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NOVEL OCULAR DOSAGE FORM IN THE TREATMENT OF GLAUCOMA

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ABSTRACT

Glaucoma is a group of disease of the eye characterized by damage to the ganglion cells and the optic nerve. If left untreated, these effects may lead to various degrees of loss of vision and blindness. Increased intraocular pressure (IOP) remains the most important risk factor for the development of glaucoma. A major problem in ocular therapeutics is the attainment of an optimal drug concentration at the site of action. To achieve effective ophthalmic therapy, an adequate amount of active ingredient must be delivered and maintained within the eye. The most frequently used dosage forms i.e., eye solution, eye ointments, eye gels and eye suspensions are compromised in their effectiveness by several limitations leading to poor ocular bioavailability. Occusert are thin discs or small cylinders made with appropriate polymeric material and fitting into the lower or upper conjunctival sac. Their long persistence in preocular area can result in greater drug availability with respect to liquid and semisolid formulation. Thus occusert can be used for the controlled delivery of drugs used in the treatment of glaucoma.

Keywords: glaucoma, ocular, novel dosages

1. GLAUCOMA[1,2,3,4,5.]

Glaucoma is a group of disease of the eye characterized by damage to the ganglion cells and the optic nerve. If left untreated, these effects may lead to various degrees of loss of vision and blindness. Increased intraocular pressure (IOP) remains the most important risk factor for the development of glaucoma.

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1.1 Types of Glaucoma

Glaucoma may be classified in a variety of ways, which describe causative factors, when known. Glaucoma is usually described as either angle closure or open angle glaucoma. These terms are based upon the mechanism of obstruction of outflow of aqueous humor and help clinicians develop treatment strategies. Open angle glaucoma occurs in 80% to 90% of cases. Angle closure glaucoma is usually a more acute form of disease and is seen in 5 to 10% of all patients. A third type is congenital glaucoma, which results from developmental ocular abnormalities and occurs in less than 2% of patients. Finally, glaucoma may be secondary to other ocular

disorders, systemic disorders, or trauma, or may be seen with medication usage, or after intraocular surgery. Open angle glaucoma can be further described as either high tension or normal tension (also known as low tension) glaucoma. (Fig. 1)

1.2 Etiology (Study of causes of disease):

Optic nerve damage caused by the different types of glaucoma is a result of a variety of initiating factors. Genetic predisposition, physical changes, systemic diseases, or medications may increase a person's risk of developing damage that may be broadly classified as intraocular pressure dependent (most commonly) or intraocular pressure independent. Increased intraocular pressure remains the major etiologic risk factor for the development of glaucoma. Glaucoma can occur as a secondary manifestation of systemic disorders or trauma.

1.3 Pathophysiology:

Shields et al describe five stages in the pathogenesis of glaucoma(1) a variety of initial events, causing (2) changes in aqueous outflow, resulting in (3) Increased IOP, which leads to (4) Optic nerve atrophy, and finally, (5) Progressive loss of vision. This description highlights the importance of aqueous humor production and elimination in the progression of glaucoma and subsequent complications.

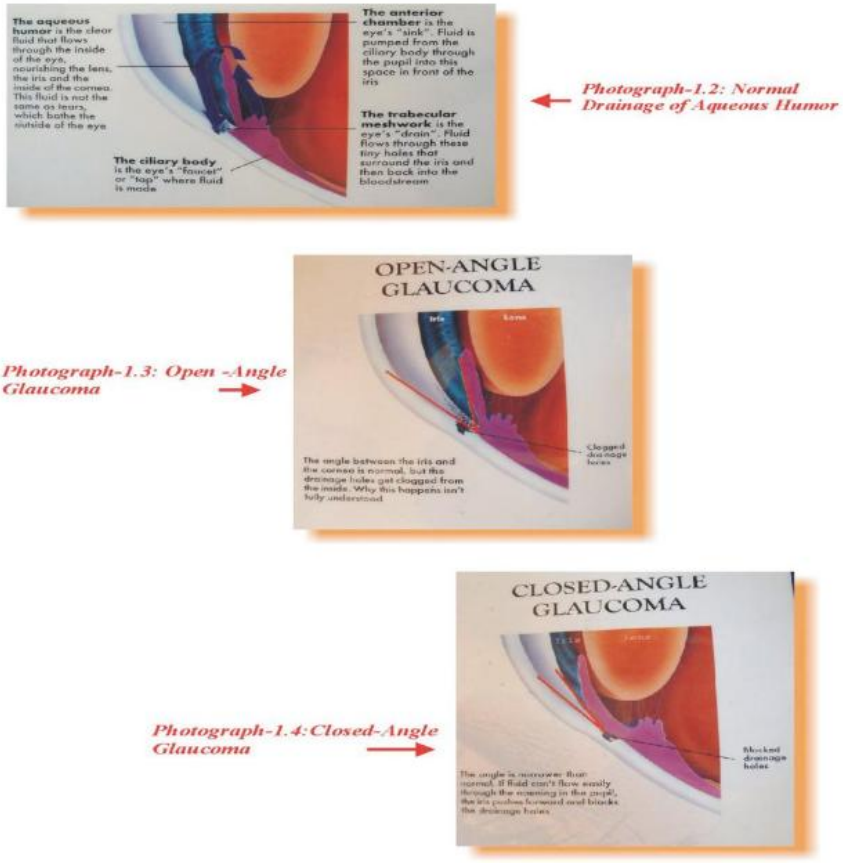

Figure-1 : Types of Gluacoma

1.4 Open-Angle Glaucoma:

In open-angle glaucoma, a physical blockage occurs within the trabecular meshwork that retards elimination of aqueous humor. The obstruction is presumed to be between the trabecular sheet and the episcleral veins, into which the aqueous humor ultimately flows. The impairment of aqueous drainage elevates the intraocular pressure to between 25 and 35 mm Hg (normal intraocular pressure is 10 to 20 mm Hg), indicating that the obstruction is usually partial. This increase in intraocular pressure is sufficient to cause progressive cupping of the optic disk and eventually visual field defects.

1.5 Angle-Closure Glaucoma

In angle-closure glaucoma, increased intraocular pressure is caused by pupillary blockage of aqueous humor outflow and is more severe. The basic requirements leading to an acute attack of angle closure are a pupillary block, a narrowed anterior chamber angle and a convex iris. When a patient has a narrow anterior chamber or a pupil that dilates to a degree where the iris comes in greater contact with the lens, there is interference with the flow of aqueous humor from the posterior to the anterior chamber. Because aqueous humor is continually secreted, pressure within the posterior chamber forces the iris to bulge forward. This may progress to complete blockage.

2. TREATMENT

2.1Pharmacotherapy:

The goal of glaucoma therapy is the immediate and reduction of Intraocular pressure to prevent deterioration of the optic nerve and loss of vision. Medications used in the treatment of glaucoma may be classified as those that increase the elimination of aqueous humor and those that decrease its formation (Table.1).

3. OPTHALMIC DRUG DELIVERY SYSTEMS:

A major problem in ocular therapeutics is the attainment of an optimal drug concentration at the site of action to achieve effective ophthalmic therapy, an adequate amount of active ingredient must be delivered and maintained within the eye. The most frequently used dosage forms i.e., eye solution, eye ointments, eye gels and eye suspensions are comprised in their effectiveness by several limitations leading to poor ocular bioavailability[6] and the limitations are;

a) They have poor bioavailability because of

-Rapid precorneal elimination

-Conjunctival absorption

-Solution drainage by gravity

-Induced lacrimation

-Normal tear turnover[7]

b) Frequent administration is needed which would increase the risk of drug toxicity and side effects[8].

c) Systemic absorption of the drug and additives drained through nasolacrimal duct may result in undesirable side effects.

d) The amount of drug delivered during external application may vary the drop size of commercial ocular medication is not

uniform and those delivered is generally not correct[9].

e) Presence of viscous vehicle can cause blurred vision[10].

Table.1 Medications Used in the Treatment of Glaucoma

Drug Class / Name	Mechanism of Intraocular pressure Lowering Effect	Duration of Activity (hr)	Pregnancy Category
β-Blockers	Increase aqueous humor outflow		
Timolol		12-24	C
Levobunolol		12-24	C
Betaxolol		12	C
Metipranolol		12-24	C
Carteolol		12	C
Miotics, direct acting	Increase aqueous humor outflow		
Pilocarpine		4-8	
Solution		18-24	
Gel		1 Week	
Ocular Insert		6-8	C
Miotics, cholinesterase inhibitors	Increase aqueous humor outflow		
Physostigmine		12-36	C
Demecarium		Days/Weeks	X
Sympathomimetics	Decrease aqueous humor formation and increase aqueous humor outflow		
Apraclonidine		7-12	C
Epinephrine		12	C
Dipivefrin		12	B
Brimonidine		12	B
Carbonic anhydrase inhibitors	Aqueous humor formation		
Acetazolamide		8-12	C
Dichlorphenamide		6-12	C
Methazolamide		10-18	C
Dorzolamide		8	C
Rinzolamide		8	C

3.1 Conventional Ophthalmic Dosage Forms:

a) Eye Drops: It is defined as the liquid preparation in which all the ingredients are completely soluble in solution in a uniformly manner. Upon instillation most of the instilled volume is eliminated from the precorneal area[11].

b) Eye Gels: It is semisolid preparation comprising of small molecules interpenetrated by a liquid, which are applied to the eye. The residence time is more in the eye region by using gels due to which the absorption rate is increased and a prolonged therapeutic effect is produced[12,13].

c) Eye ointments: Eye ointments are sterile, semi solid preparation of homogenous appearance intended for application to conjunctiva or margin of the eyelids. Due to its hydrophobic nature it produces very low level of therapeutic effect. It produces blurring of vision due to its greasy nature[14].

d) Eye Suspension: Suspensions are the dispersion of finely divided relatively insoluble drug substances in an aqueous vehicle containing suitable suspending and dispersing agent. It must contain particle of such chemical characteristics and small dimensions that they are non-irritating to the eyes[15]. The particles are better retained in cul-de-sac thus bioavailability of the drug increases and give a slow release effect[16].

3.2. Novel Ophthalmic Dosage Forms:

To overcome the drawbacks of conventional ophthalmic dosage form many progress have been done to improve the pre-corneal drug absorption and minimizing pre-corneal drug loss.

a) Mucoadhesives: Mucoadhesives are defined as they are retained in the eye by virtue of non-covalent bonds established with the corneal conjuctival mucin for extending the pre-ocular residence times[17,18].

b) Phase transition system: These are liquid dosage forms which shift to the gel or solid phase when instilled in the cul-de-sac. After converting into gel it remain in contact with the cornea of the eye for prolonged period of time due to which drug elimination is also slow down[19,20].

c) Niosomes: Niosomes are the vesicles containing non-ionic surfactant can entrap both hydrophillic and lipophillic drugs either in aqueous layer or in vesicular membrane made of lipid materials[21]. It helps in preventing the metabolism of the drug by enzymes present at the tear/corneal surface[22].

d) Liposomes: Liposomes are microscopic vesicles composed of membrane like lipid layers surrounding aqueous compartments. The lipid layers are comprised mainly of phospholipid[23]. They have the ability to entrap hydrophillic compound in the aqueous compartment and to incorporate hydrophobic molecule in the lipid bilayers[24].

e) Nanoparticles: Nanoparticles are solid particles of polymeric nature ranging in size from 10-1000nm. The drugs are bound to small particles, which are than dispersed aqueous vehicle[25]. Due to very small in size these are not washed away with tears quickly[26].

f) Contact lenses: Contact lenses are substitutes for spectacles are enjoying a certain degree of popularity. Uses of soft contact lenses soaked in drug solution have

been suggested for slow but prolonged drug delivery but particularly to corneal tissue[27].

g) Pharmacosomes: They are the vesicles formed by the amphiphillic drugs. Any drug possessing a free carboxy group can be esterified to the hydroxyl group of a lipid molecule thus generating an amphiphillic prodrug. These are converted to Pharmacosomes on dilution with tear[28].

h) Ophthalmic inserts: Inserts are defined as a thin disks or small cylinders made with appropriate polymeric material and fitting into the lower or upper conjunctival sac. Their long persistence in preocular area can result in greater drug availability with respect to liquid and semisolid formulation[29].

Advantages of occuserts[30]:

- Increased ocular residence time hence a prolonged drug activity and a higher bioavailability with respect to standard vehicle.
- Possibility of releasing drug at a slow constant rate.
- Accurate dosing (contrary to eye drop 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 with eye drops via the nasolacrimal 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 sectional) routes
- Increased shelf life with respect to aqueous solutions.
- Exclusion of preservative, thus reducing the risk of sensitivity reactions.
- Possibility of incorporating various level novel chemical/technological approaches, such as prodrugs, mucoadhesives, permeation enhancers, microparticulates, salts acting as buffers etc.

Disadvantages of occusert:

- Initial discomfort, their movement around the eye.
- Occasional inadvertent loss during sleeps or while rubbing the eye.
- Interference with vision and a difficult placement.

Classification of occusert[9]:

They are classified on the basis of their solubility.

a) Insoluble ophthalmic inserts.

b) Soluble ophthalmic inserts.

c) Bioerodible ophthalmic inserts.

a) Insoluble ophthalmic inserts: Sub classified into

- Diffusional Inserts.
- Osmotic Inserts.
- Contact Lenses.

❖ Diffusional Inserts: The diffusional inserts are composed of a central reservoir of drug enclosed in specially designed semi permeable, which allow the drug to diffuse from the reservoir at precisely determined rate. The lacrimal fluid permeating through the membrane until the sufficient internal pressure is reached to drive the drug out of reservoir controls the drug release from such a system.

The principle for its operation can be operated by the Fick's diffusion equation.

J=-DAdc/dx

J=solute flux

D=Difference co-efficient for the drug within the polymer membrane

A= Area of membrane

dc/dx= Drug concentration gradient within the membrane along the direction of drug flow.

❖ **Osmotic Inserts:** The osmotic inserts are composed of two distinct compartments. One compartment contains drug and other contains osmotic solute, which is sandwiched between the rate controlling membrane. The tears diffuse into osmotic compartment inducing an osmotic pressure due to which drug diffuses.

❖ **Contact Lenses:** Contact lenses are covalently cross-linked hydrophilic or hydrophobic polymer that forms a three-dimensional network capable of retaining water aqueous drug solution or solid components.

b) Soluble ophthalmic inserts: This type of inserts entirely soluble so that they do not need to be removed from their site of application. The release of drug from this type of inserts due to penetration of tear fluid into the inserts that induces high release rate of drug by diffusion and forms a gel layer around the core of the insert.

c) Bioerodible 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. 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.

4. 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 conjunctival sac. The advantages offered by ophthalmic inserts are numerous but only few of them have gained commercial acceptance. This is because of its comparatively high cost and reluctance of the patients to use unfamiliar types of ophthalmic medication.

There is need to apprise the patients with the benefits of such systems and also to make them familiar with the methods of using such devices. Ophthalmic inserts design, construction and technology is witnessing a rapid improvement, so in near future its use is expected to increase tremendously in ophthalmic therapy.

Future Prospect:

The advantages offered by ophthalmic inserts are numerous but only few of them have gained commercial acceptance. This is because of its comparatively high cost and reluctance of the patients to use unfamiliar types of ophthalmic medication. There is need to apprise the patients with the benefits of such systems and also to make them familiar with the methods of using such devices.

Ophthalmic inserts design, construction and technology is witnessing a rapid improvement, so in near future its use is expected to increase tremendously in ophthalmic therapy.

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