e-ISSN: 2248-9126
Vol 3|Issue 2| 2013 |74-78. Print ISSN: 2248-9118

Indian Journal of Pharmaceutical Science & Research

www.ijpsrjournal.com

OCCULAR DRUG DELEVERY- A REVIEW

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ABSTRACT

Eye is most interesting organ due to its drug disposition characteristics. For ailments of the eye, topical administration is usually preferred over systemic administration, before reaching the anatomical barrier of the cornea, any drug molecule administered by the ocular route has to cross the pre corneal barriers. For development of new drug candidates and novel delivery techniques for treatment of ocular diseases has recently accelerated. Controlled drug delivery to the eye is restricted due to these limitations imposed by the efficient protective mechanism. Ideal ocular drug delivery must be able to sustain the drug release and to remain in the vicinity of front of the eye for prolong period of time. Consequently it is imperative to optimize ocular drug delivery, one of the ways to do so is by addition of polymers of various grades, development of viscous gel, and development of colloidal suspension or using erodible or non-erodible insert to prolong the pre corneal drug retention.

Keywords: Ocular drug delivery, intravitreal, subconjunctival, Ocular insert.

INTRODUCTION

Ocular drug administration is primarily associated with treating ophthalmic diseases and is not regarded as a means for gaining systemic action. This is done to prevent the risk of eye damage from high blood concentration not intended for eyes. Major drugs include miotics, mydriatics, anti-inflammatory, anti-infective, surgical adjuvants etc.(all for local effect).

Eye drop is easy to instill but the major drawback is that majority of medication is immediately diluted in the tear and is rapidly drained away from the precorneal cavity by constant tear flow ,a process that proceeds more intensively in inflamed than in normal eyes and lacrimal nasal drainage. Only 1.2% is available in aqueous humor. Thus a relatively concentrated solution is required to be instilled for adequate level for therapeutic effect. Frequent instillation is necessary for continuous sustained level. This gives the eye a massive and unpredictable dose and thus side effects [1].

In the recent years attempt has been made towards

1. Improving ocular contact time.
2. Enhancing corneal permeability.
3. Enhancing site specificity.

ANATOMY AND PHYSIOLOGY OF EYE

It is spherical in shape with a diameter of 23 nm. The amount of light is controlled by pupil. Eye ball has three layers.

1. Outer most coats comprises of the transparent cornea and white opaque sclera.
2. The middle layer has the iris anteriorly and choroid posteriorly and ciliary body in middle.
3. Inner retina, an extension of CNS.

The eye ball is continually irrigated by a gentle stream of lacrimal fluid. Normal volume is 7 micro lit has pH 7.4.Eye also contains lysozyme whose bactericidal activity decreases the bacterial count in conjunctival sac. The aqueous humor has a volume of 300 micro lit and the rate of drainage is same of that production. The intraocular pressure is 25-30mm/Hg [2].

GLAUCOMA

It is a disease characterized by an increase in intraocular pressure that if sufficiently high persistent leads to irreversible blindness. Three types are as….
Primary, secondary and congenital.

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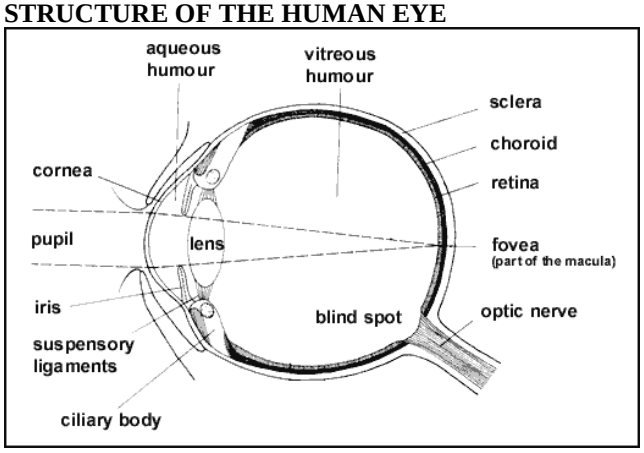
STRUCTURE OF THE HUMAN EYE



After instillation the drug in solution enters through cornea, which contains epithelium, stroma endothelium (fat water fat), so non-polar compounds enters by oil water partitioning and depends on its partition coefficient. Some drugs like large and hydrophilic drugs enter by conjunctival and scleral route [3].

APPROACHES USED FOR OCULAR DRUG DELIVERY

ROLE OF POLYMER

Polymers such as PVA (POLYVINYL ALCOHOL), Polyvinyl pyrolidine (PVP), MC, CMC and HPC are used to increase the viscosity and thereby the contact time in the eye. Increased viscosity reduces drainage. An optimum viscosity of 12-15 cps is suggested for PVA, PVP, MC and CMC.HPC has 73cps is suggested to bring about increase in bioavailability. Largest increase is by PVA (3.7 times)

Natural polymers like Hyaluronate and chondroitin are also used. However care must be taken about the lipophilicity of the drug. Very high % of the polymer may decrease the partitioning.

PHASE TRANSITION SYSTEMS

These are dosage forms which shift from solution to gels or solid form when instilled in cul-de-sac. Eg of polymers are Lutrol FC 127 and Poloxamer 407 which have increased viscosity at 37c.CAP(Ph-4.5 normally)coagulates at the tear pH(7.4).

MUCOADHESIVES

Any polymer solution placed in the first encounters mucin at the cornea and conjunctival surface if they form non-covalent bond with the mucin the phenomenon is known as mucoadhesin. Goblet cells of conjunctiva secrets mucin [4].

Macromolecules of weight 5000-10000 cannot be absorbed by mucosal tissue and forms adducts acts as depot agents. They remain in contact with the precorneal tissues until mucin turnovers causes elimination of polymers. Eg. of polymers –CMC, Carbopol, Sodium Alginate, Polycarbophil.

Good mucoadhesion is seen in polymers with correct charge, density, hydrogen bonding, HLB and Ph. Eg. carbopol gels of pilocarpine for 24hr realease, mucoadhesive dosage forms of progesterone, lidocaine, benzocaine, tropicamide etc [5].

COLLAGEN SHIELDS

Collagen shield are used to promote wound healing and for corneal delivery. Bloomfield et al showed that they can be used for delivery of gentamicin by wafer shaped collagen inserts.

They are prepared by molding the in contact lens configuration. Diameter is 14.5 mm,9 mm base curve and thickness 0.15-0.19mm.Sterilized by gama radiation. Eg. of drug is Prednisolone, Cyclosporine, Tobramycin. They are simple and convenient and cheap [6].

OPTHALMIC INSERTS

Ocular inserts made up of various polymers are very popular to be inserted in cul-de-sac. They have better patient compliance by decreasing dosing frequency. The desired criteria

1. Comfort
2. Lack of explosion
3. Ease of handling and insertion.
4. Reproducible pharmacokinetics.
5. Sterility
6. Stability.
7. Ease of manufacture.

They are of two types-ERODIBLE and NONER ODIBLE.

Erodible does not need removal from body tissues but they show variability in release kinetics from patient to patient as tear production and metabolic enzymes also vary. Thus non-erodible has reliability and erodible has convenience [6].

NONERODIBLE INSERTS

They are of two types

1. Ocusert
2. Contact Lens.

OCUSERT

Developed by ALZA Corporation. It is fat, flexible, elliptical device consisting of three layers.

The two outer layers of ethyl vinyl acetates (EVA) enclose the inner core of pilocarpine gelled with alginate.

An annual ring of EVA impregnated with Tio2 for visibility in handling and inserting the system, encloses the drug reservoir circumferentially. Release rate is 20 or 40 micro gram/hour for 7 days used in chronic glaucomas. Higher rate(40microgram)is achieved by making rate controlling membrane thinner and use of flux enhancer di(2-ethyl-hexyl)phthalate [7].

ADVANTAGES

Precise controlled rate (zero order) of delivery but dis advantages include patient comfort, placement and removal of insert leading to loss of system from eye. Smaller device are better retained and rod shaped are better than oval. Eg. Pilocarpine.

CONTACT LENS

Therapeutic soft lenses are used in corneal wound healing in infection or ulcers. but residence time is not prolonged in presoaked lens. Preservative benzalkonium chloride has toxic effect. Their problem is supply of oxygen and buildup of carbon di oxide in eye. Lens is improperly fitted.

Alternative approach to presoaking lens in drug solution is to incorporate drug as a solution or suspension monomer mix, then polymerize. Preservative need to be added.

ERODIBLE INSERTS

Many has been prepared and tested. Pilocarpine containing CMC wafer, PVA collagen containing Gentamicin etc. But only 3 are marketed to date [8].

1. Lacrisert.
2. SODI.
3. Minidisc.

LACRISERT

Rod shaped device made up of hydroxypropyl cellulose without preservative used for treatment of dry eye syndrome. Introduced by Merck, Sharp and Dohme in 1981.Weighs 5mg, measures 12.7mm in diameter, length is 3.5 mm used in keratitis sicca.

Inserted in to inferior for mix where it imbibes water from conjunctiva and cornea, forms hydrophilic film which stabilizes tear film and hydrates and lubricates the cornea. Patient acceptance is more than eye drops [9].

SOLUBLE OCULAR DRUG INSERT (SODI)

A small oval wafer from developed by soviet scientists for cosmonauts who could not use eye drops in weightlessness conditions. The unit is made from Acrylamide, N-Vinyl pyrolidone and ethacrylate designated as ABE.

Sterile oval films of 15-16 mg, when introduced in inferior cul-de-sac, wetted by tears, soften in 10-15 sec and become curved. In next 10-15 min the film turns into viscous polymer mass, then in 30-60 min polymer solution. Used in one day therapy of glaucoma [10].

OCULAR THERAPEUTIC SYSTEM OR MINI DISC

Bawa et al developed OTS which consists of a convex front and a concave back surface in contact with eye ball. It is like a miniature contact lens with 4-5 mm diameter. It is composed of a silicone based prepolymer they can be both hydrophilic and hydrophobic depending on the drug. Eg-drug Sulfixazole in hydrophilic matrix for 172hrs release. Gentamicin for 320 hrs.

NEW OPTHALMIC DELIVERY SYSTEMS (NODS)

Drugs are presented in a water soluble drug loaded film, i.e it is incorporated in water soluble PVA film or flag, which is attached to a handle film by a thin membrane. It is 50mm long, 6mm wide and flag is semicircular with area of 22mm2 and thickness of 20 micrometer and weight is 500 micro gram of which 40% may be drug. On contact with tears in inferior cul-de-sac, the membrane dissolves releasing the flag in tear followed by diffusion and absorption. Handle is provided with a paper backing for strength. Both soluble (pilocarpine) and insoluble (tropicamide) can be given as NODS.

NANOPARTICLES

Aqueous suspension of sparingly soluble drug in a finely divided particulate form often shows improved bioavailability. This can be achieved by manipulating the particle size.However this is true in case of water insoluble drugs. For water soluble drugs nanoparticles are used. They are of 10-1000 nm in size in which drug may be dispersed, encapsulated or absorbed.

They are prepared mainly by emulsion polymerization of polymers like poly alkyl acrylates. Nanoparticles of pilocarpine have shown 22-23% increase in miotic response. It has been shown that they are more effective in inflamed region of the eye [11].

LIPOSOMES

Liposomes are also used for ocular drug delivery.They have same advantages over other ocular delivery devices.

1. Controlls the rate of release of encapsulated drug.
2. Protects the drug from metabolic enzymes presents in tear, corneal epithelium interface.
3. Relatively non-toxic.
4. Biodegradable in nature.
5. Ability to form intionate contact with corneal and conjunctival surfaces so increase in absorption.
6. Nonirritant and do not obscure vision.
7. Surface properties can be altered to confer surface charges or ligands such as lecithin to improve adhesion to cell surfaces.

The phospholipids are commonly used are phosphatidycholine, phosphatidylserine, phosphatidic acid, sphingomyelins and cardiolipins. They are amphiphillic and hence can accommodate drugs with differing physicochemical properties. However results show that lipophillic drugs are best absorbed than hydrophilic ones. Exact mechanism is not understood—it may be by absorption, contact release, fusion, intermembrane transfer and endocytosis.

To enhance absorption mucoadhesive polymer coating (Eg. C 934, C1342 coating) are also used. Their

inherent advantages include
1. Short shelf life
2. Limited loading capacity.
3. Sterilization of preparation is difficult.

PRODRUGS

In ocular delivery systems prodrugs may be defined as simple, chemically or enzymatically liable derivatives of drugs which are converted to active parent drug by hydrolysis within the eye.
Prodrugs can be used to improve corneal permeability.
Also useful for poorly soluble and less stable drugs. drugs given as prodrugs are-
Epinephrine as dipivalyl epinephrine
Timolol as o-butyl timolol ester.
Methazolamide as tri fluoro methazolamide.
The concept of double prodrug (prodrug of a prodrug is also used to prolong the action) and also gaining importance. Eg-pilocarpine as bispilocarpates [12].

PENETRATION ENHANCERS

They are used to improve the bio availability. Preservative like benzalkonium chloride (0.01%) and chlorohexidine gluconate are potent agents. However prolonged administration show toxic effect like endothelial degeneration.

Another approach is the concept of ion pair formation. Eg. The extent and rate of corneal penetration of sodium chromoglycate, a dianionic drug was entered when ion paired with dodecyl benzyl methyl ammonium chloride [13].

TARGETING OF OCULAR DRUGS

Liposomes with specific properties are used for drug targeting to the ocular tissues without systemic side effects. Recent criteria of ocular DDS are not only to increase bio availability but also to decrease systemic absorption. Soft drugs approach is used.

Soft drugs are defined as biologically active drugs which are predictably metabolized to nontoxic moieties after achieving their therapeutic role. Eg. Beta blockers, anti microbials, anticholinergics.
Iontophoresis device is also used. In some inflammation topical application is of no use. Then intra corneal, intra vitreal administration are also used [14].

OCULAR DELIVERY OF PILOCARPINE

For nearly a century pilocarpine was the preferred ocular hypotensive agent used in glaucoma, obtained from pilocarpus jabarandi and p.microphyllus.

It is traditionally used at a conc of 4% in one or two drops every minute for five minute, every five minute for half an hour and a half. These seventeen doses deliver approx 40-80 mg to the eye. This dose is higher than the systemic level of 12 mg. Moreover patient compliance is less and thus management is erratic.
Low intra ocular drug bioavailability
-Potential side effects.
-Noncompliance led to the development of ocusert system [15].

BIOPHARMACEUTICS OF OCULAR PILO CARPINE ADMINISTRATION

Many factors that effect pilocarpine bioavailability of topically applied drugs are
1. The presence of lachrymal fluid in the cul- de-sac dilutes the drug solution instilled into the eye.
2. Efficient nasolacrimal drainage system acts as a drainage of drug from the precorneal area.
3. Protein present in eye may interact /degrade the drug.
4. Productive and nonproductive absorption of topically applied drug into various ocular tissues like cornea and conjunctiva.

PRECORNEAL DISPOSITION OF PILOCARPINE

It may take place by
1. Nasolacrymal drainage.
2. Tear turnover.
3. Productive corneal uptake.
4. Nonproductive corneal uptake.

Following instillation (50-70 micro lit)of PCP,80% loss as nasolacrymal drainage-80% drug is lost. After the volume returns to the normal resident tear volume of 7.5 micro lit –drug is diluted and absorbed by cornea and conjunctiva. Precorneal disposition follows 1st order kinetics. Less instillation volume shows increased bioavailability [16].

TRANSCORNEAL PERMEATION OF PILOCARPINE

Permeation may take place by
1. Lipophillic corneal epithelium partitioning.
2. Uptake through cornea.
3. Transport of PCP from cornea to anterior chamber by the corneal epithelium.
4. Pilocarpine depot in cornea.

The corneal barrier has epithelium which is lipoidal in nature; again for diffusion through deep ocular tissue-water solubility is required .Hence optimum partitioning is desired.

PCP is absorbed by cornea at 0.57 min and penetrates at0.08 min. Cmax is reached within5 min. Decline is in a biexponential manner, in cornea.

In aqueous humor Cmax is reached in 20 min and decline is by monoexponential manner [16].

EFFECTS OF PROTEIN BINDING ON PILOCARPINE BIOAVAILABILITY

Cornea contains 18.4% collagen, 0.15% albumin and globulin. Total protein content in aqueous humor is 0.01 to 0.02%.

Drug protein interaction produces a lag time for penetration of drug molecules into anterior chamber. Protein binding also affects drug bioavailability. The protein binding can be decreased by giving a competitive inhibitor for the protein along with PCP [17].

EVALUATION OF PILOCARPINE OCUSERT

A. Comparative pharmacological activities.

The hypotensive effect of ocusert compared with conventional 2% PCP eye drops in patients with open angle glaucoma or ocular hypertension.

The miotic activity action of eye drop is less than ocusert. The therapeutic effect is improved 8-10 times by ocusert.

Ocusert releases only a microdose (11mcg initially and 2-3 mcg at steady state), which is better than 1 mg of pilocarpine HCL delivered to conjunctival sac, in few seconds.

CONTINUOUS TREATMENT WITH OCUSERT SYSTEMS

Ocuserts can show prolonged and sustained continuous release up to 4 days per unit of pilo-20.dose is $1/4^{th}$ of eye drop. Advantages are patient compliance, less frequent dosing,4 days treatment, fewer ocular and systemic side effects. Some times higher strength ocusert may be required to show the same result [18].

COMPARATIVE TISSUE DISTRIBUTION

The distribution of PCP in various ocular tissues during ocusert treatment was compared in rabbits with conventional eye drop by using radio labeled pilocarpine. Low levels in iris and ciliary body seen in ocusert system. Eye drop showed 3-5 times more values in other tissues. Ocusert showed higher levels in conjunctiva, lens and vitreous humor and accumulation has also less [19].

COMPARATIVE PHYSIOLOGICAL EFFECTS

Continuous release of 20-80mcg/hr in rabbit eyes produced no effect on tear fluid. But pilocarpine in salt form as eye drop acidified the eye tears till 45-60 min after medication also. At this pH the drug is ionized and hence dose required increases. It is also seen that 30-60% patients fail to take pilocarpin eye drops as directed. As it causes miosis and myopia, discomfort and sometimes dis ability. But ocusert show less visual disturbance. Hence they are better.

REFERENCES

1. Novel drug delivery systems by Yie.w. Chien, 2nd ed, revised and expanded, Marceldekker Inc, 50, 269-300.
2. Controlled and novel drug delivery edited by NK Jain, 1st ed, CBS publishers and distributors, 82-96.
3. Controlled drug delivery –concepts and advances by SP Vyas and Roop Khar, Vallabh prakashan, 383-408.
4. Florence A & Jani PU. *Drug Safety*, 10, 1994, 233−266.
5. Florence AT, Hillery AM, Hussain N & Jani PU. *J. Control. Release*, 36, 1995, 39−46.
6. LeFevre ME, Olivo R, Vanderhoff JW & Joel DD. *Proc. Soc. Exp. Biol. Med*, 1978, 159, 298−302.
7. Lefevre ME, Joel DD & Schidlovsky G. *Proc. Soc. Exp. Biol. Med.*, 179, 1958, 522−528.
8. Jani P, Halbert GW, Langridge J & Florence AT. *J. Pharm. Pharmacol*, 41, 1989, 809−812.
9. Jani P, Halbert GW, Langridge J & Florence AT. *J. Pharm. Pharmacol*, 42, 1990, 821−826.
10. Hillery AM, Jani PU & Florence AT. *J. Drug Target*, 2, 1994, 151−156.
11. Bockman DE & Cooper MD. *Am. J. Anat.* 136, 1973, 455−478.
12. Akers MJ, Lach JL & Fischer LJ. *J. Pharma. Sci.* 62, 1973, 391−395.
13. Goodman LS & Gilman A. The Pharmacological Basis of Therapeutics, Macmillan, New York, 1975.
14. Tutwiler GF, Kirsch T & Bridi G. *Diabetes*, 27, 1978, 856−867.
15. Wolff JA *et al., Biotechniques*, 11, 1991, 474−485.
16. Lau C *et al., Hum. Gene Ther*, 6, 1995, 1145−1151.
17. Domb A, Mathiowitz E, Ron E, Giannos S & Langer R. *J. Polym. Sci*, 29, 1991, 571−579.
18. Wolff JA. *et al., Science*, 247, 1990, 1465−1468.
19. Lee SW, Trapnell BC, Rade JJ, Virmani R & Dichek DA. *Circ. Res*, 73, 1993, 797−807.