

CURRENT TRENDS IN NOVEL OPHTHALMIC DRUG DELIVERY SYSTEM: AN OVERVIEW

Sidra Farooq, Mirza Yasir Hussain and Syed Muhammad Farid Hassan

Department of Pharmaceutics, Faculty of Pharmacy, University of Karachi, Main University Road, Karachi
Email: sidra.farooq@live.com

ABSTRACT

One of the most daring tasks faced by the pharmaceutical researchers is the ophthalmic drug delivery. Their aim is to achieve and sustain a therapeutic level at the site of action for extended period of time. Therefore, to withstand drug levels at the target site for a sufficient time, novel drug delivery techniques are developed. Ophthalmic drug delivery route has seen significant advancement for future perspective. This article reviews various novel systems for ophthalmic drug delivery.

Keywords: Colloidal Carriers, Dendrimers, *In-Situ* Gels, Iontophoresis, Ophthalmic Inserts, Prodrugs.

INTRODUCTION

Novel drug delivery systems are new in the market and are the modifications of previous ones in terms of unique delivery systems or unique devices, which are to be used before during or after administration. The existing therapies are diminishing because of the development of new technologies. New drug delivery systems increase the extent and persistence of a drug in the vicinity of target cells and minimize the drug contact of non-target cells, thus boosting the therapeutic effects of a drug and reducing its toxic effects (Allen *et al*, 2005). One of the most confronting routes of delivery for the pharmaceutical researchers is ophthalmic drug delivery (Rajasekaran *et al*, 2010).

The conventional drug delivery systems as solutions, suspensions and ointments have poor ocular bioavailability i.e. less than 1%, because of various factors which cause fast tear turnover, less absorption, short dwelling time in the culdesac and relatively impermeable drugs (Sabitha *et al*, 2012).

The administered dose up to 80% may be lost by tears and nasolachrymal drainage within 5 minutes of administration. Formulations that may increase the contact period of drug with corneal exterior may use to extend period of therapy and this is achieved by the use of viscosity enhancers, by using ophthalmic solutions in which medication dissolve slowly or use of ophthalmic inserts (Allen *et al*, 2005). Ideality of ophthalmic drug delivery is that it sustains the drug release and provides longer contact with the front of the eye (Patel *et al*, 2010). The aim of the novel ophthalmic drug delivery is to enhance drug bioavailability by facilitating the transcorneal drug penetration or/and to ensure a prolonged retention time of the medication in the eye (Babizahayev, 2009). The topical ocular drug delivery has been improved from eye drops to ophthalmic iontophoresis, in situ gels, dendrimers, penetration enhancers, ocular inserts, mucoadhesive polymers, hydrogels and targeted drug delivery systems (Singh *et al*, 2011).

The objective of this paper is to briefly review the novel techniques for ophthalmic drug delivery so that the pharmaceutical researchers get the concept of the latest trends regarding this aspect.

Ophthalmic inserts

The solid devices placed in the conjunctival sac and provide slow drug delivery are called ophthalmic inserts (Babizahayev, 2009).

Classification

Classification of Ophthalmic Inserts established upon their solubility behaviour (Kumar *et al.*, 2012).

- A. Insoluble Inserts
 - a. Reservoir System
 - i. Diffusional Inserts
 - ii. Osmotic Inserts
 - b. Matrix System

- i. Contact Lenses
- B. Soluble Inserts
 - a. Based on Natural Polymers
 - b. Synthetic or Semi-synthetic Polymers

Non Erodible Insert, Erodible Insert (Kumaran *et al.*, 2010)

- A. Non Erodible Insert
 - a. Ocular Insert
 - b. Hydrogel Contact Lens
- B. Erodible Insert
 - a. SODI
 - b. Collagen Shield
 - c. Minidisc OTC
 - d. Ocufit SR

Insoluble Ocular Inserts

Reservoir systems

The drug is released either by osmosis or diffusion by the reservoir systems which contain a liquid, gel, colloid, semisolid, carrier containing drug or a solid matrix. The carriers are made of various polymers such as hydrophilic, hydrophobic, organic, natural or synthetic.

Diffusional insert or ocusert

Diffusional insert is based on porous membrane and the drug release is based on mechanism of diffusional release.

Osmotic insert

The osmotic insert comprise of a peripheral part which surrounds the central part.

Matrix systems

They are represented by contact lenses mainly which are composed of hydrophilic or hydrophobic polymers that are covalently cross linked and forms a three dimensional matrix network which retains water, solid components or aqueous drug solution (Kumar *et al.*, 2012).

Contact lenses

Absorption by contact lenses of water soluble drugs in drug solutions is achieved by soaking and is used to achieve sustain drug release and for this purpose hydrophilic contact lenses are used (Patel *et al.*, 2010).

Soft hydrogel contact lenses were developed to achieve prolonged drug release (Kumar *et al.*, 2012).

Subdivision of Contact Lenses (Kumar *et al.*, 2012)

- a) Rigid Lenses
- b) Elastomeric
- c) Semi-rigid
- d) Soft Hydrophilic
- e) Biopolymeric

Types of Polymeric Hydrogels

Types of Polymeric Hydrogels for Contact-Lens-based Novel Ophthalmic drug delivery system (Xinming *et al.*, 2008):

- a. Polymeric hydrogels for conventional contact lens to absorb and release ophthalmic drugs.
- b. Polymeric hydrogels for piggy-back contact lens binding with a drug plate or a drug solution.
- c. Molecularly imprinted polymeric hydrogels.
- d. Ion ligand-containing polymeric hydrogels
- e. Polymeric hydrogels for insertion of drugs in a colloidal structure dispersed in the lens.

f. Surface- modified polymeric hydrogels to deactivate drugs on the surfaces of contact lenses. In the veterinary patients, treatment of ocular surface and anterior segment can be achieved by specialized drug eluting contact lenses , that has proved to be beneficial (Weiner *et al.*, 2010).

Soluble Ocular Inserts

They don't need removal from the site of application because they offer the advantage of solubility, therefore they limit the intervention to insertion only (Kumar *et al.*, 2012).

Classification of Soluble Ophthalmic Inserts (Kumar *et al.*, 2012).

- a) Natural Polymers e.g. Collagen
- b) Synthetic Polymers e.g. Cellulose Derivatives
- c) Semi-synthetic Polymers e.g. Polyvinyl Alcohol

Various types of ophthalmic inserts are summarized in Table 1.

Table 1.Types Of Ophthalmic Inserts.

Reference	Type	Description
(Thakur and Kashiv, 2011), (Kumaran <i>et al.</i> , 2010).	SODI (soluble ophthalmic drug insert)	They are oval, sterile, thin films that weigh 15-16 mg.
(Bisht <i>et al.</i> , 2011)		It is like a small wafer which softens on insertion. It comprises of soluble copolymers which consist of acryl amide, N-vinyl pyrrolidone and ethyl acrylate.
(Thakur and Kashiv, 2011)	NODS (New ophthalmic delivery system)	The drugs are administered to the eye in the form of film which is loaded with water soluble drug. It is preservative free and it provides accurate and reproducible dosing, water soluble polyvinyl alcohol film incorporates the drug.
(Kumar <i>et al.</i> , 2012)	Collagen shields	It is erodible disc which consist of scleral collagen that is cross linked porcine.
(Patel <i>et al.</i> , 2010)	Artificial tear insert	It is used for the management of dry eye disorder, also called Lacrisert. It is a rod shaped pellet that is designed as artificial tear and provides sustained release. It is made up of hydroxy propyl cellulose and doesnot contain preservative.
(Kumar <i>et al.</i> , 2012)	Ocusert	Insoluble flat flexible device consisting of 2 layers in which a reservoir is enclosed. Commercially, it is used to deliver pilocarpine for seven days.
(Thakur and Kashiv, 2011)	BODI (Bio adhesive ophthalmic drug inserts)	They belong to soluble inserts group which are made up of synthetic and semisynthetic polymers.
(Kumaran <i>et al.</i> , 2010)	Hydrogel contact lenses	Their water absorbance is upto 80% which depends on their constitution, amount of hydroxyl groups, and extent of cross-linkings.
(Kumar <i>et al.</i> , 2012)	Minidisc OTC (ocular therapeutic system)	It is a monolytic device which is shaped like a miniscule polymeric contact lens. Its breadth is 4-5mm. with a convex and concave face. The concave face conforms to the eye sclera.
(Kumaran <i>et al.</i> , 2010)		The OTS provides delayed release of water-soluble and water-insoluble drugs because it may be hydrophilic or hydrophobic.
(Giudice and Galan, 2012)	Non biodegradable implants	It has non biodegradable polymers coating. It is reservoir type and exhibits the most long lasting release profile of drug because it reserves a large drug amount.

(Weiner and Gilger, 2010)	Biodegradable implants	They provide sustained drug release after being placed in the lower conjunctival sac.
(Giudice and Galan, 2012)		processing of this can be into nanoparticles, rods, discs or tablets and many varieties of configurations. As a result they stabilize the drug release profile, as well as shorten the drug release duration because the drug contained is limited.
(Kumar <i>et al.</i> , 2012)	Bio erodible ocular inserts	These comprise of bioerodible polymers such as derivatives of cross linked gelatin and polyester which undergo dissolution and chemical bonds hydrolysis.
(Kumar <i>et al.</i> , 2012)	Ocufit S.R.	It is a rod- shaped device made of silicone elastomer and provides sustained drug release.
(Kalyanwat <i>et al.</i> , 2011)	Non erodible inserts	They are non biodegradable. They have greater reliability because they are easily detected when expelled. They have better drug release kinetics.
(Kumaran <i>et al.</i> , 2010).		Non erodible ocular inserts have dispersed drug so the major mechanism of absorption is passive diffusion.
(Kumar <i>et al.</i> , 2012)	Erodible inserts	The polymer is fabricated as hydrophobic but is biodegradable. Drug is released as a result of surface erosion of the insert. After intended drug delivery period, they don't need removal.

RECENT STUDIES

Malaekheh-Nikouei *et al* (2013) prepared a sequence of imprinted and non-imprinted hydrogels by using 2-Hydroxy Ethyl Methacrylate as a mainstay monomer, Ethylene Glycol Dimethacrylate (EGDMA) being a cross-linker monomer, Methacrylic Acid (MAA) being the functional monomer & Dorzolamide (DZD) being the template molecule. The authors concluded that the use of appropriate co-monomer, and employing a molecular imprinting technique had prominent influence on loading & releasing properties of hydrogels.

Peng *et al* (2012) compared the effectiveness of timolol via contact lens to eye drops in beagle dogs that suffered from impulsive glaucoma. Experiments were conducted with Night & Day Silicone Hydrogel contact lens and Night & Day loaded with Vitamin-E, which was included in the lens to extend the drug release duration. The authors concluded that the ophthalmic drug delivery through Contact Lens increases bio-availability and reduces systemic drug uptake.

Sindhumol and Chandran (2011) formulated sodium cromoglycate ophthalmic inserts using hydroxy propyl methyl cellulose and gelatin as polymers by solvent casting method with aim of compliance and greater therapeutic efficacy. The prepared ocular inserts were then evaluated. In vitro release studies of formulated ocuserts were performed. The authors concluded that the formulation of ophthalmic inserts containing sodium cromoglycate and HPMC(1:2) seems to be promising.

Gupta and Gilhotra (2011) formulated brimonidine tartrate ophthalmic inserts exploiting HPMC, chitosan, PVA, & Sodium Alginate via Solvent Casting method. The equipped inserts were then evaluated. The authors concluded that the chitosan- based Brimonidine ocular insert could be a prospective vehicle to enhance ocular bio-availability & patient defiance.

Shanmugam *et al* (2011) prepared ocular inserts holding Acyclovir exploiting Solvent Casting method. The Drug reservoir and rate-controlling-membrane were prepared depleting different hydrophilic & hydrophobic polymers respectively with polyethylene glycol-400 as plasticizer. The prepared inserts were evaluated. The authors concluded that the developed formulation was stable, sterile & non-irritant.

Rajasekaran *et al* (2010) studied that the ocular drug-delivery system for Natamycin, which is a polyene anti-biotic is amply useful for the treatment of conjunctivitis & keratitis. They prepared ocuserts by using different polymers at various proportion and combinations. They evaluated prepared ocuserts. The authors concluded that the Natamycin ocuserts demonstrate controlled-drug release with ultimate sterility & stability.

Molokhia *et al* (2010) developed a novel intra-ocular implant for the delivery of drug. The ring of capsule drug is a reservoir which is introduced in the lens capsule during the cataract surgery, re-usable and capable of multiple drug delivery and the drug of interest in this study was Avastatin. Prototypes were fabricated. The device established nearly zero-order-release kinetics and the authors investigated the stability of Avastin with accelerated-temperatures studies.

Ramkanth *et al* (2009) prepared diclofenac sodium ocuserts by using different polymers such as HPMC, HPC, MC and EC at diverse concentrations and combinations by using dibutyl phthalate as plasticizer. They prepared ocuserts by means of Solvent-Casting method and then evaluated them. The authors concluded that the formulation has accomplished the targets of present study as prolonged zero-order-release, increase in contact time, reduction in administration frequency and therefore improves patient compliance.

Advantages of Ophthalmic Inserts

- They provide increased contact time better bioavailability and prolonged drug release.
- They provide better efficacy as well as administration of exact dose in the eye.
- They are sterile, stable without preservatives and provide reduced systemic and adverse effects with increased shelf life due to absence of water.
- They are advantageous on account of their compliance, effortlessness of handling and insertion, lack of explosion, reproducibility of release kinetics as well as non-interference with oxygen-permeability and vision (Kumar *et al*, 2012).
- Example of implantable systems that deliver sustained drug release to the eyes include membrane controlled, implantable infusion and implantable silicon devices and systems. Silicon rubber balloon with antineoplastic agent is evaluated as an eg. of implantables for management of ocular cancer (Zaki *et al*, 2012).
- Non biodegradable implants and inserts are the clinically successful cases that have been recently developed in intraocular delivery systems to enable effective ocular drug delivery (Yasukawa *et al*, 2011).
- A new hope for the fungal dermatitis patients is the concept of intracorneal insert (Bisht *et al*, 2011).

Disadvantages Of Ophthalmic Inserts

- Immediate loss of the insert or the device may be dislocated in front of the pupil.
- If the insert twists, it forms a figure eight, therefore the delivery rate diminishes and a leakage may occur (Kumar *et al*, 2012).

Colloidal Carriers

They are successful drug carriers for ophthalmic applications. The significant absorption of drug in comparison with eye drops owe to the slower elimination rate of particles in the ocular region. Smaller particles have better tolerance by the patients as compared to larger particles; therefore nano-particles may represent very promising ophthalmic delivery systems providing extended action (Kumar *et al*, 2011). Colloidal carriers may emerge as an alternative and substantially improve the current therapy, following their periocular administration (Tiwari and Shukla, 2010).

Types of Colloidal Carriers (Tiwari *et al.*, 2010).

- a) Nanoparticles
- b) Niosomes
- c) Liposomes
- d) Microparticulates
- e) Nanosuspension
- f) Microemulsion

RECENT STUDIES

Sabitha *et al* (2012) developed and evaluated moxifloxacin containing nanoparticles as potential ophthalmic drug delivery system. Nanoparticles were prepared and characterised. The *in vitro* release profile of moxifloxacin from the nanoparticles and the dispersion was observed. The authors concluded that moxifloxacin loaded chitosan nanoparticles appear promising for effective management of ocular conjunctivitis infections.

Table 2. Types of Colloidal Carriers.

Reference	Colloidal Carriers	Description
(Kumaran <i>et al.</i> , 2010)	Liposomes:	The amount of concentric alternating layers of phospholipids & aqueous phases decide that the liposome is either unilamellar or multilamellar.
(Tiwari and Shukla, 2010)	Nano Particles	They have breadth of less than 1 micrometer consisting of innumerable biodegradable or non-biodegradable polymers, lipids, phospholipids or metals. Nano-particles can be classified as nano-capsules or nano-spheres, depending upon whether the drug has been uniformly dispersed or has been coated with a polymeric material.
(Mythri <i>et al.</i> , 2011)	Bioadhesive Nano-polymers	The contact of bio-adhesive polymer chains with mucin and the prospective entrapment of particles in the mucus layer of ocular surface are the basis of the development of particulate systems for ophthalmic drug delivery.
(Tiwari and Shukla, 2010)	Micro particulates	Micron sized polymeric particles that contain the drug and are suspended in a liquid medium, or the drug can be dispersed in a polymer backbone physically.
(Talegaonkar <i>et al.</i> , 2008)	Microemulsions	They have 20-200nm droplet size usually, and are isotropic, transparent, translucent, thermodynamically stable system of oil, surfactant and water.
(Babizahayev, 2009)		They appear as clear transparent dispersions and comprise of larger swollen micelles that contain the internal phase.
(Alagusundaram <i>et al.</i> , 2009)		E.g. Polyanhydride microspheres, polyadipic acid.
(Tiwari and Shukla, 2010)	Niosomes	The irritation power of surfactants declines in the following order: Cationic > Anionic > Ampholytic > Non-ionic, therefore the nonionic surfactants are preferred. Niosomes are a suitable delivery system for hydrophilic and lipophilic drugs both.
(Katteboinaa <i>et al.</i> , 2009)	Nanocrystals	The mean diameter of pure solid drug nanocrystals is below 1000 nanometer.
(Tiwari and Shukla, 2010)	Nanosuspensions:	Nano-suspensions are inert in nature and mostly comprise of colloidal carriers such as polymeric resins.
(Hari <i>et al.</i> , 2012)	Dendrimers	Dendrimers are the macromolecules or nanosized, radially symmetric molecules having repeated tree like arms or branches, having well defined homogenous and monodisperse structure and they can resolve the increasing challenges of newly developed drugs such as bioavailability, permeability and poor solubility.

Han *et al* (2010) developed a cubosomes based novel vehicle as an ophthalmic drug delivery system for flurbiprofen to ease ocular aggravation and increase bioavailability. They prepared cubosomes loaded with flurbiprofen via homogenization through hot and high pressure. The authors concluded that cubosomes based low irritant novel vehicle might be a capable technique for efficient ocular delivery.

Advantages

- Liposomes are stable, bio-compatible, and bio-degradable liquid preparations; therefore they improve the bio-availability of ophthalmic drugs after topical administration (Kumaran *et al*, 2010).
- Nanoparticles after being topically administered are retained in the culdesac to provide sustained release of drug and prolonged therapeutic activity, because the entrapped drug is released at appropriate rate from the particles. Nanosuspensions are nonirritant and help in drug solubility enhancement and bioavailability.

- Micro particulates can be administered topically as an eye drop thus providing better patient acceptability (Tiwari and Shukla, 2010).
- By the use of nanoparticles, the surface area of drugs is increased per mole of the drug compound which increases tissue exposure and absorption (Weiner and Gilger, 2010).

Disadvantages

- Major issues for colloidal carriers involve dispersed phase percentage/ problem of entrapment coefficient i.e the amount of active ingredient present in a drop of the final product.
- Stability, shelf-life and anti-microbial preservation.
- Tolerance of surfactants that are used.
- Bulk manufacture of sterile preparations (Thakur and Kashiv, 2011).
- By the use of nanoparticles, the drug surface area is increased per mole of drug compound, which increases tissue exposure and absorption (Weiner and Gilger, 2010).

Iontophoresis

The method which is minimally invasive and has ability to propel charge compounds i.e. low m.wt. drugs, high m.wt. biological proteins (less than 14 kDa) into ocular tissues is called iontophoresis (Weiner and Gilger, 2010). A slight electric current is required to improve the ionized drug penetration into the tissues. E.g. OcuPhor system designed for trans-scleral iontophoresis is designed with a dispersive electrode, dose controller and an applicator.

Advantages

- Iontophoresis drug delivery can overcome the potential side-effects caused by intra-ocular implants and injections (Tiwari and Shukla, 2010).
- Fungal keratitis, retinitis, uveitis, retino-blastoma, proliferative-vitreous-retinopathy and several retinal degenerations are the diseases that may benefit by ocular iontophoresis (Weiner and Gilger, 2010).

Disadvantages

- If improperly used there is a possibility of burns, and pains due to excessive current density, therefore iontophoretic delivery is limited clinically for brief drug delivery period applications.
- For iontophoretic delivery, ionic form of drug in sufficient concentration is necessary. Due to high molecular weight 8000-12000, uncertain delivery rate results (Nikam *et al*, 2011).

In Situ Gels

In situ gels change in certain physicochemical parameters like temperature, ionic concentration or pH thus reveal transition of sol-to-gel phase on the ocular surface (Vodithala *et al.*, 2010).

Various Approaches of In-Situ-Gelation

Types of Systems in In-Situ Gelation (Rathore, 2010).

- a) pH Triggered system
- b) Solvent Exchange Induced Gelation
- c) Ion Activated Systems
- d) UV Induced Gelation
- e) Temperature Dependant Systems

RECENT STUDIES

Vodithala *et al* (2010) formulated and evaluated the *in-situ* ocular gelling systems (ion-activated-gelling systems) of Ketorolac Tromethamine, which involve the use of Gelrite as polymer. The formulations were evaluated and ex-vivo –corneal permeation studies carried out. The authors found that the developed

formulation showed sustained release of drug for upto 6h, and concluded that the formulation was found to be non-irritating with no ocular damage.

Hiremath *et al* (2008) prepared and evaluated ophthalmic drug delivery system of linezolid based on novel *in-situ* gum. The authors used Hydroxypropyl guar and xanthum as gum with the amalgamation of viscosity enhancing agents like carbopol, hydroxyethyl cellulose and sodium alginate. Appropriate dilution of buffering agents were used for pH adjustment to 7.4 and the evaluation and sterilization of the formulations was done. The authors found that the formulations were soothing with no ocular harm or unusual clinical indication to the iris, cornea or conjunctiva, and concluded that gums holding *in-situ* gelling systems may be a beneficial substitute to the conventional systems.

Varshoaz *et al* (2008) increased the low bioavailability and short ocular residence time of ciprofloxacin eye drops. They prepared aqueous solutions of drug in chitosan/ Pluronic (poloxamer). Mixtures of solutions of Pluronic (10-25% w/w) with chitosan (0.1-0.3% w/w) of different molecular weights (Mw) were prepared. Ciprofloxacin release was determined. The rheological behavior, phase change temperature (PCT) and anti-microbial effect of the solutions was studied. The authors found that this *in situ* gel released the drug by a Higuchi model and Fickian mechanism, it was liquid in non-physiologic conditions and transferred to the gel form upon physiologic conditions and they concluded that the PCT of this *in situ* gel did not change upon dilution and the zone of inhibition of both studied bacteria was significantly greater for it than the marketed eye-drop of ciprofloxacin.

Advantages

- Patient compliance, reducing frequency of administration and easy to instill.
- Good stability and biocompatibility characteristics (Kumar *et al*, 2011).
- The drug remains for longer period at the desired site due to increased contact time of the drug to the tissue (Kumar *et al*, 2011).
- Less blurred vision than ointments (Champalal *et al*, 2012).
- Provides sustained drug release due to increased residence time (Hiremath *et al*, 2008).

Disadvantages

The gels have open pore structure that does not extend the duration of drug beyond a few hours because gels are water predominantly (Weiner and Gilger, 2010).

Prodrugs

Prodrugs are chemically or enzymatically liable, simple derivatives of drugs, which as result of hydrolysis in the eye, are converted to their active parent. Functional groups such as phenol, alcohol, amine and carboxylic acid are present in most ophthalmic drugs and lend to derivatization. By changing the physico-chemical properties of drugs, the chemical structures are modified.

Advantages

- Prodrug technique improves corneal permeability of drugs.
- Problems related to pharmaceutical formulations such as stability and poor solubility (Kumaran *et al*. 2010).

Disadvantages

- After it reaches the site of action, the metabolism of the prodrugs is not controlled and the toxicity concerns can't be ruled out completely.
- As a result of reactive intermediate, the adverse drug reaction can possibly occur (Ramaa *et al*, 2008).

CONCLUSION

In this review, we have discussed some of the novel techniques for ophthalmic drug delivery. Numerous approaches and carriers are used in this regard, like *In-situ* gelling, Ophthalmic Inserts, Nanoparticles, Liposomal formulation, Dendrimers, Prodrugs and Ocular Iontophoresis. Conventional

ophthalmic formulations like eyedrops have less retention time in the ocular cavity, and less than 10% of the administered dose could cross the membrane. Therefore, to satisfy the need, novel drug delivery systems have been developed to improve the delivery of a therapeutic agent.

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