



A COMPARATIVE REVIEW ON CONVENTIONAL AND ADVANCED OCULAR DRUG DELIVERY FORMULATIONS

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ABSTRACT: Amongst the various routes of drug delivery, the field of ocular drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientist for past 10-20 years¹. As an isolated organ, eye is very difficult to study from a drug delivery point of view. Despite these limitation, improvements have been made with the objective of maintaining the drug in the biophase for an extended period.² Within the last few years, in response to the advent of potent and versatile therapeutic agents, the diversity of conventional ophthalmic formulations has gradually evolved, extending well beyond simple solutions, suspensions and ointments, now includes a variety of types of drug administration. In most recent publications, authors have broadened the notion of conventional ophthalmic delivery systems to encompass more than simple solutions and suspensions. While not strictly 'conventional', the ready availability of several commonly used drug vehicles suggests they have achieved acceptance, have been elevated to the category of conventional, and will be considered in this comparison. In this article, we have summarized the different types of commonly used ophthalmic formulations and compared the conventional formulations with the advanced formulation in many respects like their applicability, acceptance, characteristics and utility. This should also serve to put into perspective the discussions of more sophisticated components and elaborations.

Keywords: Ocular drug delivery; Conventional formulation; SODI, Ocusert, Collagen Shields, Ocufit, Minidisc and NODS

INTRODUCTION

Amongst the various routes of drug delivery, the field of ocular drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientist. The usefulness of this route of drug administration can be easily appreciated because the drug enters the systemic circulation circumventing the hepatic first pass effect³.

Advantages of controlled ocular drug delivery systems:

1. Increased accurate dosing. To overcome the side effects of pulsed dosing produced by conventional systems.
2. To provide sustained and controlled drug delivery.

3. To increase the ocular bioavailability of drug by increasing the corneal contact time. This can be achieved by effective adherence to corneal surface.
4. To provide targeting within the ocular globe so as to prevent the loss to other ocular tissues.
5. To circumvent the protective barriers like drainage, lacrimation and conjunctival absorption.
6. To provide comfort, better compliance to the patient and to improve therapeutic performance of drug.
7. To provide better housing of delivery system.

Despite some severe limitations, significant improvements in ocular drug delivery have been made. The improvements have been with objective of maintaining the drug in the biophase for an extended

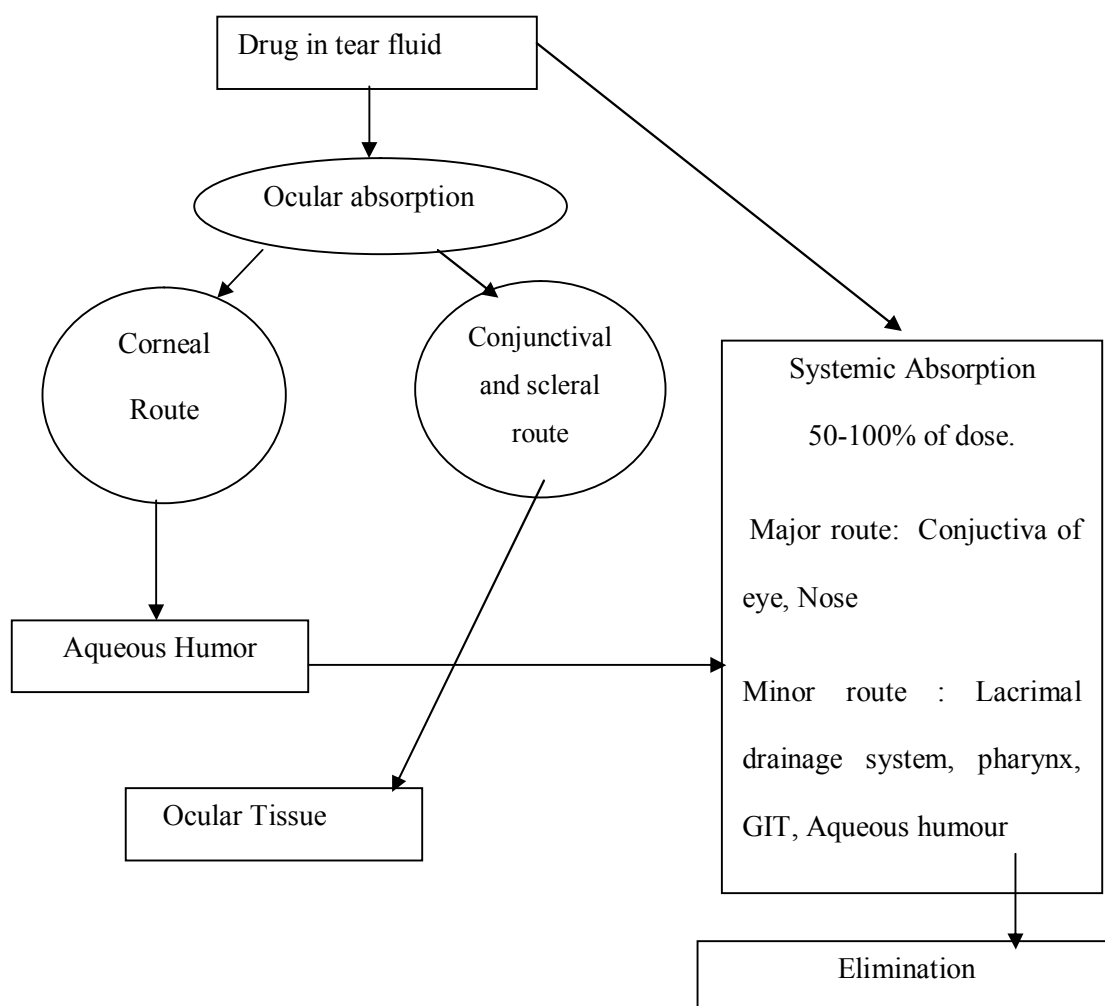
period. The anatomy, physiology and biochemistry of the eye render this organ impervious to foreign substances⁴.

Physiological barriers of ophthalmic drug delivery systems

- ❖ Physiological barriers to diffusion and productive absorption of topically applied drug exist in the precorneal and corneal spaces. The precorneal constraints responsible for poor ocular bioavailability of conventional ophthalmic dosage forms are solution drainage, lacrimation, tear dilution, tear turnover and conjunctival absorption⁵.
- ❖ Drug solution drainage away from the precorneal area has been shown to be the most significant factor in reducing the contact time of the drug with the cornea and consequently ocular bioavailability of topical dosage forms.

- ❖ The instilled dose leaves the precorneal area within 2 minutes of installation in humans. The ophthalmic dropper delivers 50-75 μl , of the eye drops. If the patient does not blink, the eye can hold about 30 μl , without spilling on to the cheek.
- ❖ The natural tendency of the cul-de-sac is to reduce its volume to 7-10 μl ⁶. However, most of the drug is rapidly lost through nasolacrimal drainage immediately following dosing. The drainage allows the drug to be absorbed across the nasal mucosa into the systemic circulation. The conjunctiva also possesses a relatively large surface area, 5 times the surface of cornea making the loss significant. Both conjunctival and nasal mucosa has been indicated as the main potential sites for systemic absorption of topically applied drugs.

Corneal barrier Limitation for topically administered drug



Mechanism of controlled sustained drug release into the eye:

- ❖ The corneal absorption represents the major mechanism of absorption for the most conventional ocular therapeutic entities.
- ❖ Passive Diffusion is the major mechanism of absorption for non-erodible ocular insert with dispersed drug.
- ❖ Controlled release can further be regulated by gradual dissolution of solid dispersed drug within this matrix as a result of inward diffusion of aqueous solution.

The existing ocular drug delivery systems are thus fair and inefficient. The design of ocular system is undergoing gradual transition from an empirical to rational basis; Interest in the broad areas of ocular drug delivery has increased in recent years due to an increased understanding of a number of ocular physiological processes and pathological conditions. The focus of this review is the approaches made towards optimization of ocular delivery systems

1. Improving ocular contact time
2. Enhancing corneal permeability
3. Enhancing site specificity⁷

Ophthalmic drug product may be classified according to route of administration.

1. Topical
2. Intraocular
3. Systemic (oral and venous).

Absorption of drugs in the eye takes place either through corneal or non-corneal route.

Maximum absorption takes place through the cornea, which leads the drug into aqueous humor. Loss of the administered dose of drug, takes place through spillage and removal by the naso-lacrimal apparatus.

The non corneal route involves the absorption across the sclera and conjunctiva into the intra ocular tissues.

CONVENTIONAL OCULAR DRUG DELIVERY SYSTEMS:

I Liquid Viscous Solutions:

1. Viscosity improver:

In order to prolong precorneal residence time and to improve bioavailability, attempts were made to increase the viscosity of the formulation. The viscosity enhancers used were hydrophilic polymers such as cellulose, polyalcohol and polyacrylic acid. Sodium carboxy methyl cellulose is one of the most important mucoadhesion polymers having good adhesive strength⁸. The effects of polyacrylic acid and polyacrylamide based hydrogels are tested on miotic response of pilocarpine. Carbomer were used in liquid and semisolid formulations as suspending or viscosity increasing agents. Formulations including creams, gels and ointments were used as ophthalmic products⁹. Polycarbophil is water insoluble cross linked

polyacrylic acid helps in the retention of the drug delivery system in the eye due to the formation of hydrogel bonds and mucoadhesive strength. Hyaluronic acid offers a biocompatible and biodegradable matrix for fabrication of ocular sustained release dosage forms. Films and microspheres were also prepared from hyaluronic acid. Polysaccharide such as xanthan gum was found to increase the viscosity¹⁰. Today, hydrophilic polymers continue to be used in formulation of numerous ophthalmic products for bioadhesion rather than viscosity enhancement. Viscosity vehicles increase the contact time and no marked sustaining effect is seen.

2. Gels :

Gel formation is an extreme case of viscosity enhancement through the use of viscosity enhancers. So the dosing frequency can be decreased to once a day¹¹. Cellulose acetate phthalate dispersion constituted a micro-reservoir system of high viscosity. Poloxamer 407 is used as an ophthalmic vehicle for pilocarpine delivery and found that the gel formation enhances the activity of pilocarpine¹². Timolol maleate form thermo gelling drug delivery system composed of cellulose ether ethylhydroxyethylcellulose¹³. The effect of flurbiprofen, a non steroidal anti inflammatory drug, formulated in carbopol 940 and pluronic F 127 hydrogels were compared in ocular hypertension. Gelrite is a polysaccharide (gellan gum), which forms a clear gel in the presence of mono or divalent cation. The high viscosity of the gel, however, results in blurring of vision and malting eyelids which substantially reduce patient acceptability. Sterilization is another drawback for large-scale production,

3. Penetration enhancers:

They act by increasing corneal uptake by modifying the integrity of corneal epithelium. Chelating agents, preservatives, surfactants and bile salts were studied as possible penetration enhancers. But the effort was diminished due to the local toxicity associated with enhancers¹⁴. Penetration enhancers have also been reported to reduce the drop size of conventional ophthalmic solutions especially if they do not elicit local irritation.

4. Prodrugs:

Prodrugs enhance corneal drug permeability through modification of the hydrophilic or lipophilicity of the drug. The method includes modification of chemical structure of the drug molecule, thus making it selective, site specific and a safe ocular drug delivery system. Drugs with increased penetrability through prodrug formulations are epinephrine, phenylephrine, timolol, pilocarpine¹⁵

5. Cyclodextrins:

Cyclodextrins act as carriers by keeping the hydrophobic drug molecules in solution and delivering them to the surface of the biological membrane, where the relatively lipophilic membrane has a much lower affinity for the hydrophilic cyclodextrin molecules, therefore they remain in the aqueous vehicle system. Optimum bioavailability can be achieved when enough cyclodextrin (< 15%) is added to the aqueous eye drop solutions to solubilise the lipophilic water insoluble drug¹⁶. But increased concentration will result in decrease in bioavailability.

6. Bioadhesive polymers:

The bioadhesive polymers adhere to the mucin coat covering the conjunctiva and the corneal surfaces of the eye, thus prolonging the residence time of a drug in the conjunctival sac¹⁷. These polymers can be neutral, synthetic or semi synthetic. Polyacrylic acid, polycarbophil and hyaluronic acid are synthetic polymers commonly used. Chitosan is a bioadhesive vehicle suitable for ophthalmic formulation since it exhibits general biological properties such as biodegradability, nontoxicity and biocompatibility. Due to its positive charge at neutral pH, ionic interaction with the negative charges of sialic acid occurs. Xanthan and carrageenan are also described as bioadhesive polysaccharides¹⁸.

Enhancement in controlled drug-delivery:

It is realized that the preferred system of ophthalmic delivery would provide improved bioavailability, site-specific delivery and with continuous drug release. So achievements have been made in the following areas:

1. In situ forming gels:

The progress has been made in gel technology for the development of droppable gel. They are liquid upon instillation and undergo phase transition in the ocular cul-de-sac to form visco-elastic gel and this provides a response to environmental changes¹⁹. Three methods have been employed to cause phase transition in the eye surface. These are change in pH, change in temperature and ion activation.

i.pH:

In this method, gelling of the solution is triggered by a change in the pH. CAP latex cross linked polyacrylic acid and its derivatives such as carbomers are used. They are low viscosity polymeric dispersion in water which undergoes spontaneous coagulation and gelation after instillation in the conjunctival cul-de-sac²⁰.

ii.Temperature:

In this method gelling of the solution is triggered by change in the temperature. Sustained drug delivery can

be achieved by the use of a polymer that changes from solution to gel at the temperature of the eye. But disadvantage of this is characterized by very high polymer concentration²¹. Methyl cellulose and smart hydrogels are the examples.

iii.Ionic strength:

In this method, gelling of the solution instilled is triggered by change in the ionic strength. For example, Gelrite is a polysaccharide, low acetyl gellan gum, which forms a clear gel in the presence of mono or divalent cations. The concentration of sodium in human tears is 2.6 g/l is particularly suitable to cause gelation of the material when topically installed into the conjunctival sac.

2. Oil in water emulsions:

Phospholipids and pluronics were used as the emulsifiers. Antioxidants were added to improve their shelf-life. The intra-ocular pressure reducing effect of a single, topically administered dose of a pilocarpine emulsion lasted for 29 h in rabbits compared to generic pilocarpine solution which lasted only for 5 h²². Oil in water emulsion is useful for delivery of water insoluble drugs, which is solubilised in the internal oil phase.

3. Colloidal particles:

The potential use of polymeric colloidal particles as ophthalmic drug delivery systems started in late 1970's. The first two systems studied in this area were pilocarpine cellulose acetate hydrogen phthalate latex systems and piloplex. But both the system could not enter commercial development because of various issues, like local toxicity, non-biodegradable polymer and large scale sterilization.

ADVANCED OCULAR DRUG DELIVERY SYSTEMS:

Films, erodible and non-erodible inserts, rods and shields are the most logical delivery systems aimed at remaining for a long period of time in front of the eye. From a therapeutic point of view, inserts have been a success in the improvement of accurate dosing, drug bioavailability and by the reduction of systemic absorption, and consequently side effects. Inserts dissolve and/or erode on contact with the ocular surface and therefore need to be used in addition with other artificial tears to initiate the dissolving process. Considering the various mucoadhesion mechanisms, hydration or degree of swelling of the polymers plays an important role. In the case of dry or partially hydrated dosage forms, water movement from the mucus layer to the formulation can be a significant factor in mucoadhesion, being more important than molecular interpenetration. Hydrophilic polymers with poor mucoadhesive properties may be added to a mucoadhesive polymer with poor swelling

characteristics to ensure fast swelling. Some additional polymers can hinder the formation of bonds between the mucoadhesive polymer and mucus by preferentially binding to the hydrated mucoadhesive polymer. There is also a reduction in the strength of the bond between the mucoadhesive polymer and mucin.

I. Non Erodible Insert:

i. Ocular Insert:

Consequently numerous ophthalmic drug delivery systems were developed to achieve a higher bioavailability of drug. Among the formulations of in-situ gelling polymers microspheres, nanoparticles, liposomes and ocular inserts, which are solid devices placed in the cul-de-sac of the eye are numerous

Although the advantage of precise controlled rate of delivery has been achieved with a number of disadvantages such as patient comfort, placement and removal of insert which may lead to inadvertent loss of system from the eye. Smaller devices are better retained than larger ones and rods shaped are better retained than oval ones²³.

ii. Hydrogel contact lenses

The first and most widely used contact lens material is poly (2-hydroxy ethyl methacrylate) (HEMA), cross linked with small amount of ethylene glycol dimethacrylate (EGDMA). Depending on their composition & amount of hydroxyl groups and degree of cross linking, these amount of polymers can absorb up to 80% of water.

II. Erodible Insert

i. Soluble Ophthalmic Drug Insert (SODI)

The soluble ophthalmic drug insert is together with the collagen shields and gelatin "Lamellae" which disappeared from pharmacopoeias in the late forties. Drug release from SODI's does not show vehicle control, and produces a prolonged-pulse entry of drug. It has been reported to replace 4-12 drops instillations or 3-6 applications of ointment. It is in the form of sterile thin films of oval shape weighing 15 to 16mg. After the introduction in the inferior cul-de-sac where wetted by the tear film, it softens in 10-15 seconds and assumes the curved configuration of the globe²⁴.

ii. Collagen shields

Collagen is the structural protein of bones, tendons, ligaments and skin and comprises more than 25% of the total body protein in mammals. Collagen shields have been used in animal model and in humans (eg. Antibiotics, antiviral etc.,) or combination of these drugs often produces higher drug concentration in the cornea and aqueous humor when compared with eye drops and contact lens

iii. Mini disc or Ocular therapeutic system (OTS)

The OTS consists of contoured disc with a convex front and a concave back surface in the contact with

the eyeball. It is like a miniature contact lens with a diameter of 4-5 mm. The OTS can be hydrophilic or hydrophobic to permit extended release of both water soluble and insoluble drugs²⁵.

iv. Ocufit SR:

Ocufit SR is a sustained release, rod shaped device made of silicon elastomer patented in 1992²⁶. It is designed to fit the shape and size of the human conjunctival fornix. Accordingly, it does not exceed 1.9 mm in diameter and 25-30 mm in length, although smaller sizes for children and newborn babies are planned. The superiority of the cylindrical shape can perhaps be traced to an earlier paper by Katz and Blackman, reporting on the effect of the size and shape of the inserts on tolerance and retention by human volunteers²⁷. These workers found that expulsion of rod shaped units was significantly ($p < 0.01$) less frequent than expulsion of oval, flat inserts. A typical example of a rod-shaped insert is the Lacrisert, a cellulosic device used to treat dry-eye patients.

Particulate systems:

i. Liposomes: They may be multilamellar vesicles or unilamellar depending upon the number of concentric alternating layers of phospholipids and aqueous phases. They can be prepared by sonication of dispersion of phospholipids, reverse phase evaporation, solvent injection, detergent removal or calcium induced fusion²⁸. Liposomes were also evaluated in an attempt to improve bioavailability of ophthalmic drugs after topical instillation, because they are stable, biocompatible and biodegradable liquid preparations. The potential of liposomes in ocular drug delivery is limited by their rapid clearance from the precorneal area. The same rapid drainage was observed as for aqueous eye drops, especially in the case of neutral liposomes and negatively charged liposomes. Positively charged liposomes on the other hand were reported to exhibit a prolonged precorneal retention, because of electrostatic interaction with the negatively charged corneal epithelium. It is proposed that these liposomes bind intimately on the eye surface, increase the residence time and thus enhance drug absorption. Accumulation of drug in the cornea could occur by endocytosis of the liposomes. In order to enhance adherence to the corneal/conjunctival surface, dispersion of the liposomes in mucoadhesive gels or coating the liposomes with mucoadhesive polymers was proposed. Several mucoadhesive polymers were employed are poly (acrylic acid) (PAA), hyaluronic acid (HA), chitosan, poloxame²⁸. In order to prolong the residence time at the site of administration, to increase efficacy, and to protect the oligonucleotides from degradation, the oligonucleotides were encapsulated in liposomes and dispersed in a thermo sensitive gel. Polymer concentration and the nature of the liposomes influence the release.

ii.Nanoparticles

Nanoparticles are the particulate drug delivery system 10 to 1000nm in size in which the drug may be dispersed, encapsulated or absorbed. The rationale for the development of various particulate systems for the delivery of ophthalmic drugs was based on possible entrapment of the particles in the ocular mucus layer and the interaction of bioadhesive polymer chains with mucins inducing a prolonged residence, and slow drainage. Furthermore, controlled drug release and enhanced absorption or even endocytosis in the case of nanoparticles should improve bioavailability. Biologically active materials can be incorporated into carriers or absorbed on the surface of the nanoparticle²⁹. Aqueous suspensions, one of the conventional ophthalmic formulations contain a sparingly soluble drug in a finely divided particulate form which is suspended in saturated solution of the drug. The drugs particulate as well as solution portion of the suspension are drained into the lachrymal systems on instillation of the suspension leaving behind some of the suspended drug particles. The suspension approach shows improved drug bioavailability by manipulation of particle size only for water insoluble drugs.

iii. Prodrugs

In the present context, prodrugs are simple, chemically or enzymatically liable derivatives of drugs which are converted to their active parent drug typically as a result of hydrolysis within the eye. Most ophthalmic drugs contain functional groups such as alcohol, phenol, carboxylic acid and amine that lend themselves to derivatization. The modification of chemical structure of the drug centers on changing the physiochemical properties of drugs such as lipophilicity, solubility and p^{Ka} . Prodrug technology is generally considered as a useful technique in improving corneal permeability of drugs. It is also useful in solving pharmaceutical formulation problems such as poor solubility and stability. The only commercially available prodrug is dipivalyl epinephrine.

iv.New Ophthalmic Delivery System:

The NODS originally patented by Smith and Nephew pharmaceuticals Ltd., is a method of delivering the drug to the eye with in water soluble, drug loaded film. It provides for accurate, reproducible dosing in an easily administered preservative free form. The drug is incorporated into a water soluble polyvinyl alcohol film. Each NODS consists of a drug loaded film or (flag) attached to a handle film by means of thin membrane. The NODS is approximately 50 mm in length, 6 mm in width, the flag is semicircular in shape

and has an area 22 mm² and a thickness of 20μm and a total weight of 500 μg of which 40% can be drug. On contact with the tear film in the lower conjunctival sac, the membrane quickly dissolves releasing the flag into the tear film.

CONCLUSION

The conventional drug delivery formulations such as viscosity improver, penetration enhancers prodrugs, cyclodextrins, bioadhesive polymers have a wide range of acceptance because of the creation of good patient psychology about the formulations, price factor - cheaper in cost, self medication is also possible-no need for the experts, irrespective of having several drawbacks like loss of drug by tear and lachrymal fluid, need of frequent administration and poor bioavailability.

The advanced drug delivery devices such as Ocular Insert, SODI, Collagen shields, Mini disc, Liposomes, Microspheres, Nanoparticles and Prodrugs, in spite of their advantages demonstrated by extensive investigations and clinical tests, have not gained a wide acceptance by ophthalmologists. At this moment, the Ocuser systems are the only medicated inserts marketed in estern countries, and the acceptance of these devices has been far from enthusiastic. According to recent information, the NODS project will not be further developed. As said before, the commercial failure of inserts has been attributed to psychological factors, such as the reluctance of ophthalmologists and patients to abandon the traditional liquid and semi-solid medications, to price factors and to occasional therapeutic failures (e.g., unnoticed=expulsion from the eye, membranerupture,etc.).The manufacturers of ocular dosage forms appear to show a continued preference for dropper-dispensed medications. Many drugs already in use have been reformulated in new longer acting liquid dosage forms,such as an '*insitu*' gelling preparation of timolol. Still, the prolonged, constant-rate release pattern achievable by inserts of the Ocuser and Ocufit type can be considered as the most desirable condition for long term therapy, both because of efficacy as well as the reduction of ocular and systemic side-effects. Shorter-acting devices might prove useful for single application after intraocular surgery or other conditions. Although at this time the advantages of newer solid ocular dosage forms are understood and appreciated, marketing strategies prevent their further commercialization, unless, of course, their potential use could be extended to applications other than long-term glaucoma or trachoma treatment, or short-term medication after ocular surgery

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