IJMPR 2023, 7(1), 34-39

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Review Article
SJIF Impact Factor: 5.273

OCULAR DRUG DELIVERY SYSTEMS

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Received on: 16/11/2022
Revised on: 06/12/2022
Accepted on: 27/12/2022

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ABSTRACT

Due to the unique architecture and physiology of the eye, drug delivery scientists and pharmacologists have faced significant difficulties. Delivery of a drug alone or in a dosage form, particularly to the posterior segment, is significantly hampered by the combination of static barriers (different layers of the cornea, sclera, and retina, including blood aqueous and blood-retinal barriers), dynamic barriers (choroidal and conjunctival blood flow, lymphatic clearance, and tear dilution), and efflux pumps. Innovative methods for the noninvasive administration of strong treatment drugs are becoming more popular in order to increase patient compliance for back of the eye illnesses. We address historical achievements, current inventions, and upcoming difficulties in ocular drug-delivery technology in this review paper. Due to the blood-ocular barrier, topical therapy is preferred for treating ophthalmic conditions. Solutions, suspensions, and ointments are the most often used traditional preparations for ocular dosage forms, however they are not very effective as therapeutic systems. The needed amount of medicine is not immediately accessible for therapeutic action because it binds to the nearby extra orbital tissues after delivery because a considerable percentage of the topically administered drug is quickly diluted in the tear film and surplus fluid overflows over the lid edge. Given these losses, regular topical administration is required to keep medication levels appropriate. To reach therapeutic levels after systemic delivery of a medication for ocular illness, a high concentration of the medication must be present in the plasma. The duration of the medicine's activity can be noticeably extended and the frequency of drug administration can be decreased by adopting prolonged drug delivery.

KEYWORDS: Ocular, Novel Administration, Opthalmic, Nanoparticles, Parentral.

INTRODUCTION

The anatomy and physiology of the eye are complicated and distinct. It has become a significant problem for researchers in the field to create a medicine delivery system that targets a specific eye tissue. Anterior and posterior are the two major portions of the eye. Following medication delivery by any route, i.e., topical, systemic, and periocular, structural diversity of each layer of ocular tissue may offer a considerable barrier.

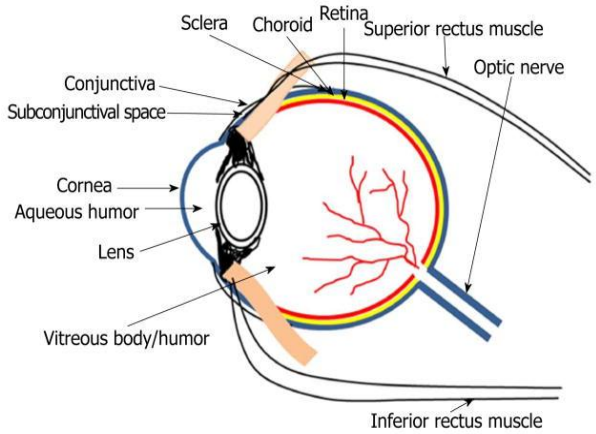
The problem for the formulator is to get past the eye's defences without enduring long-term tissue damage. The outdated ophthalmic solutions, suspensions, and ointment dosage forms are obviously insufficient to treat some of the most severe illnesses in existence today.

They fall within the categories of conventional and modern drug development systems. The most well-liked and approved route of administration for the treatment of many eye problems is the topical application of medications to the eye. The eye's effective defence systems, however, result in very low absorption for ophthalmic medicines. Drugs and other foreign substances are quickly removed from the surface of the eye by blinking, baseline and reflex lachrymation, and drainage. The anterior section is made up of tissues such the cornea, conjunctiva, aqueous fluid, iris, ciliary body, and lens. The sclera, choroid, retinal pigment epithelium, neural retina, optic nerve, and vitreous humour are all components of the posterior region of the eye. There are several disorders that might impair vision that affect the eye's anterior and posterior segments. Among the illnesses that might affect the anterior segment include glaucoma, allergic conjunctivitis, anterior uveitis, and cataract. The most common conditions affecting the posterior portion of the eye are age-related macular degeneration (AMD) and diabetic retinopathy.

The most popular non-invasive drug delivery method for treating illnesses of the anterior segment is topical instillation. 90% of the commercially available ophthalmic formulations are in conventional dose forms like eye drops.

The function of efflux pumps and methods to get over these obstacles by using a transporter-targeted prodrug strategy have also been mentioned. It has been explained how current advancements in ocular dosage forms, particularly colloidal dosage forms, are used to get beyond numerous static and dynamic obstacles. Additionally highlighted are a number of advancements in noninvasive methods for ocular medication delivery.

There are several conditions that can affect the eyes and cause vision loss. As a result, there are numerous drug delivery techniques for the eyes. These are divided into two categories: traditional (older) and unconventional (newer) medication delivery techniques. About 70% of the eye dose formulations on the market are eye drops and ointments, the most widely used ophthalmic medicines. However, after being injected into the culde-sac, these preparations are quickly washed away from the ocular chamber by tear production and lachrymal nasal drainage. Since there isn't much to use for its therapeutic impact, dosage must be frequent. In order to address these issues, more advanced pharmaceutical ophthalmic formulations have been created over the past three decades, including in-situ gel, nanoparticle, liposome, nanosuspension, microemulsion, intophoresis, and ocular inserts. These formulations increase the drug's bioavailability in a sustained and controlled manner.



Structure of the eye

Ideal Characteristics of Ocular Drug Delivery System

It need to be clean.
To bodily fluids, it ought to be isotonic
pH and buffer modification.
Less of a tendency to drain.
Minimum binding of proteins.
It is crucial to have a controlled medication release.
It must increase the speed and completeness with which the medicine is absorbed.
It must be easy for patients to use.
Talking, eating, and drinking should not be hindered or impeded by it in any way.

Routes of Administration

Topical: For treating ocular illnesses affecting the anterior segment of the eye, topical ocular medication delivery has been regarded as the best method of administration. However, due to obstacles such nasolacrimal drainage, corneal epithelium, blood-ocular barriers, and eye metabolism, topical ocular administration is a difficult undertaking. Human tears typically contain 7 µl, and the delivered eye drop can momentarily be temporarily contained in the cul-de-sac. However, tear film shows a quick recovery period of two to three minutes, and the majority of topically applied solutions are washed away within just 15 to 30 seconds of instillation. Contact time with the absorptive membranes is shorter when all precorneal variables are taken into account, which is thought to be the main cause of less than 5% of the applied dose reaching the intraocular tissues.

Systemic (parenteral) administration: T -aqueous barrier and blood-retinal barrier act as important obstacles to the distribution of drugs to the anterior and posterior segments of the eye, respectively, after systemic injection. The endothelium of the iris/ciliary blood vessels and the nonpigmented ciliary epithelium make up the two distinct cell layers that make up the blood-aqueous barrier, both of which are found in the anterior portion of the eye. Both cell layers have tight junctional complexes, which block the entry of solutes such aqueous humour into the intraocular environment. Researchers are working to identify ways to get through the blood-retinal barrier as a result of recent advances in nanotechnology. In one experiment, C57BL/6 mice were used as the test subjects. The results showed that intravenously injected 20-nm gold nanoparticles could cross the blood-retinal barrier and disperse across all layers of the retina without harm. Retinoblastoma cells, astrocytes, and retinal endothelial cells all maintained their viability unaffected. Larger 100-nm nanoparticles, in contrast, were not found in the retina. A few attempts have also been made to transfer genes by intravenous infusion to the eye. Upon intravenous treatment of polyethylene glycol (PEG) attached immunoliposomes, a diffuse expression of the SV40/-galactosidase gene was seen in the mouse inner retina, RPE, iris, as well as conjunctival epithelium. Transferrin, arginine-glycine-aspartic acid peptide, or dual-functionalized poly(lactide-co-glycolide) (PLGA) nanoparticle IV injection are useful, according to a more recent study. Targeted delivery of the antivascular endothelial growth factor intraceptor plasmid to choroidal neovascularization (CNV) lesions using these functionalized PLGA nanoparticles was successful. The leaky blood-retinal barrier caused by CNV in the laser-treated rat eye was blamed for allowing nanoparticles to reach the neovascular eye.

Intra-vitreal administration: With recent improvements in surgical techniques, therapeutic agents can now be administered intra-vitreally by being directly injected into the midvitreous region, and intra-vitreal implants with sustained, controlled release have also become a mainstay treatment for diseases affecting the posterior

segment. Following this method of administration, longer retention period and greater vitreous concentration of medicines were attained.

Scleral administration: The sclera has lately emerged as a possible vector for posterior segment drug delivery due to its enormous surface area, ease of accessibility, and relatively high permeability to macromolecules. Different methods of scleral medication administration have been tried, including subtenon injection, sun conjunctival injection, and scleral plugs and implants. A potential therapeutic strategy for the management of numerous posterior segment illnesses is medication trans-scleral delivery.

CLASSIFACATION OF OCULAR DRUG DELIVERY SYSTEM

Conventional Ocular Drug Delivery System

A popular and patient-friendly medication delivery method is topical drop instillation into the lower precorneal region. Only 20% (or about 7 L) of the instilled dosage is kept in the precorneal pocket after being applied topically, since most of it is lost to reflux blinking. The drug's concentration in the precorneal region serves as a catalyst for its passive diffusion through the cornea. However, greater corneal Penetration with extended drug cornea contact time are necessary for effective ocular medication administration using eye drops. Improvements in precorneal residence duration and corneal penetration have been accomplished in a number of ways. Iontophoresis, prodrugs, ion-pair forming substances, and cyclodextrins are used to enhance corneal permeability.

Novel Ocular Drug Delivery System

The typical ocular dosage forms have a number of drawbacks, necessitating the deployment of a novel drug delivery mechanism. The primary issue with such traditional therapy is the lowest ocular bioavailability, which causes the bulk of the medication to be lost and just a little portion to actually reach the intended spot. The distinctive architecture of the eye and the makeup of its tissues are to blame for this loss. These factors have made medicine delivery to the eye a persistently difficult problem. Eye drops are not used to treat the posterior portion of the eye. Eye drops are often used to treat "only" conditions affecting the eye's front segment. The majority of the medicine is lost from the site throughout the process as a result of eye drop drainage, fast tear turnover, blinking, and tear inducement. Thus, less than 5% of the little amount only enters the intraocular tissues.

Advantages of The Ocular Route of Drug Administration

- The direct application to the site of action and guarantee that the active pharmaceutical ingredient (API) is present in higher quantities than the medicine received by oral administration are the two main benefits of the ocular route of drug delivery.
- Faster medication absorption and less systemic and visual adverse effects are associated with the ocular route.
- It provides precision and consistency in dosage rate by eliminating the pulsed doses of traditional systems.
- Better housing for delivery systems is provided.
- Since the medicine is not intended to be taken, there is no problem with its disagreeable taste or odour (bypasses the first-pass metabolism).
- As well, it is appropriate for all patients (child and elderly also).
- The ocular route can increase patient compliance, offer comfort, and improve the drug's therapeutic effectiveness.
- To stop the loss of ocular tissue, one targets within the ocular globe.
- It does not cause any of the kind of suffering that the paternal route causes (intravenous, intramuscular, and subcutaneous route).
- The technique that enables self-administration of medication is straightforward.
- The formulation just needs a minimal quantity of medication.
- The ocular route allows for the drug to be released gradually and under control.

Disadvantages of The Ocular Route of Drug Administration

- The primary drawback of using standard eye drops to administer medications intraocularly is their quick and widespread clearance, which can result in significant drug loss and poor retention of the medication at the site of action.
- The medication's limited duration of therapeutic efficacy is caused by its rapid clearance through tear production and eye blinking, which may necessitate repeated doses.
- There may be a brief blurring of vision following the use of the ointment, drops, or other treatment.
- Only a few number of medications may be formulated for the ocular route.
- Ophthalmic medication absorption is decreased as a result of its restricted permeability to the cornea.
- Ophthalmic dosage forms must be produced using specialised procedures, tools, and conditions (sterile), which increases their cost to the pharmaceutical industry.

Limitations of Ophthalmic Drug Delivery

1. Dosage form cannot be terminated during emergency.
2. Visual interference.
3. Complicated installation and removal.
4. Occasional loss while dozing off or scratching one's eyes.

The transport of drugs into the eyes has significantly improved despite these drawbacks. The modifications

were made in order to keep the medication in the bio-phase for a longer amount of time. The eye is immune to foreign chemicals due to its architecture, physiology, and biochemistry.

Mechanisms of Ocular Drug Absorption

The most popular method of delivering drugs to the eyes is by far topical distribution into the cul-de-sac. This place may experience corneal or non-corneal adsorption. The so-called noncorneal route of absorption entails entry into the intraocular tissues through the sclera and conjunctiva. The substance that penetrates the eye's surface past the corneal-scleral limbus is absorbed by the local capillary beds and removed to the bloodstream, rendering this method of absorption often ineffective. Entry into the aqueous humour is often prohibited by this noncorneal absorption.

However, imply that medication molecules with limited corneal permeability may benefit from noncorneal routes of absorption. According to research on inulin (3), timolol maleate (3), gentamicin (4), and prostaglandin PGF2a (5), these medications enter the eye through diffusing over the conjunctiva and sclera. Inulin and timolol maleate were examined for non-corneal absorption by Ahmed and Patton (3). Instead of returning to the systemic circulation or being absorbed into the local vasculature, it appears that these drugs enter the intraocular tissues by diffusion between the conjunctiva and sclera. Both substances entered the iris-ciliary body but did not enter the anterior chamber.

It was discovered that noncorneal absorption was responsible for up to 40% of the inulin absorbed into the eye.Although the predominant mechanism of absorption for the majority of therapeutic entities is corneal absorption, the noncorneal route of absorption may be substantial for medications that are weakly cornea-permeable. So the cornea is thought to be the rate limiter of these medicines' topical absorption. The cornea's structural features have specific differential solubility demands on potential medication candidates. A cross-sectional image of the cornea is shown in Figure 2. The epithelium, stroma, and endothelium are the three main diffusional barriers that prevent medications from crossing the cornea, making the cornea a trilaminate structure in terms of transcorneal drug flux. On the order of 100 times as much lipid material is present in the epithelium and endothelium per unit mass as there is in the stroma. The diffusional resistance presented by these tissues varies significantly depending on the physiochemical characteristics of the drug entity.

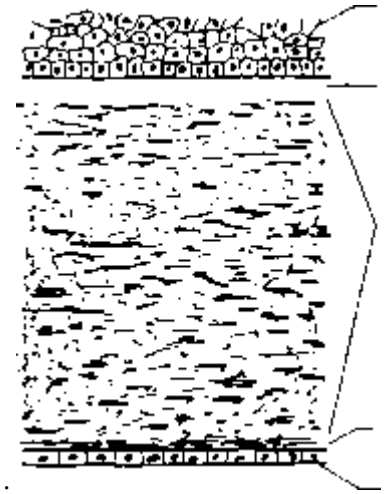


Fig: 2.

Sidewalk epithelium Pavement epithelium made of 5 or 6 layers of bowman's membrane stroma descemet's membrane and endothelium made of 5 or 6 layers of bowman's membrane stroma descemet's membrane.Figure 2 shows several obstacles to medication absorption in a cross-sectional image of the corneal membrane.

The epithelium, which is the top layer, acts as the rate-limiting barrier for the transcorneal diffusion of the majority of hydrophilic medications. There are five to seven cell layers in the epithelium. Because the basement cells are columnar in shape, little paracellular transport is possible. But distal to Bowman's membrane, the epithelial cells constrict, resulting in flattened epithelial cells with zonulae occludentes interjunctional complexes. This cellular configuration restricts lateral mobility inside the front epithelium and prevents paracellular transfer of the majority of ophthalmic medications. The intracellular pore size of the corneal surface epithelium is thought to be around 60 A. These holes appear to allow small hydrophilic and ionic molecules to enter the anterior chamber; nevertheless, interjectional complexes prevent paracellular transport for the majority of medicines.

The stroma sits in the gap between the corneal endothelium and epithelium (substantia propia). The majority of the corneal mass, between 85% and 90%, is made up of the stroma, which is mostly made of hydrated collagen. Due to its hydrophilic makeup, the stroma acts as a diffusional barrier to highly lipophilic medications. The stroma lacks tight connection complexes, allowing paracellular transit through the tissue.

The endothelium is the cornea's innermost layer, situated between the stroma and Descermet's membrane. Despite being lipoidal in nature, the endothelium does not provide a substantial barrier to the transcorneal diffusion of the majority of medications. Endothelial permeability is completely determined by molecular weight, not by the compound's charge or hydrophilic character.

Better Ocular Drug Delivery Developed

Although the eye is a portion of the human body that is easily accessible, medicine administration there is exceedingly challenging. Topical medications are often used to treat eyes. Due to poor penetration, the bioavailability of ophthalmic medications might be as low as 5%. Large amounts are slathered on to reach therapeutic levels in order to make up for this loss.

However, patients typically prefer this to alternative therapies. Injections with needles or laser (photocoagulation) surgery are two more agonising methods.

A composite contact lens with outstanding mechanical integrity was created by this team. It is steady for more than six months and may be handled with ease. A number of biodegradable silica nanoneedles are present in the lens (Si NNs). These needles are only 900 nm in diameter and 1o or 60 um in length. At the needle's broadest base, this has a diameter that is 80 times smaller.

In order to use this innovative technique, the medicine of choice is manually applied to the cornea while the rigid yet tear-soluble lens is loaded. Once inside the corneal barrier, the Si NNs do little to no harm. A burst of the loaded medicine is delivered into the pierced cornea within a minute of the lens being placed. The Si NN lens surface's covalent binding affinity keeps drug molecules bound, preventing medication spillage both before and during administration. The lens will then gradually dissolve into the cornea over the course of a month.

Researchers employed a rabbit model of corneal neovascularization to evaluate the therapy (CNV). CNV is a disorder that can cause blindness and is characterised by the proliferation of new blood vessels from the already-existing corneal vasculature into non-vascularized regions of the cornea. Surgery including photocoagulation performed worse than treatment utilising the new Si NN lenses. The corneal endothelial cells and the stem cells at the corneal limbus were unaffected by the therapy, which exhibited no rise in inflammation or harmful effects. The good news is that both the 60 um and the 10 um long microneedles behaved equally well.

Drugs for the treatment of cataracts, melanoma, or glaucoma can be put into the Si NNs. We owe a debt of gratitude to the Purdue team for adding the qualifier "nano" before the word "needle" in relation to our eye therapies.

CONCLUSION

The prior period's substantial study on medication administration to the eyes. The goal is to increase the amount of time that medications administered topically stay in the cornea and conjunctiva. Drug delivery for each route of ocular drug administration is influenced by key pharmacokinetic factors, including bioavailability, drug elimination from the target tissue, dosing regimen, and drug release and/or dissolution. For optimum therapeutic activity, an ocular drug delivery system should have the following characteristics.

Future ideal ocular delivery systems must be created to maintain the drug's effectiveness in the intraocular space while also providing sustained drug release and minimally invasive administration. The more recent trend in these ocular administration systems involves combining drug delivery technologies to enhance the therapeutic effect or therapeutic response of an effective medicine. Effective medication concentration at the target tissue should be possible with these perfect systems. This time frame had a minimal systemic impact. The design of any pleasant ophthalmic medication delivery system must prioritise patient acceptability. Sustained drug release, larger-scale manufacturing, and stability all need significant improvements.

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