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OCULAR DRUG DELIVERY SYSTEM: CURRENT SCENARIO AND FUTURE PERSPECTIVES

Pallavi Tembhare*[1], Saurabh Kotangale[2], Prameshwar Wankhede, Tulsidas Nimbekar and Dilip Sanghi

Shri Laxmanrao Mankar Institute of Pharmacy Amgaon, Dist-Gondia, 441902.

***Corresponding Author: Pallavi Tembhare**

Shri Laxmanrao Mankar Institute of Pharmacy Amgaon, Dist-Gondia, 441902.

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ABSTRACT

Ocular drug delivery's distinct anatomy and physiology have presented pharmacologists and drug delivery experts with significant challenges. Delivering a drug alone or in a dosage form is made extremely difficult by the combination of static barriers (the various 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, particularly to the posterior segment. In recent years, there has been a growing movement to identify influx transporters on different ocular tissues and develop a parent drug delivery system that targets these transporters. To get over a variety of static and dynamic obstacles, colloidal dosage forms such liposomes, nanoparticles, nanomicelles, and microemulsions have been extensively studied in parallel. To maintain drug levels at the target region, innovative drug delivery techniques such fibrin sealant-based methods and bioadhesive gels were created. Drug delivery may be significantly improved in the years to come by developing noninvasive sustained drug delivery methods and investigating the viability of topical application to deliver medications to the posterior section. Today's advancements in ocular medication delivery hold great promise for addressing the difficulties presented by a variety of anterior and posterior segment disorders.

KEYWORDS: Anatomy and physiology, Cornea, Contact lens, Drug delivery, Eye, Emulsions, Formulations, Ointments, Suspensions.

INTRODUCTION

The most popular non-invasive drug delivery method for treating conditions affecting the anterior segment is topical instillation. Most ophthalmic formulations on the market are in the form of eye drops or other conventional dosage forms.The reason may be due to the ease of administration and the patient compliance. Nevertheless, the bioavailability of the eyes is very low in local drop administration. Many anatomical and physiological limitations, such as tear secretion, nasolacrimal drainage, reflex blinking, and static and dynamic ocular barriers, pose challenges and impede deeper penetration of ophthalmic drugs. Thus, less than 5% of a topically administered dose reaches the deep ocular tissues. Drug administration via the transscleral route with periocular delivery has been developed as an alternative means of drug delivery to posterior ocular tissues. Although transscleral administration is relatively simple, less inavasive and patient friendly, drug penetration is impaired by static and dynamic ocular barriers.

Eye barriers for transisspexpecal delivery of drugs include: static barriers, that is, sclera, epithelium of pigment with vascular and retina (RPE) and dynamic barriers, that is, a lymphatic flow in conjunctiva and episode, as well as blood flow together. To overcome the barriers of ocular drug delivery and improve ocular bioavailability, various conventional and novel drug delivery systems have been developed, including emulsions, ointments, suspensions, aqueous gels, nanomicelles, nanoparticles, liposomes, dendrimers, implants, contact lenses, nanosuspensions, microneedles, and in situ thermosensitive gels for the aforementioned ocular diseases. This review will provide an overview on various conventional and novel ophthalmic drug delivery systems developed to deliver drug to diseased ocular tissues for the treatment of ocular disease.

Anatomy & Physiology of Eye

Pupil-Control the amount of light entering the eye and dilates and contracts accordingly.

Cornea-Optically transparent tissue, act as principle refractive element of an eye.

Ciliary body-Structure containing muscle and is located behind the iris, which focuses the lens.
Retina- The nerve lining the back of the eye.it sense light and create electrical impulses that are send throught the optical nerve to the brain.
Sclera- White outer coat of the eye,surrounding the iris
Iris- Eye colored part and coordinate with pupil .
Lens- focuses light rays on to the retina.
Conjuctiva-The mucus membrane that being at the age of cornea and line inside the surface of the eyelid and the sclera, serve as lubricant of eye.
Aqueous humour- The transparent fluid that circulates behind the cornea and in front of the lens.
Vitreous humour- The material(like transparent jelly) that filles the eye ball between the lens and the retina.

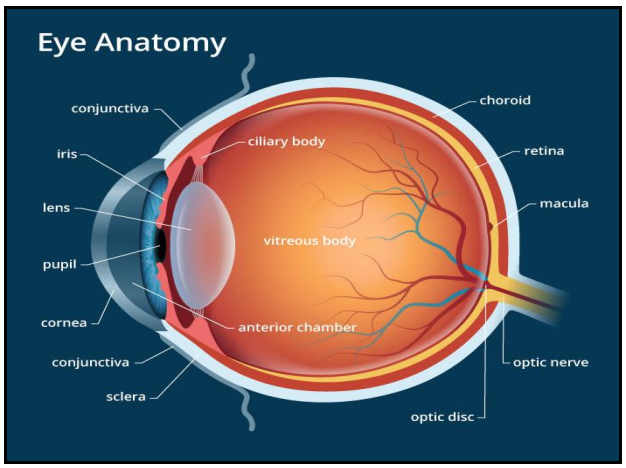


Fig.1. Structure of Eye.

Composition of Eye

- Water -98%
- Solid -1.8%
- Organic element

Protein-0.67%
Sugar -0.65%
Nacl-0.66%

- Other mineral element: sodium , potassium and ammonia-0.79%

Barrier of drug permeation:

1. Anatomical barrier
i) Corneal route
ii) Non-corneal route
2. Physiological barrier
3. Blood ocular barrier
i) Blood aqueous barrier
ii) Blood retinal barrier

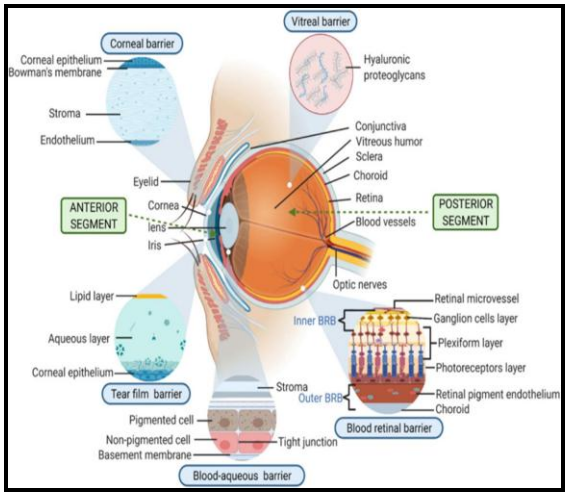


Fig.2. Barriers of drug permeation.

1. Anatomical barrier

When a dosage form is topically administered there are two routes of entry through the cornea or via the non-corneal route. The cornea is a very tight multilayered tissue that is mainly composed of five sections;

- Epithelium,
- Bowman's membrane,
- Stroma,
- Descemet' membrane and
- Endothelium.

i) Corneal Route

Out of five layers it's the epithelium which acts as the principal barrier. It acts as a major barrier to hydrophilic drug transport through intercellular spaces. On the other hand stroma, allow hydrophilic drugs to easily pass through but it acts as significant barrier for lipophilic drugs.Thus for a drug to have optimum bioavailability, it should have the right balance between lipophilcity and hydrophilicity. The remaining layers are leaky and do not act as significant barrier.

ii) Non corneal route

Non corneal route involves movement across conjunctiva and sclera. This route is important especially for large and hydrophilic molecule such as peptides. Proteins and siRNA (small or short interfering RNA). The conjunctiva is more permeable than cornea especially for hydrophilic molecule.

2. Physiological barrier

The eyes primary line of defense is its tear film. Bioavailabilities of topically administered drugs are further reduced by precorneal factors such as solution drainage, tear dilution, tear turnover, and increased lacrimation. The lacrimal fluid is an isotonic aqueous solution containing a mixer of protein (such as lysozyme) as well as lipids. Rapid clearance from the precorneal area by lacrimation and through nasolacrimal drainage and spillage further reduces contact time between the tissue and drug molecules. This in turn lowers the exact time for absorption leading to reduced

bioavailability. The average tear volume is 7-9ul with a turnover rate of 16% per minute. Thus drugs administered as eye drops need to be isotonic and non irritating to prevent significant precorneal loss.

3. Blood ocular barriers

The blood ocular barriers normally keep most drugs out of the eye. However, inflammation breaks down this barrier allowing drugs and large molecules to penetrate into the eye.

i) Blood –aqueous barrier: It is formed by non pigmented ciliary epithelial cells of ciliary body and endothelial cells of blood vessels in iris.

ii) Blood-retinal barrier: Non-fenestrated capillaries of retinal circulation and tight –junctions between retinal epithelial cells preventing passage of large molecules from chorio-capillaris into the retina.

Methods to overcome barriers

1. Physical methods
i) Iontophoresis
ii) Sonophoresis
iii) Micro needles
2. Chemical approaches

1. Physical method

Physical force-based techniques, which were first applied to transdermal drug delivery, often call for a physical device that is powered in order to supply energy to the barriers and improve transient drug transport.

i)Iontophoresis

By inducing elecrorepulsion and electro-osmosis of the drug molecule, Iontophoresis—the application of a low intensity electrical current to ions in cells or tissue—improves drug delivery across biological membranes.

ii)Ultrasound/Sonophoresis

In order to enhance medication transport across biological membranes, including ocular barriers, a sound field with frequencies higher than 20 kHz is applied.

iii) Microneedle

Microneedles (MLs) are needles or arrays of micrometer-sized needles that are created by modifying microelectronics instruments. Drugs can pass through these barriers by creating a small transport route when MLs are applied to biological membranes.

2. Chemical approaches

The most crucial tactics in chemical techniques for ocular delivery involve creating prodrugs, or ocular medications that are inactive at locations other than the eye. Creating medications that go through a series of metabolic changes before ultimately reaching their intended target (retro metabolic design). In order to restore therapeutic action, a known inactive metabolite or analog is chemically modified. This results in a predictable one-step biotransformation (SD) back into the metabolite.

Advantages

i. Increased accurate dosing.
ii. To overcome the side effects of pulsed dosing produced by conventional systems.
iii. To provide sustained and controlled drug delivery.
iv. To increase the ocular bioavailability of drug by increasing the corneal contact time. This can be achieved by effective adherence to corneal surface.
v. To provide targeting within the ocular globe so as to prevent the loss to other ocular tissues.
vi. To circumvent the protective barriers like drainage, lacrimation and conjunctival absorption.
vii. To provide comfort, better compliance to the patient and to improve therapeutic performance of drug.
viii. To provide better housing of delivery system.

Disadvantage

i. It is expensive.
ii. An insertion technique is difficult and expulsion of shields may occur not invidually fit for each patient.
iii. Its poor bioavailability.
iv. The necessity of using preservative.
v. Foreign body sensation.
vi. Dosage form cannot be terminated during emergency.
vii. The instability of the dissolved drug.

Routes for ocular drug delivery

1) Topical Administration
2) Intracameral Injections
3) Intravitreal Injections/Implants
4) Juxtascleral Injections
5) Retrobulbar Injection
6) Subconjunctival Injection

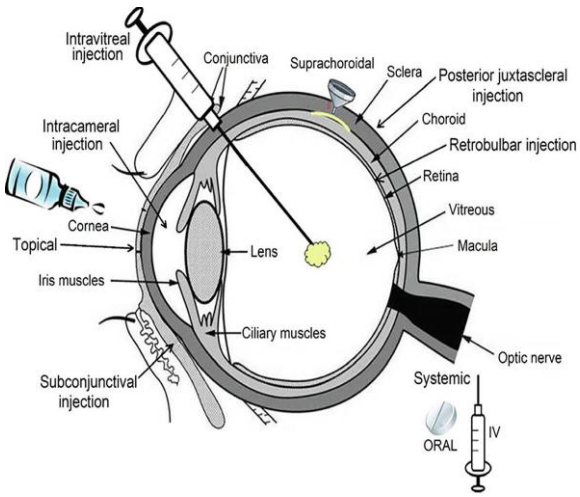
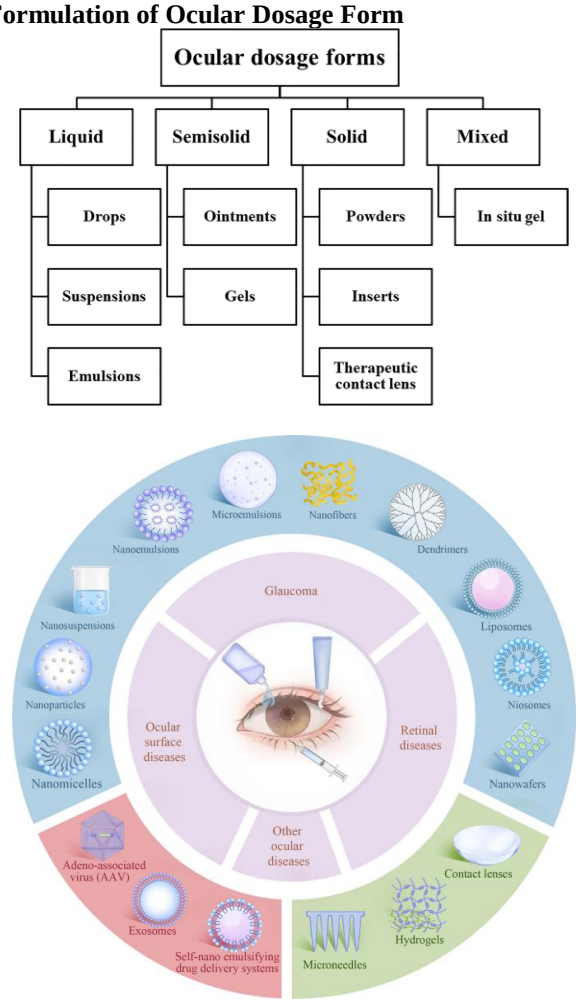


Fig.3. Routes of ocular drug delivery.

Formulation of Ocular Dosage Form



Novel Ocular Dosage Form

Advances in ocular drug delivery modalities, especially nanotechnology-based ocular drug delivery systems, are recommended, and some typical research is highlighted. Based on the related research, systematic and comprehensive characterizations of the nanocarriers are summarized, hoping to assist with future research.

CONCLUSION

As mentioned earlier in this review, the eyes are one of the most complicated and complex organs. Many of the previous DDS successes to extend the saving time have been reduced in the frequency of administration, but this area requires additional requirements to improve patients and compliance. Meanwhile, as a result of research, several new eye drop drug delivery system products have been commercialized, but the performance of these new products is still far from satisfactory. An ideal ophthalmic drug delivery system should be able to achieve minimum effective drug concentration at the target tissue of eye for prolonged period with minimizing systemic exposure and these systems should be comfortable to use. Each of the technologies discussed in this review requires further research. For ophthalmic delivery system some formulations are relatively easy to manufacture, but limited in their ability to provide sustain and controlled drug release for prolong time period. The novel advanced delivery systems offer more protective and effective means of the therapy for the nearly inaccessible diseases of eyes.

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