

OCULAR DRUG DELIVERY: RECENT UPDATES

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REVIEW ARTICLE

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DOI: <https://doi.org/10.22270/ijdra.v4i4.190>

ABSTRACT

Ophthalmic route is one of the most promising delivery systems for the treatment of eye ailments. Delivery of medicaments to anterior segment of the eye is an easy task. However with the rising number of posterior segment diseases such as diabetic retinopathy, age-related macular degeneration etc. delivery to the target has become a challenging task. A number of scientists have tried various approaches to accomplish the objective. Novel drug delivery system is an effective strategy to combat anterior and posterior eye ailments. In addition, the technique improves the pharmaceutical and pharmacological performance of the drug molecule. The advent of nanotechnology and its use in devising newer and effective ocular systems has added impetus to ocular therapy. However the need of the hour is to create stable as well as non-toxic systems which are able to be used for chronic therapies. The role of various novel delivery stratagem such as nanoparticles, nanomicelles, liposomes, niosomes, dendrimers in ocular drug delivery has been discussed in addition to their recent advances in the area.

Keywords: Novel Drug Delivery, Ocular, Nanoparticles.

INTRODUCTION

Ophthalmic route is one of the most promising delivery systems for treatment of eye ailments. Most of the conventional ocular delivery systems include eye drops which has gained wide attention due to patient compliance, easy scale-up, stability and cost effectiveness. However reflux blinking leads to drainage of the drug, and less than 5% of the drug is bioavailable, therefore longer contact time is required so that the drug residence is increased.(1) This was achieved by increasing the viscosity of the formulation by using suitable gelling agents such as hydroxymethyl cellulose, sodium carboxy methyl cellulose, hydroxy ethyl cellulose and polyalcohols.(2) The preparation of eye ointments was another step in this regard. In spite of these approaches, the formulation could not overcome precorneal loss. Topical instillation is an easy approach for topical delivery of medicaments (anti-inflammatory drugs, intra-ocular pressure decreasing anti-glaucoma drugs) to the anterior portion. But for the drug to reach to the posterior portion of the eye becomes a challenging task. Drugs used for the treatment of glaucoma, antibiotics and corticosteroids

have to reach the posterior segment of the eye for adequate therapeutic action. Posterior segment ocular diseases such as diabetic retinopathy, age-related macular degeneration have been on the rise. Some scientists have claimed that administration of high doses by intravitreal injection to posterior sites can be an effective approach. Similarly systemic delivery have also been tried to target the drug to posterior portion. (3) However, with rising incidence of side effects patient compliance cannot be ignored. In order to develop a suitable delivery system one should be able to comprehend the various challenges in ocular delivery-

1. Drug drainage from ocular region- The lachrymal turnover rate is 1 μ l/min, therefore the lachrymal fluid washes the drug to the nasolacrimal duct within a couple of minutes. Additionally the drug can flow from the conjunctival sac to the capillaries and reach the systemic circulation. The small molecular weight drugs are particularly prone to this problem. The nasolacrimal drainage is one of the main reasons for reduced bioavailability.

2. Corneal epithelium barrier- The corneal epithelium is made up of epithelial cells which

comprises of tight junctions that hinders paracellular transport of drug molecules. Despite of tightness, due to the lipophilic nature of this layer, hydrophobic drugs can easily permeate through this barrier. Therefore, delivery of hydrophilic drugs becomes a challenging task.

3. Blood ocular barrier- it is a physical barrier that separates the local blood capillaries with the parts of eye usually comprising of iris or retina. Blood ocular barrier can be further subdivided into anterior blood aqueous barrier and posterior blood retina barrier.

Blood aqueous barrier- This barrier is composed of endothelial cells. It prevents the transport of albumin and hydrophilic drugs from plasma to aqueous humor. In disease state, the barrier may become inflamed and the permeability can be compromised.

Blood retina barrier- It is consist of retinal pigment epithelium and retinal capillaries. However, unlike the anterior capillaries, these are highly leaky and easily allows the drugs to reach the choroidal extravascular space. In spite of easy permeability the drug cannot reach the retina because of limited distribution of capillaries into retina.

The presence of blood ocular barrier makes the systemic delivery of drugs to posterior portion of the eye a daunting task, unless specific targeting techniques are applied^[1]. There have been many advances in the area of posterior drug delivery, nanotechnology being one of them.

ROLE OF NANOTECHNOLOGY IN OCULAR DRUG DELIVERY

With the advent of nanotechnology based ocular delivery systems, precise and safe drug delivery to the target site have become possible. Nanotechnology based delivery systems can be

Table 1: Nanomicelles in ocular drug delivery

Drug	Polymers/Surfactants	Result	Reference
Dexamethasone	polyhydroxyethylaspartamide [PHEAC(16)] and pegylated PHEAC(16)	40% higher bioavailability compared to dexamethasone suspension	(7)
LacZ gene	poly (ethylene oxide)-poly (propylene oxide)-poly	Effectively transferred plasmid DNA to rabbit and mice ocular	(8)

explored for both anterior and posterior segment drug delivery. On understanding the various barriers as mentioned previously, it is imperative that we outline the major objectives in ocular drug delivery-

To enhance the permeation of drug

To provide controlled release of the drug from the formulation

To target the drugs to the posterior portion of the eye. (4)

Since the formulation has to bypass various barriers comprising of tight junctions, appropriate particle size is of immense significance. Additionally the formulation should be non-irritant, satisfactorily bioavailable ensuring not more than 2 administrations per day, compatible with ocular tissues and use minimum preservatives. (5) The nano-delivery systems have been able to successfully circumvent problems like poor solubility, poor stability by encapsulating the drug within the polymers/lipids and provide controlled release. Furthermore, hydrophilic drugs can be coated with various lipids as in case of liposome, solid lipid nanoparticles and maintain adequate HLB to facilitate permeation of drugs through ocular membranes. (6) Additionally various targeting moieties can be attached to the nanoparticles so that the delivery system reaches the posterior segment of the eye.

Nanomicelles

Nanomicelles are nano-sized carrier systems made up of amphiphilic monomer units. They can be surfactant or polymer based and encapsulate hydrophobic drugs. Nanomicellar formulation have gained tremendous interest because of ease of preparation, high drug payload, enhanced bioavailability of therapeutic moieties. Some recent studies conducted on nanomicelles in ocular area have been summarized in Table 1.

	(ethylene oxide) copolymer (PEO-PPO-PEO)	tissues.	
Dexamethasone and rapamycin	-	Delivered therapeutic concentrations to posterior segment	(9)

Nanoparticles

Nanoparticles are composed of proteins, lipids and natural and synthetic polymers such as PLGA, PLA, chitosan, sodium alginate etc. The

typical size range of nanoparticles is 10-100nm. The various studies on nanoparticles in the area of ocular delivery has been summarized in Table II.

Table 2: Recent updates on the use of nanoparticles on ocular drug delivery

Drug	Polymer	Result	Reference
Carboplatin	Chitosan, sodium alginate	Nanoparticles showed enhanced antiproliferative activity	(10)
5-fluorouracil	Chitosan coated sodium alginate nanoparticles	Coated NP showed increased drug concentrations in aqueous humor compared to uncoated NP and drug solution	(11)
Brimonidine tartarate	Sodium alginate	Prolonged drug release for 8 hours	(12)
Levofloxacin	PLGA	47.43% drug was permeated across cornea in 4h compared to 36.9% in marketed formulation	(13)
Pilocarpine	PLGA	Mitotic response increased by 40%	(14)
Gatifloxacin/ Prednisolone	Eudragit RS 100 and RL 100, coating with hyaluronic acid	1.76 fold enhanced bioavailability compared to eye drops	(15)
Sparfloxacin	PLGA	Nanoparticles were retained for longer duration on corneal surface compared to aqueous solution	(16)
Pranoprofen	PLGA	Good entrapment efficiency (80%) with sustained release profile and negligible irritation	(17)

Nanosuspensions

Nanosuspensions are submicron colloidal particles stabilized by surfactants or polymers. It is a promising strategy to improve the solubility/bioavailability of hydrophobic drugs in tear fluids. (4) Nanosuspensions also have the

capability to prolong the release of drug. Other advantages offered by the carrier system for use in ocular delivery are ease of sterilization, minimal irritation and augmented precorneal residence time. (18) Nanosuspensions has been used as a carrier system for various ocular drugs (table 3).

Table 3: Nanosuspensions as a carrier system for various ophthalmic drugs

Drug	Result	Reference
Prednisolone	Improved bioavailability compared to solution	(19)
Hydrocortisone	Higher AUC values, 28.06 ± 4.08 and 30.95 ± 2.2 $\mu\text{g/mL}$ for nanosuspensions prepared by precipitation and milling method when compared to solution (15.86 ± 2.7 $\mu\text{g/mL}$).	(20)

Ketotifen fumarate	Nanosuspension prepared by Eudragit RL polymer showed higher drug release and permeability through bovine cornea when compared to PLGA nanosuspension.	(21)
dexamethasone acetate and polymixin B	The formulation improved the saturation solubility of the drug. The cationic nature of the excipients offered mucoadhesion and increased residence time in the eye	(22)
Sparfloxacin	Chitosan nanosuspension prolonged the drug of Sparfloxacin upto 9h as compared to 6h for HPMC nanosuspension	(23)
Moxifloxacin	PLGA nanosuspensions showed enhanced antibacterial activity against <i>S. aureus</i> and <i>P. aeruginosa</i>	(24)
pilocarpine nitrate	Nanosuspensions prepared using Eudragit RL 100 showed sustained release effect for 24 hr	(25)
Dexamethasone	N-isopropylacrylamide, vinyl pyrrolidone and methacrylate nanosuspensions prepared in the presence of N,N-methylene bis-acrylamide showed better mucoadhesiveness and anti-inflammatory activity compared to aqueous suspension of drug.	(26)
Sulfacetamide	40% encapsulation efficiency with good stability was achieved by preparing nanosuspension using Eudragit® RL100	(27)

Liposomes

Liposomes are amphiphilic vesicular carrier systems prepared using phospholipids and cholesterol. Liposomes have gained a lot attention in ophthalmic delivery because of their biocompatibility and ability to target both

anterior and posterior segment of the eye. Additionally due to their amphiphilic nature they can encapsulate both hydrophilic and lipophilic drugs. Studies have shown that positively charged liposomes have higher binding affinity to the cornea due to electrostatic interaction.(28) (Table 4).

Table 4: Liposomes in Ocular drug delivery

Drug	Result	Reference
Acetazolamide	Significant reduction in iop	(29)
Latanoprost	Reduced iop with sustained effect for 50 days	(30)
Acyclovir	80 ng/mL of drug was absorbed from positively charged liposomes compared to 45ng/mL and 30 ng/mL from negatively charged liposomes and aqueous solution in aqueous humor	(31)
Fluconazole	Half-life of drug was increased by 8 times	(32)
Tacrolimus	Drug concentration in vitrea was 50 ng/mL with sustained effect for 14 days	(33)
Ciprofloxacin	Mean residence time was increased by three fold when compared to Ciprocin	(34)
Diclofenac	Drug concentration in retina-choroid was increased by 1.8 times compared to diclofenac solutin	(35)
Timolol maleate	Chitosan coated liposomes reduced the iop (19.67±1.14 mmHg) compared to timolol eye drops (23.80±1.49 mmHg). The formulation showed improved mucoadhesion and 3 times better permeability through cornea.	(36)
Flurbiprofen	Significantly enhanced permeation and pre-corneal retention	(37)

	time by chitosan coated deformable liposomes compared to conventional liposomes and drug solution	
Brinzolamide	The formulation reduced iop to 5mmHg compared to drug suspension(10mm Hg) in New Zealand rabbits	(38)
Distamycin A	Improved uptake by the cornea and bioavailability in the tear fluid	(39)
Voriconazole	Improved anti-fungal activity from species isolated from corneal keratitis	(40)

Niosomes

Niosomes are non-ionic surfactant vesicles similar to liposomes. Niosomes are preferred over liposomes in topical ocular delivery because of ease in handling and flexibility.

Further, the vesicle systems are non-toxic, biodegradable and biocompatible. The niosome delivery system can be modified accordingly by adding suitable excipients to maximize therapeutic efficacy i.e. discosomes, spanlastics, ultra deformable niosomes (Table 5).

Table 5: Various vesicular delivery systems in the area of ocular drug delivery

Drug	Formulation	Result	Reference
Terconazole	Ultra-deformable bilosomes	The formulation showed 90% entrapment efficiency and superior drug flux through rabbit cornea compared to niosomes, bilosomes and drug suspension	(41)
Itraconazole	Spanlastics	1.34 times increase in the amount of drug permeated through excised bovine cornea after 24 hrs compared to niosomes. Increased anti-fungal activity (p<0.05)	(42)
Lomefloxacin Hcl	Niosomes	Improved anti-bacterial activity and higher bioavailability (4-fold) compared to commercial product	(43)
Tacrolimus	Hyaluronic acid coated niosomes	The modified niosomes showed enhanced mucoadhesion to mucin and 2.3 times and 1.2 times better bioavailability compared to suspension and noncoated niosomes, respectively.	(44)

Dendrimers

Dendrimers are nanosize polymeric macromolecular compounds (1-10nm) that can be highly branched or star shaped. The terminal functional group in dendrimers can be functionalized for targeting. The added

advantage of easy preparation and the ability to incorporate both hydrophilic and hydrophobic drug renders it a suitable delivery system in ocular therapeutics. (45) Because of these advantages dendrimers have also been explored for ocular therapeutics (Table 6).

Table 6: Use of dendrimers in ocular drug delivery

Drug	Polymer	Result	Reference
Dexamethasone	Poly (amidoamine)	Enhanced permeation of formulation through ocular tissues	(46)
Ciprofloxacin	piperazine core 1,3,5-triazine	Improved anti-bacterial activity	(47)
Triamcinolone acetonide	Poly (amidoamine)	100 fold improvement in anti-inflammatory activity	(48)

Acetazolamide	Poly (amidoamine)	Significant reduction in iop	(49)
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FUTURE PERSPECTIVES

Treatment of ocular chronic diseases has always remained a challenge for the health practitioners and the patients alike. The advent of nanotechnology and its use in devising newer and effective ocular systems has added impetus to ocular therapy. However the need of the hour is to create stable as well as non-toxic systems which are able to be used for chronic therapies. The futuristic system is essentially be needed to be equipped with better efficacy, controlled release, non-toxic and also cost effective.

ACKNOWLEDGEMENT

The authors would like to acknowledge the support of Jamia Hamdard and the editorial team at 'International Journal of Drug Regulatory Affairs' for their valuable inputs in the making of this manuscript.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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