[16].

In comparison with the traditional ophthalmic preparation i.e., eye drops, the solid ophthalmic devices presents some advantages such as[17]

- Increasing contact time and thus improving bioavailability.
- Possibility of providing a prolong drug release and thus a better efficacy.
- Reduction of systemic side effects and thus reduced adverse effects.
- Reduction of the number of administrations and thus better patient compliance.

Classification of Patented Ocular Insurts:

(Based upon their solubility behaviour)

1) **Insoluble inserts**
   a) Diffusion based
   b) Osmotic based
   c) Soft contact lenses
2) **Soluble inserts**
3) **Bioerodible inserts**

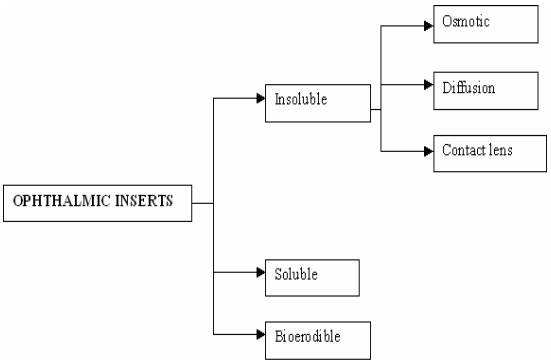

Fig. 2. Classification of Ophthalmic inserts.

The desired criteria for a controlled release ocular are as follows[12].

The foreign-body sensation, presents a challenge to overcome the discomfort leads to poor-patient compliance, excessive lachrymation that accompanies irritation, dilutes the drug and causes reduction in its concentration[19]. A properly designed ocular inserts will minimize the sensation caused by its insertation and wear[20].

1) Ease of handling and insertion
2) Lack of expulsion during wear
3) Reproducibility of release kinetics (Zero-order drug delivery)
4) Applicability to variety of drugs
5) Non-interference with vision and oxygen permeability.
6) Sterility[21].
7) Stability.
8) Ease of manufacture

Insoluble ophthalmic inserts

The insoluble inserts have been classified into three groups:-

i. Diffusion systems
ii. Osmotic systems
iii. Hydrophilic contact lenses.

The first two classes include a reservoir in contact with the inner surface of the rate controller and supplying drug thereto. The reservoir contains a liquid, a gel, a colloid, a semisolid, a solid matrix or a carrier-containing drug homogeneously or heterogeneously dispersed or dissolved therein[22]. Carriers can be made of hydrophobic, hydrophilic, organic, inorganic, naturally occurring or synthetic material [23] .

The third class including the contact lenses. The insoluble of these devices is their main disadvantages, since they have to be removed after use.

Diffusion inserts

The diffusion systems are compared of a central reservoir of drug enclosed in specially designed semi permeable or micro porous membranes, which allow the drug to diffuse the reservoir at a precisely determined rate.

The drug release from such a system is controlled by the lachrymal fluid permeating through the membrane until a sufficient internal pressure is reached to drive the drug out of the reservoir. The drug delivery rate is controlled by diffusion through the membrane, which one can be controlled[24] .

Table 1: Components of diffusional inserts.

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

Osmotic inserts:

The osmotic inserts are generally compared of a central part surrounded by a peripheral part[25]. The first central part can be composed of a single reservoir or of two distinct compartments.

In first case, it is composed of a drug with or without an additional osmotic solute dispersed through a polymeric matrix, so that the drug is surrounded by the polymer as discrete small deposits[26] . In the second case, 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 of these osmotic inserts comprises in all cases a covering film made of an insoluble semi permeable polymer[27].

The tear fluid diffuse into peripheral deposits through the semi permeable polymeric membrane wets them and induces their

dissolution. The solubilized deposits generate a hydrostatic pressure against the polymer matrix causing its rupture under the form of apertures. Drug is then released through these apertures from the deposits near the surface of the device which is against the eye, by the sole hydrostatic pressure[28]. This corresponds to the osmotic part characterized by zero order drug release profile.

Table 2: Components of osmotic inserts.

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.

Soft contact lenses

These are shaped structure made up of a covalently cross-linked hydrophilic or hydrophobic polymer that forms a three-dimensional network or matrix capable of retaining water, aqueous solution or solid components[6].

When a hydrophilic contact lens is soaked in a drug solution, it absorbs the drug, but does not give a delivery as precise as that provided by other non-soluble ophthalmic systems. The drug release from such a system is generally very rapid at the beginning and then declines exponentially with time. The release rate can be decreased by incorporating the drug homogeneously during the manufacture[29] or by adding a hydrophobic component. Contact lenses have certainly good prospects as ophthalmic drug delivery systems[30].

Soluble Ophthalmic inserts

Soluble inserts correspond to the oldest class of ophthalmic inserts. They offer the great advantage of being entirely soluble so that they do not need to be removed from their site of application thus, limiting the interventions to insertion only[31].

Types

a) Based on natural polymers e.g. collagen.

b) Based on synthetic or semi synthetic polymers.

The therapeutic agents is preferably absorbed by soaking the insert in a solution containing the drug, drying and re-hydrating in before use on the eye. The amount of drug loaded will depend upon the amount of binding agent, upon the concentration of the drug solution into which the composite is soaked, as well as the duration of the soaking[32] .

The soluble ophthalmic inserts containing synthetic/semi synthetic polymers

Offers the additional advantages of being generally of a simple design.

a) Based on products well adopted for ophthalmic use.
b) Easily processed by conventional methods – slow evaporating extrusion, compression or injection molding.

The release of the drug from such system is by penetration of tears into the insert which induces release of the drug by diffusion and forms a gel layer around the core of the insert, this external gelification induces the further release, but still controlled by diffusion. The release rate, J, is derived from Fick's law yields the following expression[33].

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

When A - Surface are of the membrane.
K – Diffusion coefficient of the drug
L – Membrane thickness
C_S – Drug solubility in water
D – Diffusion coefficient of the Ocuserts membrane.

Since all the terms on the right hand side of the above equation are constant, so is the release rate of the device [8]. The other factors affecting drug release from these Ocuserts include:

- Penetration of the inclusion.
- Swelling of the matrix.
- Dissolution of the drug and the polymers.
- Relaxation of the polymeric chain.

The soluble insert made of cellulose derivatives can be sterilized by exposure to gamma radiation without the cellulose components being altered[34]. A decreased release rate is obtained by using a component of the matrix a polymer normally used for enteric coatings[31] or by introducing a suitable amount of hydrophobic polymer capable of diminishing the tear fluid penetration and thus of decreasing the release of the drug without modifying the solubility of the insert when added in proper proportion.

Table 3: Components Of Soluble Inserts Containing Synthetic Polymers.

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

Biodegradable ophthalmic inserts

The biodegradable inserts are composed of material homogeneous dispersion of a drug included or not into a hydrophobic coating which is substantially impermeable to the drug. They are made of the so-called biodegradable polymers[35]. Successful biodegradable materials for ophthalmic use are the poly (orthoesters) and poly (orthocarbonates). The release of the drug from such a system is the consequence of the contact of the device with the tear fluid inducing a superficial diversion of the matrix[36].

The use of solid ophthalmic devices will certainly increase owing to the development of new polymers, the emergence of new drugs having short biological half-lives or systemic side effects and the need to improve the efficacy of ophthalmic treatment by ensuring an effective drug concentration in the eye over an extended period of time[37].

Conclusion:

The main efforts in ocular drug delivery during the past two decades has been on the design of systems to prolong the residence time of topically applied drugs in conjuctival sac. Various newer approaches like ocular inserts, collagen shield, *in-situ* activated gel forming solution, non-corneal route of ocular drug penetration and nanoparticles based polymeric solutions and gels are a cynosure for pharmaceutical scientists.

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