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OCULAR DRUG DELIVERY SYSTEM: A NOVEL APPROACHES

Sonali*, Mohd. Aqil Siddiqui, Amresh Gupta, Arpita Singh, Swarnima Pandey and Nitish Kumar

Goel Institute of Pharmacy and Sciences Lucknow, Uttar Pradesh, India 226028.

***Corresponding Author: Sonali**

Goel Institute of Pharmacy and Sciences Lucknow, Uttar Pradesh, India 226028.

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ABSTRACT

This technique has been a major challenge for scientists due to its unique anatomy and physiology which contains various types of barriers such as different layers of cornea, sclera, retina including the blood-aqueous and blood–retinal barriers, choroidal and conjunctival blood flow, etc. To overcome these problems various types of dosage forms such as nanoparticles, nano micelles, liposomes, and micro-emulsions have been developed. Also, therapeutic drug levels are not maintained for a longer duration in target tissues. Last few decades, ocular drug delivery research accelerated advanced towards developing novel, safe, and patient compliant formulation and drug delivery devices/techniques, which may surpass these barriers and maintain drug levels in tissues. There are many eye ailments that affected the eye and one can lose eyesight also. Therefore, many ophthalmic drug delivery systems are available. It divided into two types one is conventional and another is non-conventional drug delivery systems. Generally, available ophthalmic preparations are eye drops and ointments about 70% of the eye dosage formulations in the market.

INTRODUCTION[1-13]

Ocular drug delivery has remained one of the most challenging tasks for pharmaceutical scientists. The structure of the eye restricts the entry of drug molecules at the required site of action. Traditional, technique like eye drops, suspensions, and ointments cannot be considered optimal in the treatment of vision-threatening ocular diseases. A topically applied drugs is washed off from the eye by various mechanisms (lacrimation, tear dilution, and tear turnover) resulting in low ocular bioavailability of drugs. Moreover, the human cornea comprising of epithelium, substantia propria, and endothelium also restricts the ocular entry of drug molecules. As a result of these factors, less than 5% of the administered drug enters the eye. Ideal ophthalmic drug delivery must be able to release the drug in a sustained manner and to remain in the area of the front of the eye for prolong period of time. As a result, it is necessary to optimize ophthalmic drug delivery; the best way to do so is by adding polymers of various grades, development of colloidal suspension or using the drug in suitable type of dosage form, upon erodible or non-erodible insert, development of viscous gel to prolong the precorneal drug retention. First modifications to conventional forms of ophthalmic drugs were introducing polymers to formulation, which enabled longer contact time of active ingredient and the corneal surface, thus increasing its bioavailability. The next possibility to modify the ophthalmic forms of active ingredients 'bioavailability involved introducing excipients to the formulation, which enhanced drugs' penetration into the eyeball. The excipients like, chelating agents, surfactants, and cyclodextrins, which, along with active ingredients, form inclusion complexes. This increases the solubility, permeability, and bioavailability of poorly soluble drugs. Few newer, sensitive and successful ocular delivery systems like inserts, biodegradable polymeric systems, collagen shields are being developed in order to attain better ocular bioavailability and sustained action of ocular drugs.

The following recent trends are in vogue

a) Mucoadhesive dosage forms
b) Ocular inserts
c) Collagen shields
d) Drug presoaked hydrogel type contact lens and pledges
e) Ocular iontophoresis
f) Phase transition systems
g) Microspheres and nanoparticles
h) Chemical delivery systems vesicular systems.

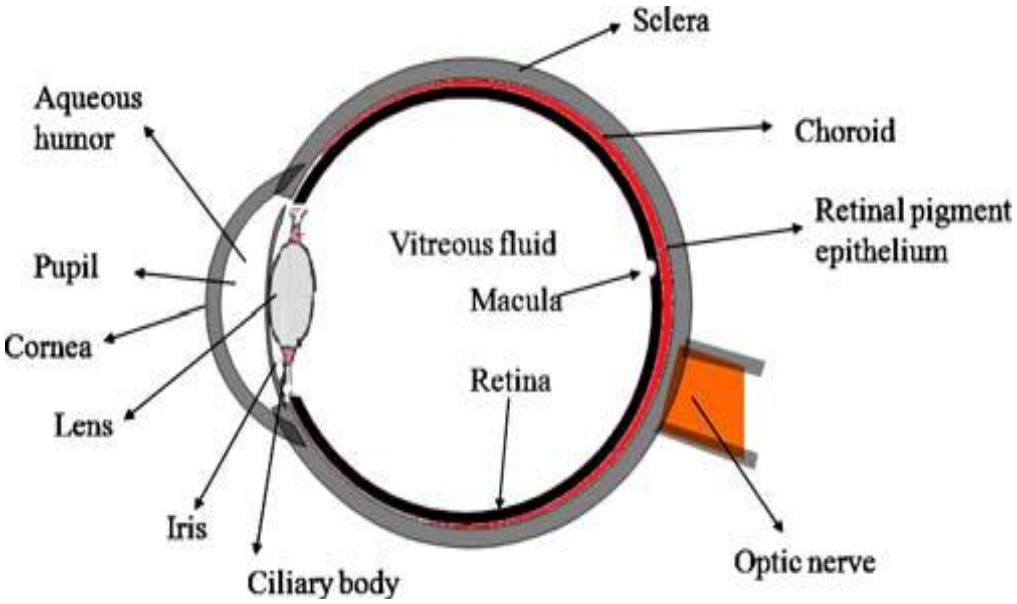

Fig. 1: Structure of Eye.

DELIVERY ROUTES[14-22]

Traditionally, many ocular diseases are treated with either topical or systemic medications. Topical application of drugs has remained the most preferred method due to ease of administration and low cost. A fraction of drugs following topical administration is lost by lacrimation, tear dilution, nasolacrimal drainage, and tear turnover. Typically, less than 5% of the total administered dose reaches aqueous humor. Upon topical instillation, drugs are absorbed either by corneal route (cornea → aqueous humor → intraocular tissues) or non-corneal route (conjunctiva → sclera → choroid/RPE). Unlike topical administration, systemic dosing helps in the treatment of diseases affecting the posterior segment of the eye. A major drawback associated with systemic administration is only 1–2% of administered drug reaches to the vitreous cavity. This method involves the injection of drug solution directly into the vitreous via pars plana using a 30 G needle. Unlike other routes, intravitreal injection offers higher drug concentrations in the vitreous and retina. Elimination of drugs following intravitreal administration depends on their molecular weight. Though intravitreal administration offers high concentrations of drugs in the retina, it is associated with various short-term complications such as retinal detachment, endophthalmitis, and intravitreal hemorrhages. Periocular refers to the region surrounding the eye. It is a broad term that includes peribulbar, posterior juxta scleral, retrobulbar, sub-tenon, and subconjunctival routes. Sclera which is made up of fibrous tissue offers less resistance to the permeability of drugs. The study concluded that administration of drug via sub tenon injection resulted in the highest and sustained vitreous concentration of sodium fluorescein compared to retrobulbar and subconjunctival routes. These include a rise in intraocular pressure, cataract, hyphemia, strabismus, and corneal decompensation.

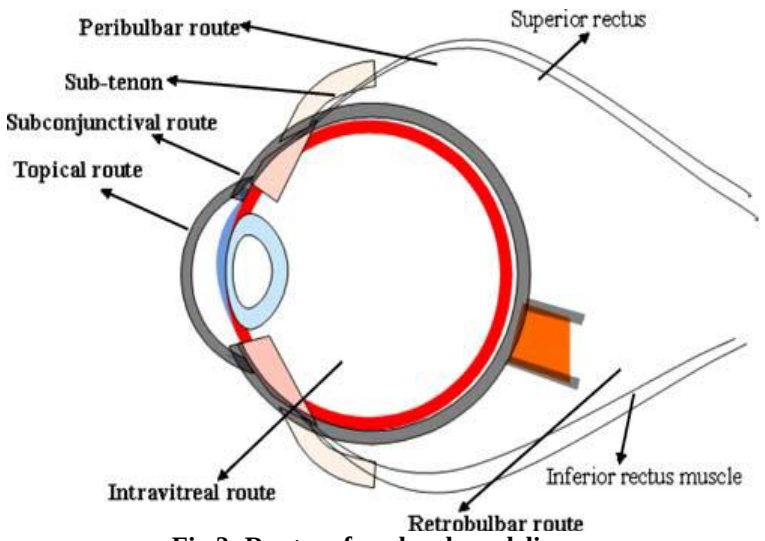

Fig.2- Routes of ocular drug delivery.

ADVANTAGES OF OCULAR DRUG DELIVERY SYSTEMS[23-30]

1. Increased accurate dosing
2. To provide sustained and controlled drug delivery.
3. To increase the ocular bioavailability of the drug by increasing the corneal contact time. This can be achieved by effective adherence to the corneal surfaces.
4. To circumvent the protective barriers like drainage, lacrimation, and conjunctival absorption.
5. To provide comfort, better compliance to the patient, and to improve therapeutic performance of the drug.
6. To provide better housing of the delivery system.
7. Easy convenience and needle-free drug application without the need of trained personnel assistance for the application, self-medication, thus improving patient compliances compared to parenteral routes.
8. Good penetration of hydrophilic, low molecular weight drugs can be obtained through the eye.
9. Rapid absorption and fast onset of action because of large absorption surface area and high vascularization. Ocular administration of the suitable drugs would therefore be effective in emergency therapy as an alternative to other administration routes.
10. Avoidance of hepatic first-pass metabolism and thus the potential for dose reduction compared to oral delivery.

LIMITATION

Various disadvantages of the ocular drug delivery system are given below.

1. The physiological restriction is the limited permeability of the cornea resulting in low absorption of ophthalmic drugs.
2. A major portion of the administered dose drains into the lacrimal duct and thus can cause unwanted systemic side effects.
3. The rapid elimination of the drug through the eye blinking and tear flow results in a short duration of the therapeutic effect resulting in a frequent dosing regimen.

NOVEL OCULAR DRUG DELIVERY SYSTEMS[31-32]

Nanotechnology based ocular drug delivery

In a last few decade, many approaches have been utilized for the treatment of ocular diseases. These technologies based ophthalmic formulations are one of the approaches which is currently being pursued for both anterior, as well as posterior segment drug delivery. It based systems with an appropriate particle size can be designed to ensure low irritation, adequate bioavailability, and ocular tissue compatibility. Several nanocarriers, such as nanoparticles, nanosuspensions, liposomes, nano micelles and dendrimers have been developed for ocular drug delivery.

Nano micelles[33-34]

Nano micelles are the most commonly used carrier systems to formulate therapeutic agents in to clear aqueous solutions. In general, these nano micelles are made with amphiphilic molecules. Recently, reviewed in detail about ocular barriers and application of nano micelles-based technology in ocular drug delivery. Currently, tremendous interest is being shown towards development of nano micellar formulation-based technology for ocular drug delivery. The reasons may be attributed due to their high drug encapsulation capability, ease of preparation, small size, and hydrophilic nano micellar corona generating aqueous solution. For instance, developed dexamethasone loaded nano micelles by employing copolymers of polyhydroxyethylaspartamide [PHEAC (16)] and pegylated PHEAC (16) for anterior segment delivery. Results suggest that nano micellar formulations are a viable option for topical ocular delivery of small molecules. Researchers have also utilized nano micelles for ocular gene delivery. In a study, attempts to deliver genes by topical drop administration to cornea.

Nanoparticles[35-37]

It is colloidal carriers with a size range of 10 to 1000 nm. Nanoparticles for ophthalmic delivery are generally composed of lipids, proteins, natural or synthetic polymers such as albumin, sodium alginate, chitosan, poly (lactide-co-glycolide) (PLGA), polylactic acid (PLA) and polycaprolactone. Drug loaded nanoparticles can be nano capsules or nanospheres. In nano capsules, drug is enclosed inside the polymeric shell while in nanospheres; drug is uniformly distributed throughout polymeric matrix. Last few decades, nanoparticles have gained attention for ocular drug delivery and several researchers have made attempts to develop drug loaded nanoparticles for delivery to both anterior and posterior ocular tissues. It represents a promising candidate for ocular drug delivery because of small size leading to low irritation and sustained release property avoiding frequent administration.

Nanosuspensions[38,39]

It is colloidal dispersion of submicron drug particles stabilized by polymer or surfactant. The Ocular drug delivery system provides several advantages such as sterilization, ease of eye drop formulation, less irritation, increase precorneal residence time and enhancement in ocular bioavailability of drugs which are insoluble in tear fluid. It improves efficacy of nanosuspensions in improving ocular bioavailability of glucocorticoids has been demonstrated in several research studies. The glucocorticoids like prednisolone, dexamethasone and hydrocortisone are widely recommended for the treatment of inflammatory conditions affecting anterior segment ocular tissues. Current therapy of nanosuspension with these drugs requires frequent administration at higher doses which induce cataract formation, glaucoma, and damage optic nerve. For instance, compared ocular bioavailability of various

glucocorticoids (prednisolone, dexamethasone and hydrocortisone) from nanosuspensions, solutions and microcrystalline suspensions.

Liposomes[40,41]

It is lipid vesicles with one or more phospholipid bilayers enclosing an aqueous core. The size of liposomes usually ranges from 0.08 to 10.00 μm and based on the size and phospholipid bilayers, liposomes can be classified as small uni-lamellar vesicles (10–100 nm), large uni-lamellar vesicles (100–300 nm) and multilamellar vesicles (contains more than one bilayer). Applications of ophthalmic, liposomes represent ideal delivery systems due to excellent biocompatibility, cell membrane like structure and ability to encapsulate both hydrophilic and hydrophobic drugs. It has demonstrated good effectiveness for both anterior and posterior segment ocular delivery in several research studies.

Dendrimers[42,43]

It characterized as nanosized, highly branched, star shaped polymeric systems. Dendrimer branched polymeric systems are available in different molecular weights with terminal end amine, hydroxyl or carboxyl functional group. It is being employed as carrier systems in drug delivery. The selection of molecular weight, size, surface charge, molecular geometry and functional group are critical to deliver drugs. The structure of dendrimers allows incorporation of wide range of drugs, hydrophobic as well as hydrophilic. Dendrimer role in ocular drug delivery, few promising results were reported with these branched polymeric systems.

In-situ gelling systems[44,45]

In this system hydrogels refer to the polymeric solutions which undergo sol-gel phase transition to form viscoelastic gel in response to environmental stimuli. The ocular delivery, research studies have been more focused toward development of thermosensitive gels which respond to changes in temperature. Various type of thermogelling polymers have been reported for ocular delivery which includes poloxamers, multiblock copolymers made of polycaprolactone, polyethylene glycol, poly (lactide), poly (glycolide), poly (*N*-isopropylacrylamide) and chitosan. Drug delivery for this system, these polymers are mixed with drugs in the solution state and solution can be administered which forms an in-situ gel depot at physiological temperature. Gao et al have evaluated suitability of thermosensitive gel made of triblock polymer PLGA-PEG-PLGA (poly-(DL-lactic acid co-glycolic acid)-polyethylene glycol-poly-(DL-lactic acid co-glycolic acid) as a ocular delivery carrier for dexamethasone acetate (DXA). Following topical administration, the C max of DXA in the anterior chamber was significantly higher for the PLGA-PEG-PLGA solution (125.2 μg/mL) relative to the eye drop (17.6 ± 2.18 ng/mL) along with higher AUC values.

Contact lens[46,47]

The contact lenses are curved and thin shape plastic disks which are designed to cover the cornea. Application of contact lens adheres to the film of tears over the cornea due to the surface tension. The drug loaded contact lens have been developed for ocular delivery of numerous drugs such as β-blockers, antihistamines and antimicrobials. Practically, efficient than topical drops, these contact lenses suffer from disadvantages of inadequate drug loading and short-term drug release. Overcome, particle-laden contact lenses and molecularly imprinted contact lenses have been developed. Contact lenses like Particle-laden, drug is first entrapped in vesicles such as liposomes, nanoparticles or microemulsion and then these vesicles are dispersed in the contact lens material.

Implants[48,49,50]

Implant devices help in circumventing multiple intraocular injections and associated complications. Basically, for this drug delivery to posterior ocular tissues, implants are placed intravitreally by making incision through minor surgery at pars plana which is located posterior to the lens and anterior to the retina. Invasive procedure through implantation, these devices are gaining interest due to their associated advantages such as sustained drug release, local drug release to diseased ocular tissues in therapeutic levels, reduced side effects and ability to circumvent blood retina barrier. Various, implantable devices have been developed for ocular drug delivery especially for the treatment of chronic vitreoretinal diseases. Polymers such as polyvinyl alcohol (PVA), ethylene vinyl acetate (EVA), and polysulfide capillary fiber (PCF) are being employed for fabricating non-biodegradable implants.

Microneedles[51,52,53]

Its technique is an emerging and minimally invasive mode of drug delivery to posterior ocular tissues. Microneedle's technique may provide efficient treatment strategy for vision threatening posterior ocular diseases such as age-related macular degeneration, diabetic retinopathy and posterior uveitis. This new microneedle-based administration strategy may reduce the risk and complications associated with intravitreal injections such as retinal detachment, hemorrhage, cataract, endophthalmitis and pseudo endophthalmitis. These needles help to deposit drug or carrier system into sclera or into the narrow space present between sclera and choroid called "suprachoroidal space" (SCS). In another study, Jiang *et al* made attempts to evaluate the performance of microneedles to infuse drug solutions, nanoparticles and microparticles into scleral tissues. Nanoparticle's suspensions and microparticles were also delivered into sclera by microneedles however; microparticles were delivered only in the presence of collagenase spreading enzymes and hyaluronidase.

CONCLUSION

Ocular administration of drug solutions as topical drop with conventional formulations was associated with certain drawbacks which initiated the introduction of different carrier systems for ocular delivery. In this article, researchers are thriving hard to improve *in vivo* performance of conventional formulations. In this technique drug molecules are being encapsulated into nanosized carrier systems or devices and are being delivered by invasive/non-invasive or minimally invasive mode of drug administration. Several nanotechnology-based carrier systems are being developed and studied at large such as nanoparticles, liposomes, nano micelles, nanosuspensions and dendrimers. In this delivery system, nanotechnology is benefiting the patient body by minimizing the drug induced toxicities and vision loss. And it also, these nanocarriers/devices sustain drug release; improve specificity, when targeting moieties are used, and help to reduce the dosing frequency. In the current pace of ocular research and efforts being made and put in, it is expected to result in a topical drop formulation that retains high precorneal residence time, avoids non-specific drug tissue accumulation and deliver therapeutic drug levels into targeted ocular tissue.

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