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A COMPREHENSIVE INSIGHT ON OCULAR DRUG DELIVERY SYSTEM

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Abstract:

The eye is the most distinctive organ in the human body. Various drug delivery methods are utilised to deliver drugs into the eyes, however because of the drawbacks of conventional systems, researchers are looking for novel approaches to improve contact time, bioavailability, and residence length, as well as minimise patient pain and dosage frequency. 90% of currently available ophthalmic formulations are in conventional dose forms. The ideal ophthalmic drug delivery system must be able to continue drug release for a lengthy period of time while remaining in close contact to the front of the eye. Due to its unique structure and physiology, including multiple types of barriers such as distinct layers of cornea, sclera, and retina, blood aqueous and blood–retinal barriers, choroidal and conjunctival blood flow, and so on, ocular drug delivery has been a big issue for scientists. These obstacles make delivering a single medicine or a dose form to the posterior portion of the eye difficult. To resolve these concerns, novel dosage forms like nanoparticles, liposomes, and microemulsions etc. have been designed. In this review, information on various ocular drug delivery systems, such as eye ointments, gels, and the use of viscosity enhancers, prodrugs, penetration enhancers, microparticles, liposomes, niosomes, ocular inserts, implants, intravitreal injections, nanoparticles, nanosuspension, microemulsion, dendrimers, iontophoresis, and periocular injections is illustrated. Barriers to drug penetration, routes of ocular drug administration, and ways to increase ocular bioavailability were the focus of this review.

Keywords: *Ocular absorption, Ocular bioavailability, Nanoparticles, Microemulsion*

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INTRODUCTION:

One of the most fascinating and difficult tasks facing pharmaceutical researchers is ocular delivery of drug[1].The eye is a complicated organ that has its own anatomy and physiology. The anterior segment and posterior segment are the two primary components of the eye's structure. The anterior part of the eye takes up about one third of the space, while the posterior section takes up the rest. The anterior region of the eye is made up of tissues such as the cornea, conjunctiva, aqueous fluid, iris, ciliary body, and lens. Sclera, choroid, retinal pigment epithelium, neural retina, optic nerve, and vitreous humour make up the back of the eye, often known as the posterior region of the eye[2].The formulator faces a huge difficulty in circumventing (bypassing) the eye's protective defences without inflicting irreversible tissue damage[3]. Ocular delivery methods with excellent therapeutic efficacy continue to be developed as better, more sensitive diagnostic procedures and innovative treatment substances are developed. There are two types of techniques that have been tried to boost the bioavailability and duration of therapeutic activity of ocular drugs. The first is based on the use of sustained drug delivery systems, which allow ophthalmic drugs to be delivered in a regulated and continuous manner. The second step entails increasing corneal drug absorption while reducing precorneal drug loss. The ideal ophthalmic drug delivery system must be able to maintain drug release and stay in close proximity to the front of the eye for a long time[4].A well-established mode of administration for the treatment of many eye illnesses such as dryness, conjunctivitis, and eye fever is topical application of medications to the eye. Topical administration is usually preferable to systemic administration for eye illnesses because any drug molecule supplied via the ocular route must first penetrate the precorneal barriers before reaching the anatomical barrier of the cornea. The tear film and the conjunctiva are the first barriers to drug penetration into the eye, slowing it down. As a result, just a limited amount of drug passes through the cornea and into the intraocular tissue[5]. Various conventional and novel drug delivery systems, such as emulsions, ointments, suspensions, aqueous gels, nano micelles, nanoparticles, liposomes, dendrimers, implants, contact lenses, nanosuspensions, microneedles, and in situ thermosensitive gels, have been developed to overcome ocular drug delivery barriers and improve ocular bioavailability for the ocular diseases. 90% of all marketed ophthalmic formulations are conventional dosage forms[2].

Advantages of Ocular drug delivery systems[3,6]:

The following are some of the benefits of ocular drug delivery systems;

1. Easy convenience and needle-free drug application without the requirement for skilled people assistance, allowing patients to self-medicate, resulting in higher patient compliance as compared to parenteral routes.
2. Drugs that are hydrophilic and have a low molecular weight can be absorbed well through the eye.
3. Avoidance of hepatic first-pass metabolism, allowing for a lower dose when compared to oral administration.
4. To distribute drugs in a consistent and controlled manner.
5. Increase the corneal contact time to increase medication ocular absorption. This is accomplished through efficient corneal surface adhesion.
6. To offer targeting within the ocular globe to avoid ocular tissue loss.
7.Bypassing protective barriers such as drainage, lacrimation, and conjunctive absorption
8. To create a more suitable location for the delivery system.

Disadvantages of Ocular drug delivery system:

The ocular drug delivery method has a number of drawbacks, which are listed below

1. The physiological restriction is the cornea's limited permeability, which results in minimal ophthalmic drug absorption.
2. As a large amount of the injected dose drains into the lacrimal duct, undesirable systemic side effects may occur.
3. As the drug is rapidly eliminated by eye blinking and tears flow, the therapeutic action lasts for only a short time, necessitating a frequent dose regimen.

Ideal characteristics of ocular drug delivery system[1]:

- Good corneal penetration is an ideal feature of an ophthalmic drug delivery system.
- Extending contact duration with corneal tissue to increase ocular drug absorption.
- The patient's instillation is simple.
- The frequency of administration has been reduced.
- Patient cooperation.
- Toxicity and adverse effects are reduced.
- Minimize drug loss in the precorneal area.
- Non-irritating and relaxing shape (viscous solution should not provoke lachrymal secretion and reflex blinking).
- There should be no blurring of eyesight.

• It's not too greasy.
• Appropriate viscous system rheological properties and concentrations.

Anatomy and physiology:
The structure of the eye is divided into two parts: (a) the anterior segment, and (b) the posterior segment. The anterior segment includes the pupil, cornea, iris, ciliary body, aqueous fluid, and lens, while the posterior section includes the vitreous humour, retina, choroid, macula, and optic nerve.[7]The cornea and the sclera make up the outer region. The iris, ciliary body, and choroid are the three layers that make up the eye's middle layer. The retina is a complex, layered system of neurons that capture and process light in the inner layer of the eye[3, 8].

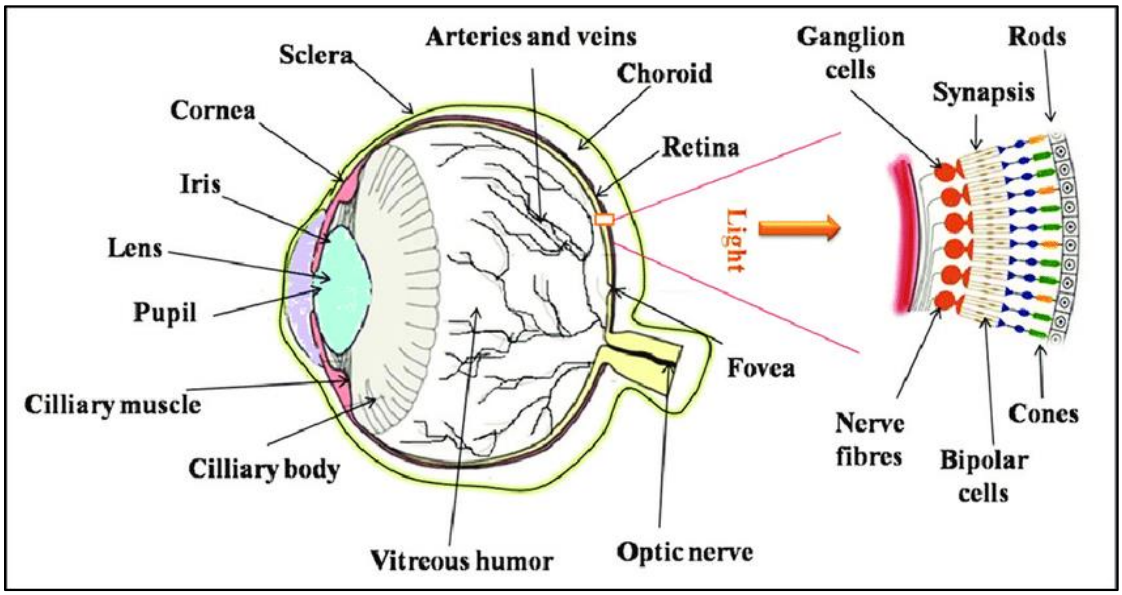


FIG 1: STRUCTURE OF EYE

a) Anterior segment[4]

1. **Pupil:** Pupil is the circular aperture in the centre of the iris through which light passes into the eye, but it is more appropriately defined as the dark "centre" of the eye. The pupillary reflex (also known as the "light reflex") regulates the size of the pupil (and thus the amount of light admitted into the eye).
2. **Cornea:** At the front of the eye, the cornea is a powerful transparent bulge. The adult cornea's surface has a radius of about 8mm. It performs a vital optical function by refracting light as it enters the eye, passing through the pupil and onto the lens (which then focuses the light onto the retina). The capillaries that terminate in loops around the periphery of the cornea, which is a non-vascular structure (it lacks blood vessels), provide the necessary nutrition. Many nerves arising from the ciliary nerves supply it. These make their way into the cornea's layered tissue. As a result, it is exceedingly sensitive.
3. **Iris:** The iris is a thin circular contractile curtain that lies behind the cornea and in front of the lens. The iris is a diaphragm with a changeable size that regulates the amount of light let into the eye by adjusting the size of the pupil. It refers to the coloured portion of the eye (shades may vary individually like blue, green, brown, hazel, or grey).
4. **Ciliary muscle:** The ciliary muscle is a ring of striated smooth muscles located in the middle layer of the eye that regulates the flow of aqueous humour into Schlemm's canal and controls accommodation for viewing objects at various distances. Parasympathetic and sympathetic nerves supply energy to the muscle. The curvature of the lens is changed by contracting and relaxing the ciliary muscle. This process can be easily stated as a balance between two states: Ciliary Muscle relaxed (which allows the eye to focus on distant objects) and Ciliary Muscle tightened (which prevents the eye from focusing on distant objects) (This enables the eye to focus on near objects).
5. **Aqueous humour:** The aqueous humour is a jelly-like fluid that resides in the eye's outer/front

chamber. The "anterior chamber of the eye," which is placed just beneath the cornea and in front of the lens, is filled with a watery fluid. The aqueous humour is an alkaline salt solution with trace amounts of sodium and chloride ions. It is continuously created, primarily by the ciliary processes, flows from the posterior chamber into the anterior chamber through the pupil, and exits by the trabecular and uveoscleral routes. Schlemm's canal (also known as the Schlemm canal or the scleral venous sinus) is a circular channel that receives aqueous humour from the anterior chamber and transports it to the bloodstream via the anterior ciliary veins. It is situated at the point where the cornea and the sclera meet. Aqueous humour turnover in humans is between 1% and 1.5% of the anterior chamber capacity each minute. Aqueous formation occurs at a rate of 2.5 µl/min. There are pressure-dependent and pressure-independent routes in aqueous humour. The trabecular meshwork-canal-venous schlemm's system is referred to as pressure dependent outflow, whereas uveoscleral outflow refers to any non-trabecular outflow[9].

6. **Lens:** The lens is encased in a tiny transparent capsule. The ciliary muscles encircle it, which is placed behind the pupil of the eye. It aids in the refraction of light entering the eye (which first refracted by the cornea). The lens concentrates light onto the retina, creating an image. It is able to do so because the shape of the lens changes depending on the distance between the object(s) the person is looking at and the distance between the person's eye and the object(s). The ciliary muscles contract and relax to change the curvature of the lens, a process known as accommodation.
7. **Sclera:** The tight white sheath that forms the outer layer of the ball is the sclera (white component of the eye). It is a strong fibrous membrane in the posterior portion of the eye that keeps the shape of the eye as a globe. It is thicker at the back/posterior of the eye than at the front/anterior[10].
8. **Conjunctiva:** The conjunctiva is a thin mucous epithelial barrier that borders the inside of the eyelids and covers the front one-third of the eyeball. Palpebral and bulbar conjunctiva refers to the two parts of the conjunctiva. The conjunctiva is made up of two layers: an outer epithelium and stroma beneath it (substantia propria). The conjunctiva and cornea are exposed surfaces of the eye, which are covered by the tear film. The conjunctiva helps to produce the tear film by secreting significant amounts of electrolytes, fluid, and mucins.

Posterior segment[4]:

1. **Vitreous humour:** The vitreous humour (also known as the vitreous body) is a huge area in each eye that takes up around 80% of the human body's surface area. The vitreous humour is a thin, jelly-like material that fills the chamber behind the eye's lens. The hyaloid membrane is a fragile translucent membrane that surrounds an albuminous fluid.
2. **Retina:** The retina is a layer of tissue that covers the back of the eye. The retina can be thought of as a "screen" on which light that has travelled through the cornea, aqueous humour, pupil, lens, and ultimately the vitreous humour forms a picture. The retina's job isn't just to be a screen on which a picture can be generated, but also to gather the information contained in that image and send it to the brain in a way that the body can understand. As a result, the retinal "screen" is a light-sensitive structure that lines the inside of the eye. It comprises photosensitive cells (called rods and cones) and nerve fibres that convert light into nerve impulses that are then transmitted to the brain via the optic nerve.
3. **Macula:** The macula is the centre of the retina. The macula is densely packed with photoreceptor cells that turn light into nerve signals. With the macula, we can perceive small details like newspaper due to the high concentration of photoreceptors. The fovea, located at the very centre of the macula, is the site of our sharpest eyesight.
4. **Choroid:** Behind the retina, the choroid layer collects unneeded radiation and nourishes the retina's outer layers. It's a thin, dark brown membrane with a pigment that absorbs excess light and prevents blurry vision (due to too much light on the retina). One of the highest blood flow rates in the body is in the choroid. The lamina fusa holds the choroid loosely to the sclera's inner surface.
5. **Optic nerve:** The optic nerve (a bundle of over a million nerve fibres) transmits nerve signals from the eye to the brain. The information on an image is included in these nerve signals, which the brain must process. The optic disc is the visible portion of the optic nerve's front surface on the retina.

Disease of eye[11]

The eye, a perceptive and delicate organ on the body's surface, is readily wounded and infected. Ocular problems are divided into two categories based on their location.

a) Periocular illness: It is a condition that affects the eyes and surrounds them.
b) Intraocular illness: This is a type of eye disease that affects the inside of the eyeball.

a) **Periocular illness:**

The following is a list of periocular diseases:

1. **Conjunctivitis:** This is a condition in which the eye is inflamed and there is a foreign body sensation. Conjunctivitis can be caused by a variety of factors, but the majority of cases are caused by an acute infection or an allergy. The most frequent type of eye illness is bacterial conjunctivitis.
2. **Keratitis:** Reduced vision, ocular pain, red eye, and a cloudy/opaque cornea are common symptoms of this illness. Bacteria, viruses, fungi, protozoa, and parasites are the leading causes of keratitis.
3. **Trachoma:** The infection of the conjunctiva is known as "active trachoma," and it most commonly affects youngsters, particularly pre-schoolers. It's marked by white lumps on the underside of the upper eyelids, as well as non-specific inflammation and thickening, which is frequently linked with papillae. Chlamydia trachomatis is responsible for this. Inflammation and a watery discharge are common signs of active trachoma.
4. **Dry eye:** The symptom of dry eye is caused by a change in the content of tears or an insufficient volume of tears being generated. Dry eye disease is more than simply a source of ocular pain; it can also lead to corneal damage.

Topical preparations are generally easy to treat periocular illnesses like these.

b) Intraocular diseases:

The following are the several intraocular diseases:

1. **Intraocular infections:** Infections of the aqueous fluid, iris, vitreous humour, and retina are examples of intraocular infections. They're more difficult to treat, and they're more likely to happen after ocular surgery, trauma, or endogenous reasons. Such infections are associated with a significant risk of eye damage, as well as the potential for infection to travel from the eye to the brain.
2. **Glaucoma:** Glaucoma is one of the world's most common ocular clinical disorders. More than 2% of people over the age of 40 suffer from this condition, in which elevated intraocular pressure (IOP) of more than 22 mm Hg impairs blood flow to the retina, resulting in peripheral optic nerve loss. Visual field loss and, eventually, blindness occur from this procedure. Aside from these typical eye issues, cataracts and macular degeneration are also frequent, and illnesses with a systemic origin, such as diabetes or hypertension, can have an impact on the eye.

Mechanism of drug release into the eye:[8,12]

The following three mechanisms are used to release the drug:

a. Diffusion
b. Osmosis
c. Bioerosion

a. Diffusion

The drug is continually released as a predetermined, regulated manner in the diffusion process. When the ocular is placed into the eye, the fluid in the eye produces swelling in the polymer, which causes the chain to relax and drug diffusion to occur.

b. Osmosis:

The insert in the Osmosis mechanism has a transverse impermeable elastic membrane that divides the interior of the insert into a first and a second compartment, with the first compartment being bounded by a semi-permeable membrane and the impermeable elastic membranes, and the second compartment being bounded by an impermeable material and the elastic membrane. In the impermeable wall of the insert, there is a drug release opening. The first compartment holds a solute that can't flow through the semipermeable membrane, while the second compartment serves as a reservoir for the medication, which is still in liquid gel form. When the insert is put in the eye's aqueous environment, water diffuses into the first compartment, stretching the elastic membrane, causing the first compartment to expand and the second compartment to contract, forcing the drug through the drug release aperture.

c. Bioerosion:

The body of the insert is constructed from a matrix of bioerodible material in which the medicine is disseminated in the Bioerosion process. When the insert comes into contact with tear fluid, bioerosion of the matrix results in a regulated, long-term release of the medicine. Although the drug can be disseminated equally throughout the matrix, it is thought that if the drug is superficially concentrated in the matrix, a more controlled release can be achieved. A chemical or enzymatic hydrolytic process that leads to polymer solubilization, or degradation to smaller, water soluble

molecules, controls the pace of drug release in fully erodible or E-type devices. According to Heller, these polymers can be hydrolyzed in bulk or at the surface. If the devices retain a stable surface shape and the medication is poorly water soluble, erodible inserts

subjected to surface hydrolysis can exhibit zero order release kinetics.

Mechanism of ocular absorption[13,14]:
The corneal and/or non-corneal pathways for local drug administration into the eye cul-de-sac are used, and the drugs may be transported away by the lacrimal fluids. The absorption mechanism is largely determined by the chemicals, physiochemical properties as well as the target tissue's biological membranes and barriers.

Non corneal absorption: Intra-ocular penetration via the sclera and conjunctiva. Because the penetrating medicine gets absorbed by the general circulation and it is ineffective. Despite this limitation, chemicals with low corneal permeability, such as timolol maleate, gentamicin, and prostaglandin PGF 2 have been demonstrated to diffuse over the conjunctiva and sclera and enter the intraocular portion.

Corneal absorption: For most ophthalmic medicines,

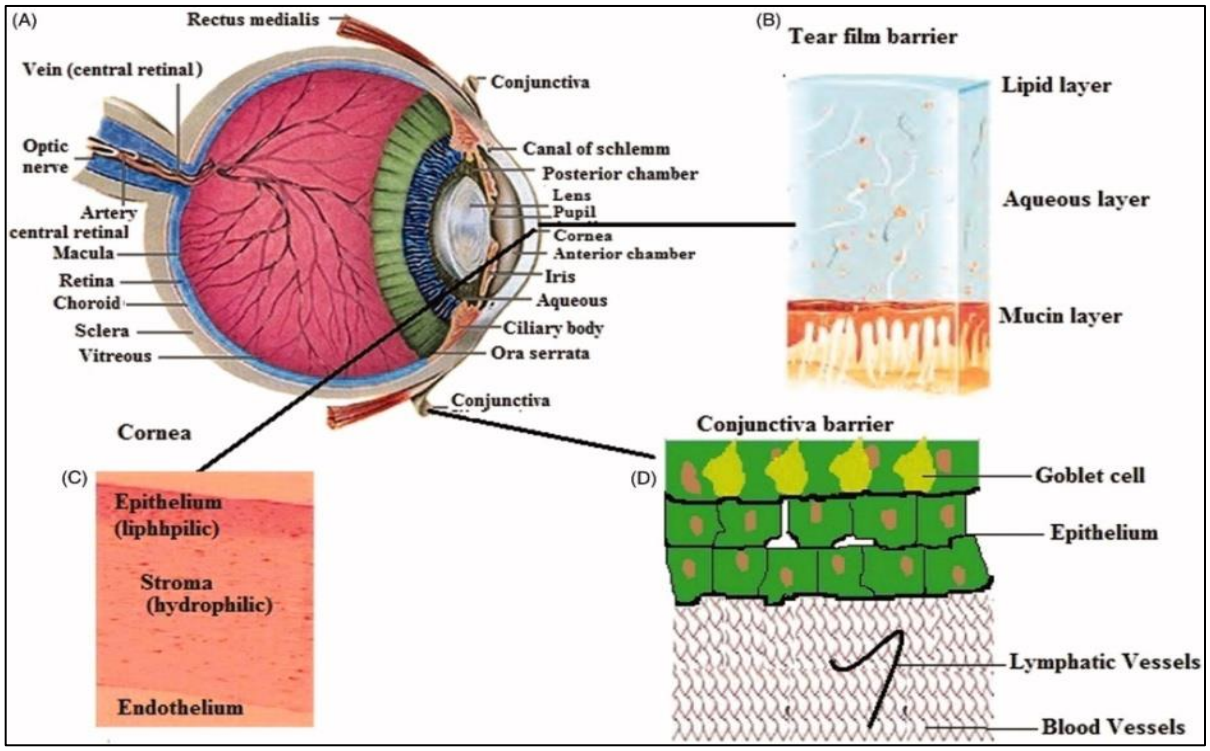


FIG. 2: OCULAR BARRIERS

the corneal pathway is the primary route of absorption. Due to the existence of the corneal epithelium, corneal absorption is likewise thought to be a rate-limited process.

Outer Epithelium: Only tiny ionic and lipophilic molecules can pass through a rate-limiting barrier with a pore size of 60å.

Transcellular transport: Transcellular transport is the movement of cells between the corneal epithelium and the stroma.

Barriers to drug permeation[15-19]:
Barriers to ocular drug distribution include the following.

1.Ocular surface barriers: The ocular surface in touch with the tear film is made up of the corneal and conjunctival superficial layers. The purpose of the ocular surface is to form a barrier against unwanted molecule penetration.

Tear film: Tear film is one of the precorneal barriers, since it dilutes the effective concentration of the administered medications owing to tear turnover (about 1 L/min), faster clearance, and drug molecule binding to tear proteins. Furthermore, instillation dosage volumes range from 20 to 50 litres, whereas cul-de-sac sizes range from 7 to 10 litres. The surplus volume may leak out onto the cheek or through the nasolacrimal duct.

Cornea: The cornea is made up of three layers: epithelium, stroma, and endothelium, as well as a mechanical barrier that prevents external substances from entering the eye. Each layer has a distinct polarity and a drug penetration rate-limiting structure. The corneal epithelium is lipophilic, and tight connections between cells prevent paracellular drug absorption via the tear film. The stroma is made up of collagen fibrils arranged in a lamellar pattern. The stroma's highly hydrated structure acts as a barrier to the passage of lipophilic medicinal molecules. Corneal endothelium is the innermost monolayer of hexagonal-shaped cells that functions as a barrier between the stroma and the aqueous humour. Endothelial junctions are porous, allowing macromolecules to move between the aqueous humour and the stroma.

Conjunctiva:
The conjunctiva of the eyelids and globe is a thin, transparent membrane that plays a role in tear film production and maintenance. Furthermore, capillaries and lymphatics abound in the conjunctiva or episclera. As a result, medicines that have been administered in the conjunctival or episcleral region may be removed through the bloodstream and lymphatic system. Drug molecules can enter the bloodstream via pinocytosis and/or convective transport through paracellular holes in the vascular endothelial layer because the conjunctival blood vessels do not form a tight junction barrier. The conjunctival lymphatics function as an efflux system, allowing for effective removal of waste from the conjunctival space. In rat eyes, at least 10% of a small molecular weight hydrophilic model molecule (sodium fluorescein) is removed through lymphatics during the first hour after administration in the subconjunctival area. Because the interstitial fluid is returned to the systemic circulation after filtration through lymph nodes, medicines carried by lymphatics in combination with their removal by blood circulation can contribute to systemic exposure.

1. **Ocular Wall Barriers:**

The stiff scleral collagenous shell, which is lined internally by the uveal tract, serves as the skeleton of the eye globe.

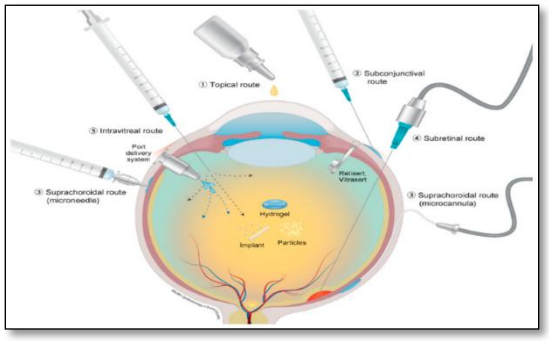
Sclera: Collagen fibres and proteoglycans are mostly found in the sclera, which is surrounded by an extracellular matrix. Scleral permeability has been demonstrated to be strongly influenced by molecular radius, with permeability decreasing nearly exponentially as molecular radius increases. Furthermore, the posterior sclera has a looser weave of collagen fibres than the anterior sclera, and the human sclera is thick towards the limbus (0.53 0.14 mm) but thin near the equator (0.39 0.17 mm).

2. **Blood-ocular barriers:**

Xenobiotics are protected from the eye by blood-ocular barriers, which are present in the circulation. The blood-aqueous barrier and the blood-retina barrier are the two components. Endothelial cells in the uvea, or middle layer of the eye behind the sclera, iris, ciliary body, and choroid, make up the anterior blood-eye barrier. This barrier acts to keep hydrophilic medicines in plasma from entering the aqueous humour and to keep plasma albumin from entering the aqueous humour as well. The retinal pigment epithelium (RPE) and retinal capillaries make up the posterior barrier, which forms a tight wall connection between the eye and the stream of plasma.

Routes of ocular drug delivery[15]:
The following are the numerous pathways for ocular medication administration that can be used:

FIG 3: SCHEMATIC OF SEVERAL



OCULAR DRUG ADMINISTRATION ROUTES.

1. **Intravitreal route:**
   The drug is injected into the vitreous fluid of the eye through this method. This ocular method of administration is used to treat a variety of eye problems.

2. **Intracameral route:**
   The drug's site of action in this mode of administration is the anterior or posterior

chambers of the eye. It is proved by injecting anaesthesia into the anterior chamber of the eye, which is generally done during surgery.

3. **Periocular route:**
   In this technique, the medication is given around the eye. Peril ocular steroid injection, which involves injecting steroids into the eye to treat intraocular inflammation or swelling, can explain it.
4. **Suprachoroidal route:**
   This method of administration focuses on the supra choroid area of the eye. Suprachoroidal space is the area between the sclera and the choroid. The subconjunctival pathway is the most common.

   The medicine is delivered to the mucus membrane, which includes the open area of the eyeball and the inner surface of the eyelids, by this route.
5. **Topical route:**
   In comparison to ointments, gels, and emulsions, which are used to treat illnesses of the anterior segment of the eye, eye drops are the greatest example of ophthalmic dosage forms for topical administration of medications in the eye. Because of its ease of use and low cost, it is the most convenient form of medication delivery to the eye.
6. **Systemic route:**
   Blood-aqueous barrier (BAB) and blood-retinal barrier (BRB) for the anterior and posterior portions of the eye, respectively, are common obstacles to the systemic administration of ophthalmic medicines.

Approaches to improve Ocular Bioavailability: Formulation Approaches

Conventional ocular dosage forms[6]

Topical administration of treatments to the eye is commonly done in the form of solutions. Solubility, ocular toxicity, pKa, pH effect, tonicity, buffer capacity, viscosity, compatibility with other formulation ingredients, preservatives to be utilised, comfort when inserted into the eye, and simplicity of production are all factors to consider when making ophthalmic solutions.

1. **Viscosity enhancers**: Polymers are commonly added to ophthalmic medication solutions, which enhances viscosity and corresponds to a slower elimination from the preocular region, resulting in better precorneal residence time and hence a larger trans corneal penetration of the drug into the anterior chamber. It has modest impact on humans in terms of increasing bioavailability. Methylcellulose, polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), hydroxy ethyl cellulose, hydroxypropyl methylcellulose (HPMC), and hydroxypropyl cellulose (HPC) are among the polymers utilised. Viscosity enhancers can also be made from natural polymers including HA, veegum, alginates, xanthan gum, gelatin, acacia, and tragacanth. These, on the other hand, have the disadvantage of containing germs and fungus.
2. **Eye ointments:** Ointments are often made from a combination of semisolid and solid hydrocarbons (paraffin), which have a melting or softening point around body temperature and are non-irritating to the eyes. Simple bases, in which the ointment forms a single continuous phase, or compound bases, in which a two-phased system (e.g., an emulsion) is used, are the two types of ointments. The medicinal substance is added to the base as a solution or as a highly micronized powder. Ointments break down into little droplets after being injected into the eye, and they stay in the cul-de-sac for a long time as a drug depot. As a result, ointments can help improve medication bioavailability and maintain drug release. Ointments, although being safe and well-tolerated by the eye, have low patient compliance because to blurred vision and occasional discomfort.
3. **Penetration enhancers:** The transport characteristics across the cornea can be maximised by increasing the permeability of the corneal epithelial membrane, so one approach used to improve ophthalmic drug bioavailability is to increase the permeability characteristics of the cornea transiently with suitable substances known as penetration enhancers or absorption promoters. There are several drawbacks, such as eye discomfort and toxicity. Permeation enhancers improve corneal absorption by changing the integrity of the corneal epithelium, which is a rate-limiting step in the transport process from the cornea to the receptor site.
4. **Prodrugs:** Prodrugs work by altering the drug's hydrophilicity (or lipophilicity) in order to increase corneal drug permeability. The prodrug is converted chemically or enzymatically to the active parent molecule either within the cornea or after corneal penetration. As a result, the optimal prodrug must have a high enzyme susceptibility as well as enhanced lipophilicity and partition coefficient.
5. **Ophthalmic inserts[21]:** The purpose of ophthalmic inserts is to stay in front of the eye for a long time. These solid devices are designed to be inserted into the conjunctival sac and release the medicine at a slower rate. These are solid

dosage forms that can solve the drawbacks of standard ophthalmic systems such aqueous solutions, suspensions, and ointments, according to studies. The ocular inserts keep medication concentrations in target tissues at a safe level. Depending on their composition and application, inserts are available in a variety of styles.

I) **Non erodible inserts:** Ocusert, contact lens.

A. **Ocuserts:** Ocuserts are sterile, thin, multilayered, drug-impregnated solid or semisolid consistency devices with a size and form specifically tailored for use in the eye. For ocular inserts including or not containing the medication, a polymeric support is required. The medication can then be entrapped, disseminated, or included as a solution in polymeric supports, which has the advantage of increasing the drug's residence time in the eye, resulting in a sustained release dosage form. Three processes would be followed to release the medication from the inserts. Diffusion, osmosis, and bioerosion are the three processes that occur in the human body.

B. **Contact lenses:** When immersed in medication solutions, contact lenses can absorb water-soluble medicines. These drug-saturated contact lenses are inserted into the eye and allow the medication to be released over an extended length of time. The hydrophilic contact lenses can be utilised to increase the drug's ocular residence period. The Biotite lens, which is constructed of a hydrophilic polymer (2-hydroxy ethyl methacrylate), has been found to allow more fluorescein to penetrate in people. For the production of these lenses, a variety of polymers were utilised. They are constructed up of hydrogels that absorb a certain quantity of aqueous solution and have been shown to be beneficial for medication administration to the anterior of the eye as a result of this characteristic. Hydrophilic contact lenses are used to extend the drug's ocular residence duration.

II) **Erodible ophthalmic insert:** Lacriserts, SODI, and Minidisc are three erodible medication inserts that are currently on the market.

a) **Lacrisert:** Dry eye syndrome is treated using a sterile rod-shaped device manufactured of hydroxyl propyl cellulose without any preservatives. In 1981, Merck, Sharp, and Dohme launched this device. It has a diameter of 12.7 mm and a length of 3.5 mm, and weighs 5 mg.

b) **SODI:** Soluble Ocular Drug Insert was created for cosmonauts who couldn't use eye drops in zero gravity. ABE is a sterile oval-shaped thin film consisting of acrylamide, N-vinylpyrrolidone, and ethyl acrylate. It softens after 10-15 seconds after being introduced into cul-de-sacs, where it is wetted by tear film, and takes the curved form of the globe. After 10-15 minutes, the film transforms into a viscous polymer mass, and after 30-60 minutes, it transforms into a polymer solution.

c) **Minidisc:** In contact with the eyeball, the minidisc is a contoured disc with a convex front and concave rear. With a diameter of 4-5mm, it's similar to a contact lens. The minidisc is constructed of bis (4-methacryloxy) butyl polydimethyl siloxane, a silicone-based prepolymer. Minidiscs can be either hydrophilic or hydrophobic, allowing both water soluble and insoluble medications to be released for longer periods of time.

Novel ophthalmic dosage forms[22-24]:

Various approaches such as mucoadhesive polymers, polymer coated particulates (Nanoparticles, microparticles), inserts, controlled delivery systems (implants, iontophoresis, dendrimers, microemulsion, nanosuspension, microneedle) and vesicular system including liposomal and niosomal formulations are used in the novel drug delivery system. These delivery techniques prolong the active ingredient's clearance from the eye while also improving drug molecule corneal penetration.

A. Vesicular System:

a. Liposome: Liposomes are biocompatible and biodegradable lipid vesicles with a diameter of 25-10,000 nm made out of natural lipids. They make close contact with the corneal and conjunctival surfaces, which is advantageous for medications that are poorly absorbed, such as those with a low partition coefficient, poor solubility, or medium to high molecular weights, since it enhances the likelihood of ocular drug absorption. The corneal epithelium is sparsely covered with negatively charged mucin, which the liposome's positive charged surface may bond to. Soft contact lenses coated with ciprofloxacin encapsulated in a liposome were developed and tested.

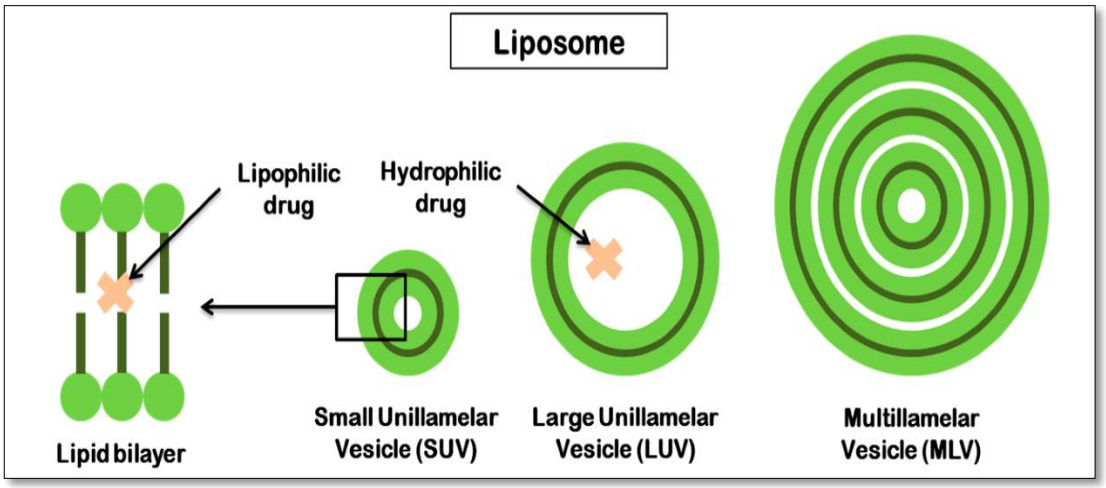


FIG 4: LIPOSOMES

b. Niosomes:

These are bilayer, lamellar structures that are mostly made up of non-ionic surfactants and a rigidizing agent that are hydrated in various ways to produce vesicles. They have an aqueous compartment and are either unilamellar or multilamellar. It is natural to be amphiphilic. Niosomes are made up of two important components: cholesterol and non-ionic surfactants.

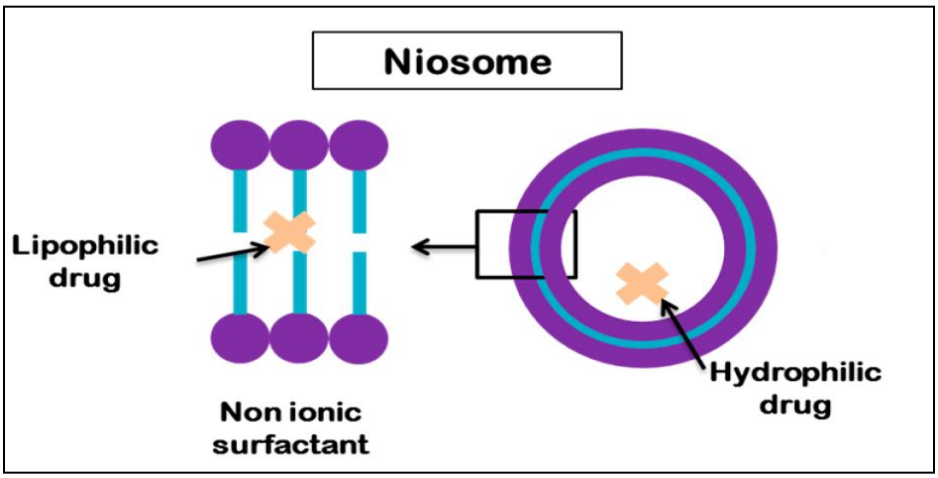


FIG 5: NIOSOMES

Cholesterol:

Cholesterol, a waxy steroid metabolite present in cell membranes, is a waxy steroid metabolite. Cholesterol is employed in the production of niosomes to give the niosomal bilayer stiffness and orientational order. It uses non-ionic surfactants to produce vesicles, which decreases agglomeration and improves stability. Cholesterol is also known to hinder niosomal systems from transitioning from gel to liquid phase, resulting in niosomes with reduced leakage.

Non-ionic Surfactant: In Niosome formulations, non-ionic surfactants are the most important ingredient. They have a hydrophilic head group and a hydrophobic tail, and they have a lot of interfacial activity. The hydrophobic moiety can be made up of 1/2/3 alkyl chains, per fluro group or even a single stearyl group in some situations. The most often utilised surfactants are sorbitan fatty acid esters. Surfactants from non-ionic groups, such as spans, come in a variety of grades, including span 20, span 40, span 60, span 80, and span 85. Tweens also have varying grades of surfactant, such as Tween 20, Tween 40, Tween 60, and Tween 80. The HLB value of the surfactant, the chemical structure of the components, and the essential packing parameter all influence the generation of bilayer vesicles rather than micelles.

B. Controlled Delivery System

a. Implants: Implants are an efficient medicine delivery mechanism for persistent ocular illnesses like CMV retinitis. Non-biodegradable polymers were

previously utilised, but insertion and removal required surgical procedures. Biodegradable polymers, such as Poly Lactic Acid, are being used to deliver medications in the vitreous cavity, and they are safe and effective. Eye implants provide a number of benefits, including the potential to deliver consistent therapeutic doses of medication to the location of ocular illness while limiting systemic adverse effects. Biodegradable (i.e. eroding) and nonbiodegradable devices for regulated, continuous medication release are two types of devices (i.e., noneroding). Biodegradable implants offer the benefit of being able to be shaped into a variety of forms and not needing to be removed. Nonbiodegradable implants have the benefit of providing a consistent, regulated release of a medicine for potentially lengthy periods of time (years), but they also have the disadvantage of requiring removal and/or replacement after the substance has been depleted[25].

b. Iontophoresis[26]:

Due to its non-invasive method of distribution to both the anterior and posterior segments, ocular iontophoresis has lately attracted a lot of attention. It necessitates the use of a low-voltage electric current to aid in the penetration of ionised drugs into tissue. The possible negative effects of intraocular injections can be avoided with this method of administration. This gadget also distributes the active drug into the retina and choroid. Iontophoresis, both transcorneal and transscleral, has been widely used to transport a wide range of pharmacological molecules, including gentamicin and dexamethasone.

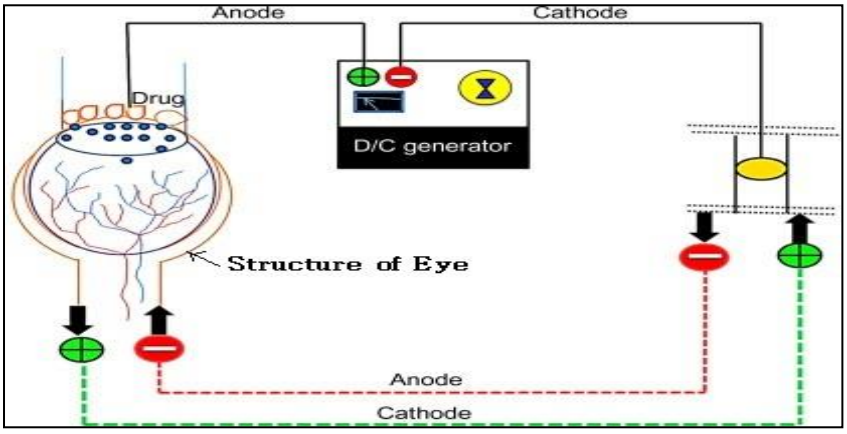


FIG 6: DIAGRAM OF OCULAR IONTOPHORESIS

Dendrimers:[20, 22, 27]

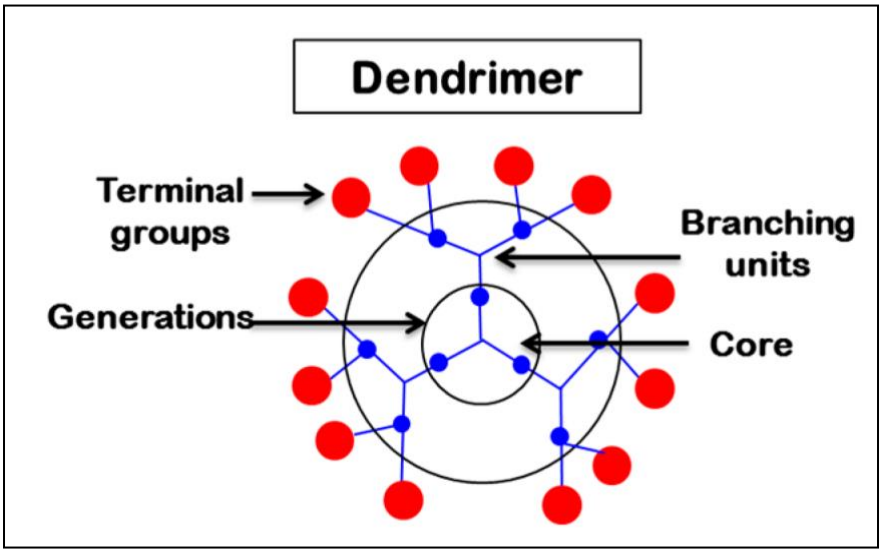


FIG. 7: DENDRIMER

Dendrimers are monodispersed macromolecules with multiple reactive end groups that form an interior cavity around a tiny molecule. Dendrimers are synthetic three-dimensional repeating-unit branching macromolecules; polyamidoamine (PAMAM) and DAB polypropyleneimine (PPI/DAB) are common biological dendrimers. Drug molecules are encapsulated in dendrimer particles, allowing for regulated release in the intraocular space.

Applications of dendrimers:

1. When it comes to overcoming the epithelial and retinal barriers in the cornea and retina, PAMAM dendrimers routes can be quite useful.
2. Dendrimers containing phosphorus are used to treat glaucoma.
3. Intraocular tumours and retinoblastoma are treated using porphyrin glycodendrimers.

d. Microemulsion[28]:

MEs are thermodynamically stable phase transition systems with low surface tension and tiny droplet size (5–200 nm), which might lead to high drug absorption and penetration, and hence a high chance of drug delivery to the posterior portion of the eye. In 1943, Hoar and Schulman created the phrase ME. MEs are surfactant-stabilized colloidal nano dispersions of the o/w or w/o kinds. The aqueous phase, organic phase, and surfactant/cosurfactant systems that are chosen are all important factors that might impact the system's stability. The solubility of a medicinal molecule, such as indomethacin or chloramphenicol, improves significantly when these components are optimised. Microemulsion systems have been used to increase permeability through the cornea in addition to solubility. A pilocarpine-based oil-in-water system with lecithin, propylene glycol, PEG 200 as surfactant/co surfactant, and isopropyl myristate as the oil phase has been developed.

e. Nanosuspension[29]:

This is a sub-micron colloidal system made up of a weakly water-soluble medication suspended in a surfactant-stabilized dispersion medium.An increase in the dissolution rate and bioavailability is observed in the reduction of drug particles into the sub-micron range. Nanosuspensions are generated for poorly water-soluble drugssuspended at nano size range in a suitable dispersion medium. Colloidal carriers, such as polymeric resins, are generally used in nanosuspension formulations. They aid in improving medication solubility and thus bioavailability. Thecarriers having such type of properties can be used as inert carriersfor ophthalmic drugs, because they do not cause any irritation to thecornea, iris or conjunctiva. AnThey are popular because, unlike microemulsions, they are non-irritant.

f. Microneedles[30]:

Microneedles allow for the administration of free or encapsulated drugs in a less invasive manner. Microneedles were used for overcoming the stratum corneum and were used for transdermal drug delivery. The effectiveness of microneedles for transdermal drugdelivery systems inspired researchers to investigate their potential to treat anterior and posterior segment ocular disorders. The microneedle research and production technique is based on a preference for least invasiveness. These microneedles have the ability to deliver a wide variety of medications to the ocular tissues in the back of the eye. Additionally, some features of therapies, such as intravitreal injections, which have several dreadful side effects such as cataracts, endophthalmitis, haemorrhage, and retinal detachment, may be overcome, allowing the prior implication to be overcome. In disorders including diabetic retinopathy and age-related macular degeneration, therapy results may be improved.

g. Mucoadhesive polymers[31]:

Various natural and synthetic viscosity modifying agents were added to the medium to increase the viscosity of the preparation, lower the drainage rate, and therefore improve the therapeutic effect. Mucoadhesion, hydration or swelling, molecular weight, functional groups, molecular conformation or chain flexibility, motility, and concentration are all influenced by polymer-associated variables. Compared to non-ionic celluloseethers or polyvinyl alcohol, charged polymers, both anionic and cationic, have higher mucoadhesive ability. Mucoadhesive polymers are divided into three groups: Poly (acrylic acid), Carbomer (neutralised), Hyaluronan, sodium carboxy methyl cellulose, Poly (galacturonic acid), sodium alginate, Pectin, Xanthan gum, Xyloglucan gum. Anionic: Poly (acrylic acid), Carbomer (neutralised), Hyaluronan, sodium carboxy methyl cellulose, Poly (galacturonic acid), sodium alginate, Pectin.

C. Particulates

Microparticles and Nanoparticles[32]:

Microparticles and nanoparticles have been designed to efficiently carry medications into the intraocular space and can contain a variety of compounds. These injected particles are disseminated in the vitreous due to the alteration and manufacturing of particle surfaces, compositions, polysaccharide mixes, and ionic charges, allowing for longer intravitreal half-

lives through continuous drug release and delayed breakdown and removal.

Depending on the production procedure and the substance used, nanoparticles can be crystalline or amorphous. In terms of consistency of size and polydispersity index, manufacturing nanoparticles is a difficult undertaking. The particle properties are heavily influenced by critical process factors in preparation processes. Galindo-Rodriguez and colleagues used three distinct ways to make nanoparticles: emulsion-based, salting out, and nanoprecipitation. With diverse procedures and changes in the physicochemical parameters of the aqueous and organic phases, the particle size ranges altered. With salting out, emulsification-diffusion, and nanoprecipitation techniques, particle sizes of 123–710 nm, 108–715 nm, and 147–245 nm, respectively, were reported.

CONCLUSION:

The entire study concludes that ocular drug delivery provides a unique carrier mechanism for numerous drugs. Topical and intravitreal drug delivery are not regarded safe, efficacious, or patient-friendly. In ocular illnesses affecting both segments, drug administration via the periocular channel has the potential to circumvent several of these constraints while simultaneously providing sustained drug levels. Because of the nature of ocular disorders, the unique structure of the eye, and the barriers inherent in the system, particularly the posterior ocular segments, treating ocular diseases effectively is a big problem for scientists working in the field of ocular drug delivery. Many attempts have been made to improve ocular bioavailability by adjusting product formulation parameters like viscosity and the use of mucoadhesive polymers. These methods for extending corneal contact duration have resulted in a small increase in ocular bioavailability. As a result, it appears sensible to examine novel drug delivery systems such as nanotechnology, microspheres, liposomes, suitable prodrug in situ forming gel, and iontophoresis to improve ocular absorption and decrease adverse effects.

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