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Novel Approaches for Ocular Targeted Drug Delivery Systems

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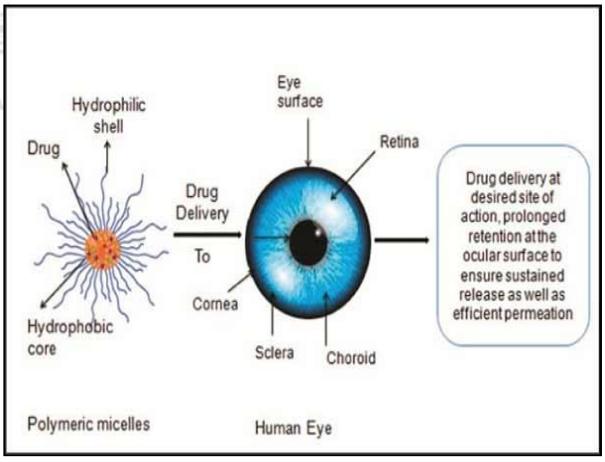
ABSTRACT

The major challenge faced by today's pharmacologist and formulation scientist is ocular drug delivery. The topical eye drop is the most convenient and patient-compliant route of drug administration, especially for the treatment of anterior segment diseases. Delivery of drugs to the targeted ocular tissues is restricted by various precorneal, dynamic and static ocular barriers. Also, therapeutic drug levels are not maintained for a longer duration in target tissues. In the past two decades, ocular drug delivery research accelerated advanced toward developing novel, safe, and patient compliant formulation and drug delivery devices/techniques, which may surpass these barriers and maintain drug levels in tissues. Anterior segment drug delivery advances are witnessed by modulation of conventional topical solutions with permeation and viscosity enhancers. Also, it includes the development of conventional topical formulations such as suspensions, emulsions, and ointments. Various nanoformulations have also been introduced for anterior segment ocular drug delivery. On the other hand, for posterior ocular delivery, research has been immensely focused on the development of drug-releasing devices and nanoformulations for treating chronic vitreoretinal diseases. These novel devices and/or formulations may help to surpass ocular barriers and associated side effects with conventional topical drops.

1. INTRODUCTION

Novel drug delivery systems are the new system Recent advances in the understanding of pharmacokinetic & pharmacodynamic behavior of drugs have to offer a more rational approach to the development of an optimal drug delivery system. The novel drug delivery systems (NDDS) are carriers that maintain the drug concentration in the therapeutic range for a longer period. Delivering ocular drugs to their target tissues often requires them to traverse the fat-water-fat structure of the corneal barrier while ensuring minimum wastage through tear washout and systemic absorption. This is why delivering drugs effectively to the posterior of the eye is a challenge that many companies have aimed to overcome. This instalment of the Innovations in Retina column describes recent developments in methods of ophthalmic drug delivery to the posterior segment of the eye.

Advantages of novel drug delivery systems over conventional drug delivery.



1. Optimum therapeutic-drug concentration in the blood or tissue may be maintained over a prolonged period.

2. Pre-determined release rates of an extended period may be achieved.

3. Duration for short half-life drug may be increased.

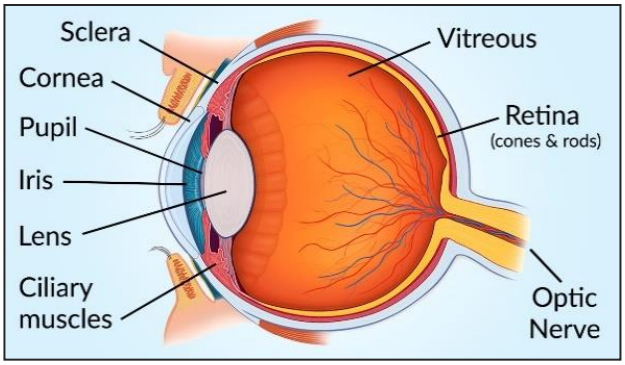
4. By targeting the site of action, side effects may be eliminated.

5. Frequent dosing and wastage of the drug may be reduced or excluded.

6. Better patient compliance may be ensured.

2. ANATOMY OF EYE

How we see depends upon the transfer of light. Light passes through the front of the eye (cornea) to the lens. The cornea and the lens help to focus the light rays onto the back of the eye (retina). The cells in the retina absorb and convert the light to electrochemical impulses which are transferred along the optic nerve and then to the brain. The eye works much the same as a camera. The shutter of a camera can close or open depending upon the amount of light needed to expose the film in the back of the camera. The eye, like the camera shutter, operates in the same way. The iris and the pupil control how much light to let into the back of the eye. when it is very dark, our pupils are very large, letting in more light. the lens of a camera can focus on objects far away and up close with the help of mirrors and other mechanical devices. The lens of the eye helps us to focus but sometimes needs some additional help to focus clearly. Glasses, contact lenses, and artificial lenses all help us to see more clearly.



THERE ARE VARIOUS PARTS OF THE EYE WHERE THE OCULAR DELIVERY ROUTE SYSTEM PLAYS A VERY IMPORTANT ROLE.

- **Choroid**

Layer containing blood vessels that line the back of the eye and is located between the retina (the inner light-sensitive layer) and the sclera (the outer white eye wall).

- **Ciliary Body**

Structure containing muscle and is located behind the iris, which focuses the lens.

- **Cornea**

The clear front window of the eye transmits and focuses (i.e., sharpness or clarity) light into the eye. Corrective laser surgery reshapes the cornea, changing the focus.

- **Fovea**

The center of the macula provides sharp vision.

- **Iris**

The coloured part of the eye helps regulate the amount of light entering the eye. When there is a bright light, the iris closes the pupil to let in less light. And when there is low light, the iris opens up the pupil to let in more light.

- **Lens**

Focuses light rays onto the retina. The lens is transparent and can be replaced if necessary. Our lens deteriorates as we age, resulting in the need for reading glasses. Intraocular lenses are used to replace lenses clouded by cataracts.

- **Macula**

The area in the retina contains special light-sensitive cells. In the macula these light-sensitive cells allow us to see fine details clearly in the center of our visual field. The deterioration of the macula is a common condition as we get older (age-related macular degeneration or ARMD).

- **Optic nerve**

A bundle of more than a million nerve fibers carrying visual messages from the retina to the brain. (To see, we must have light and our eyes must be connected to the brain.) Your brain controls what you see since it combines images. The retina sees images upside down but the brain turns images right side up. This reversal of the images that we see is much like a mirror in a camera. Glaucoma is one of the most common eye conditions related to optic nerve damage.

- **Pupil**

The dark center opens in the middle of the iris. The pupil changes size to adjust for the amount of light available (smaller for bright light and larger for low light). This opening and closing of light into the eye are much like the aperture in most 35 mm cameras which lets in more or less light depending upon the conditions.

- **Retina**

The nerve layer lining the back of the eye. The retina senses light and creates electrical impulses that are sent through the optic nerve to the brain.

- **Sclera**

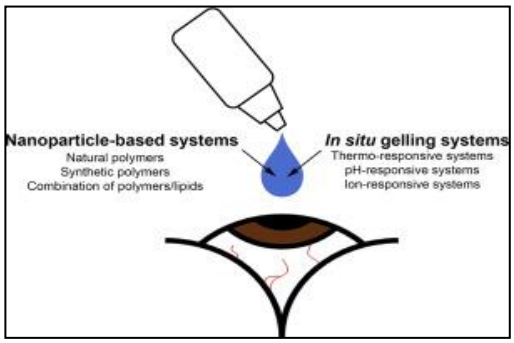
The white outer coat of the eye surrounds the iris.

- **Vitreous Humour**

The clear, gelatinous substance fills the central cavity of the eye.

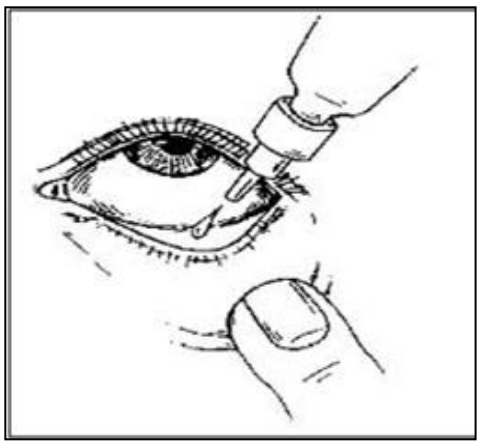
3. CONVENTIONAL OCULAR DRUG DELIVERY SYSTEMS

A] SOLUTION EYE DROPS



Topical drops are the most convenient, safe, immediately active, patient compliant, and non-invasive mode of ocular drug administration. An eye drop solution provides a pulse drug permeation post topical drop instillation, after which its concentration rapidly declines. The kinetics of drug concentration decline may follow an approximate first order. Therefore, to improve drug contact time, permeation, and ocular bioavailability; various additives may be added to topical eye drops such as viscosity enhancers, permeation enhancers, and cyclodextrins. Viscosity enhancers improve precorneal residence time and bioavailability upon topical drop administration by enhancing formulation viscosity. Permeation enhancers improve corneal uptake by modifying the corneal integrity. Other additives such as chelating agents, preservatives, surface-active agents, and bile salts were studied as possible permeation enhancers.

B] EMULSIONS

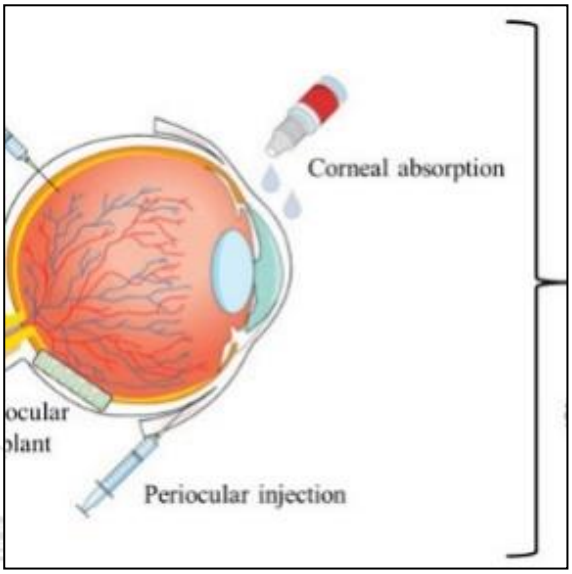


An emulsion-based formulation approach offers an advantage to improve both solubility and bioavailability of drugs. Two types of emulsions are commercially exploited as vehicles for active pharmaceuticals: oil in water (o/w) and water in oil (w/o) emulsion systems. For ophthalmic drug delivery, o/w emulsion is common and widely preferred over the w/o system. The reasons include less irritation and better ocular tolerance of o/w emulsion. Restasis, Refresh Endura (a non-medicated emulsion for eye lubrication) are examples of currently

marketed ocular emulsions in the United States. Several studies have demonstrated the applicability of emulsions in improving precorneal residence time, drug corneal permeation, providing sustained drug release, and thereby enhancing ocular bioavailability.

C] SUSPENSION

Suspensions are another class of non-invasive ocular topical drop drug carrier systems. Suspension may be defined as a dispersion of finely divided insoluble API in an aqueous solvent consisting of a suitable suspending and dispersing agent. In other words, the carrier solvent system is a saturated solution of API. Suspension particles retain in the precorneal pocket and thereby improve drug contact time and duration of action relative to drug solution. Duration of drug action for suspension is particle size-dependent. Smaller size particle replenishes the drug absorbed into ocular tissues from the precorneal pocket. While on the other hand, larger particle size helps retain particles for a longer time and slow drug dissolution. Thus, optimal particle size is expected to result in optimum drug activity. Several suspension formulations are marketed worldwide to treat ocular bacterial infections. TobraDex suspension is one of the widely recommended commercial products for subjects responding to steroid therapy. TobraDex is a combination product of antibiotic, tobramycin (0.3%), and steroid, dexamethasone (0.1%). The major drawback of this commercial product is its high viscosity.



D] OINTMENT

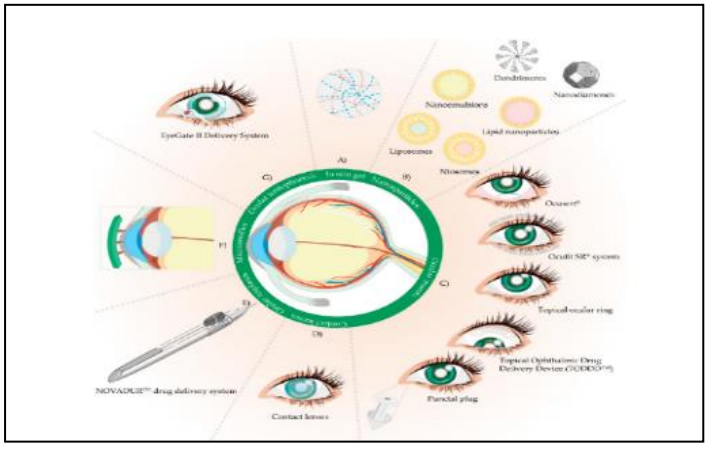
Ophthalmic ointments are another class of carrier systems developed for topical application. Ocular ointment comprises a mixture of semisolid and a solid hydrocarbon (paraffin) that has a melting point at physiological ocular temperature (34 °C). The choice of hydrocarbon is dependent on biocompatibility. Ointments help to improve ocular bioavailability and sustain the drug release. Vancomycin HCl (VCM) is a glycopeptides antibiotic with excellent activity against aerobic and anaerobic gram-positive bacteria and methicillin and cephem resistant *Staphylococcus aureus* (MRSA). Despite the better activity of VCM, no appropriate

topical formulation was available in the market. Better ocular tissue permeability of VCM was not expected in a normal eye but few clinical effects of VCM solution were reported in ocular disease treatment. The reason for the observed effects was hypothesized due to a broken ocular barrier system, which might have improved drug permeation.

ADVANTAGES AND DISADVANTAGES OF CONVENTIONAL OCULAR DELIVERY SYSTEM

CARRIER	ADVANTAGES	DISADVANTAGES
EYE SOLUTION	Easy to instill Economic	Drainage Low bioavailability
SUSPENSION	Prolonged contact time Patient compliance	Irritation (particle size)
OINTMENT	No tear dilution	Blurring vision
CREAMS	Improved stability	Presence of gritty particles

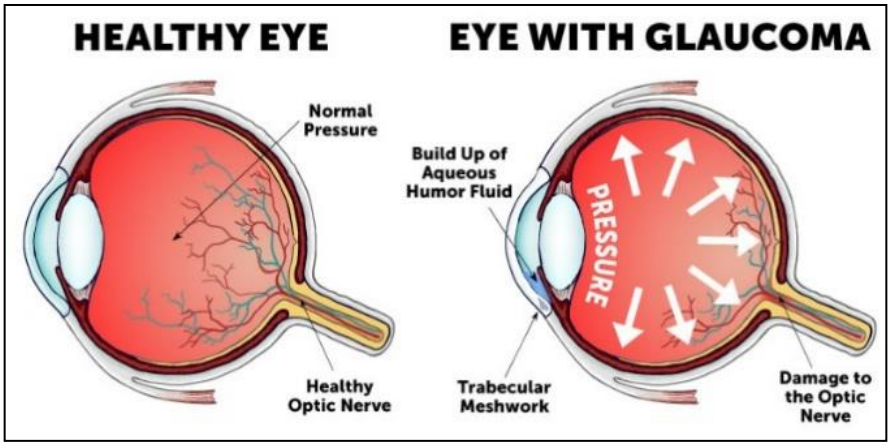
4. GLAUCOMA AND ITS TREATMENT



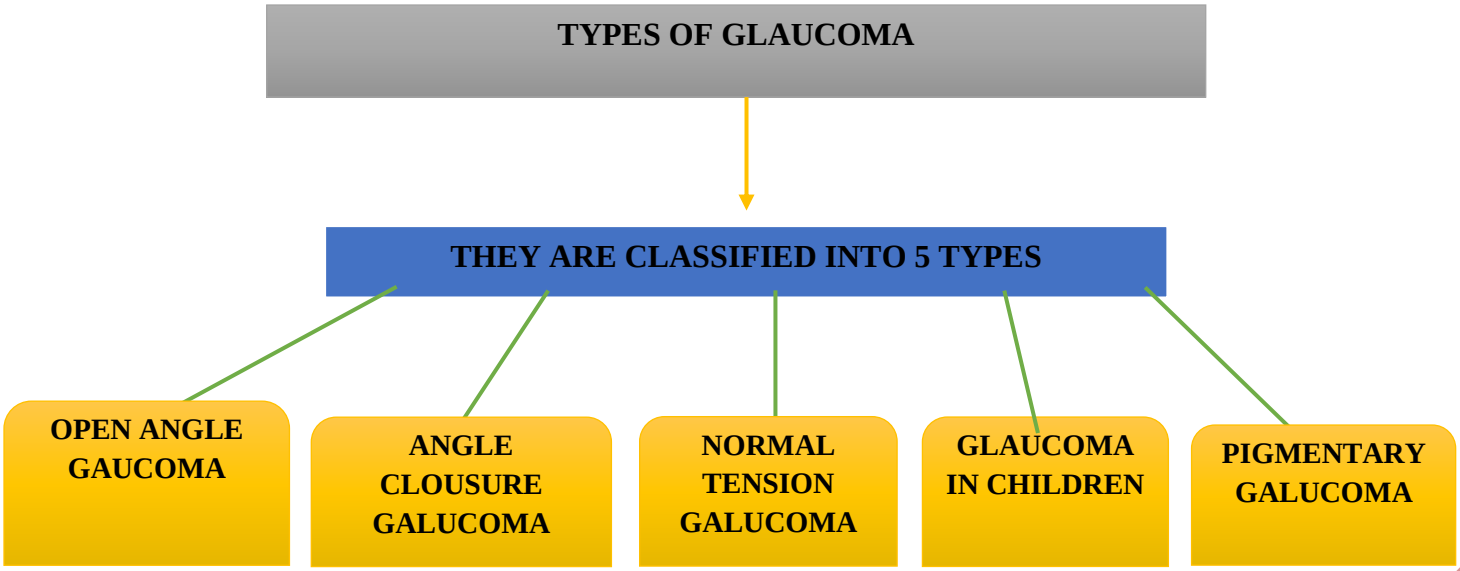
Glaucoma is a group of eye conditions that damage the optic nerve, the health of which is vital for good vision. This damage is often caused by abnormally high pressure in your eye. Glaucoma is one of the leading causes of blindness for people over the age of 60. It can occur at any age but is more common in older adults. Many forms of glaucoma have no warning signs. The effect is so gradual that you may not notice a change in vision until the condition is at an advanced stage.

CAUSE OF GLAUCOMA:

Glaucoma is the result of damage to the optic nerve. As this nerve gradually deteriorates, blind spots develop in your visual field. For reasons that doctors don't fully understand, this nerve damage is usually related to increased pressure in the eye. Elevated eye pressure is due to a build-up of a fluid (aqueous humor) that flows throughout the inside of your eye. This internal fluid normally drains out through a tissue called the trabecular meshwork at the angle where the iris and cornea meet. When fluid is overproduced or the drainage system doesn't work properly, the fluid can't flow out at its normal rate, and eye pressure increases. Glaucoma tends to run in families. In some people, scientists have identified genes related to high eye pressure and optic nerve damage.



5. TYPES OF GLAUCOMA



TREATMENT

Regular comprehensive eye exams can help detect glaucoma in its early stages before significant damage occurs.

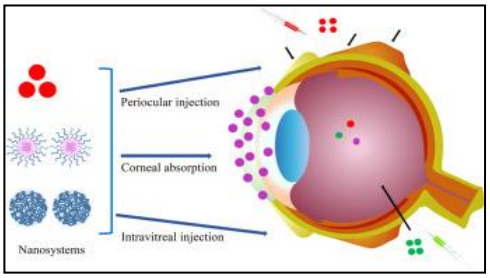
- Glaucoma eyedrops can significantly reduce the risk that high eye pressure will progress to glaucoma. To be effective, eyedrops prescribed by your doctor need to be used regularly even if you have no symptoms.

- **Wear eye protection.** Serious eye injuries can lead to glaucoma. Wear eye protection when using power tools or playing high-speed racket sports in enclosed courts.

Regular, moderate exercise may help prevent glaucoma by reducing eye pressure. Talk with your doctor about an appropriate exercise program.

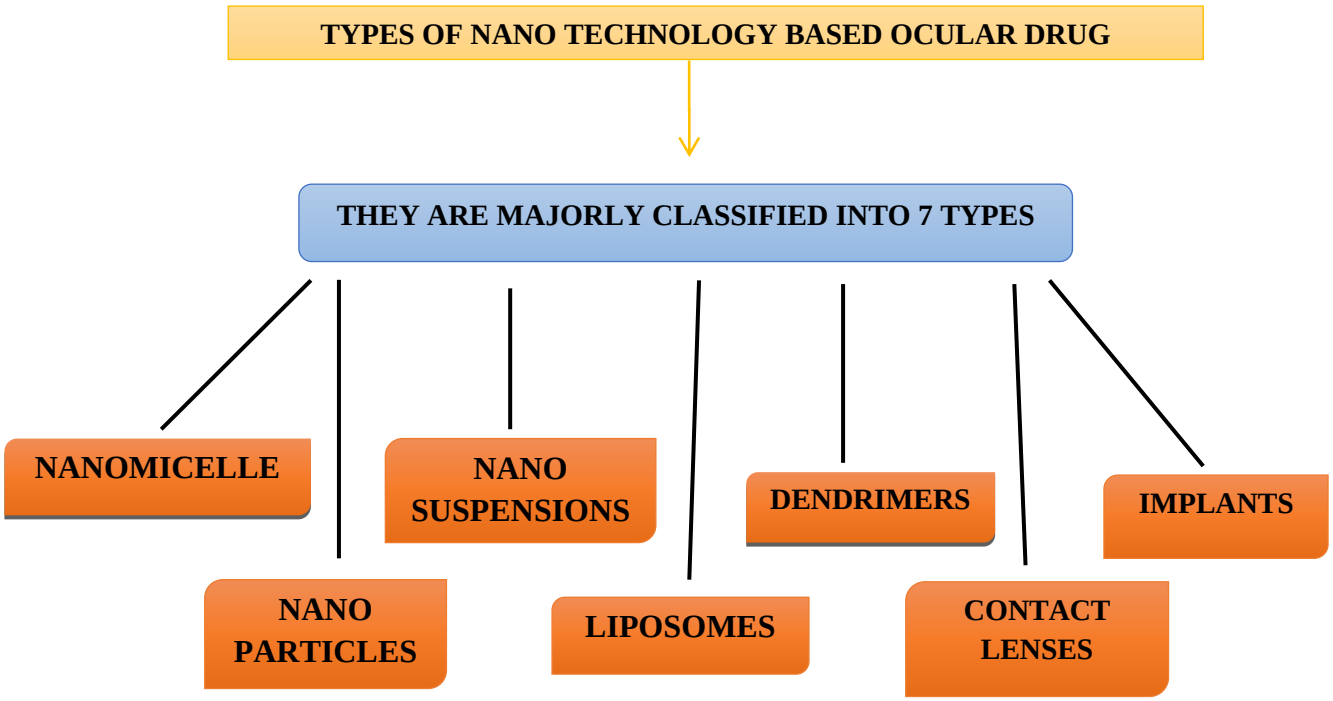
6. NOVEL OCULAR DRUG DELIVERY SYSTEMS

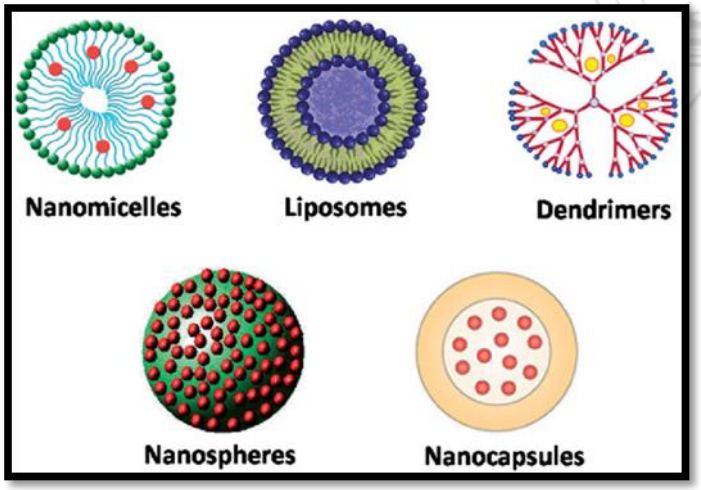
1] NANOTECHNOLOGY-BASED OCULAR DRUG DELIVERY:

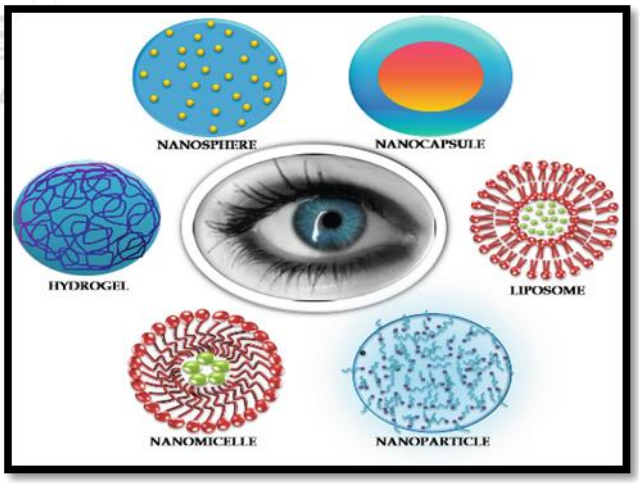


Nanotechnology-based drug delivery is also very efficient in crossing membrane barriers, such as the blood-retinal barrier in the eye, and can function as an excellent system for chronic ocular diseases requiring frequent drug administration, like chronic cytomegalovirus retinitis (CMV).

TYPES OF NANOTECHNOLOGY-BASED OCULAR DELIVERY







A] NANO MICELLE

Micelles consist of amphiphilic molecules that, generally, self-assemble in aqueous media to form organized supramolecular structures. Micelles are formed in various sizes (10-1000 nm) and shapes (spherical, cylindrical, star-shaped, etc.) depending on the molecular weights of the core and corona forming blocks. The self-assembly takes place above a certain concentration, referred to as critical micelle concentration (CMC).

The force driving the self-assembly and maintenance of supramolecular assembly is hydrophobic interactions of core-forming blocks, for typical micellar structures. The corona-forming block is water-soluble that renders micelles soluble in the aqueous phase. Taking the advantage of the hydrophobic core, the nanocarriers can be utilized to enhance the water solubility of hydrophobic molecules.

Classification of Nanomicelle

Nanomicelles investigated for ODD thus far be divided into three broad categories, *i.e*.,

- Polymeric Nanomicelle
- Surfactant Nanomicelle
- PolyIon Complex Nanomicelle

Polymeric Nanomicelle: Polymeric nano micelle is formed by amphiphilic polymers with distinct hydrophobic and hydrophilic segments. The polymer self-assembles to form micelles in an aqueous solution, wherein the water-insoluble segment forms the core and the hydrophilic segment forms the corona. In some cases, the self-assembly is not spontaneous and micelle formation is assisted by additional means, such as temperature. The self-assembly occurs above the CMC. The hydrophilic segments forming corona aid the solubilization of the entire supramolecular structure. Polymeric micelles are characterized by their low CMC in addition to excellent kinetic and thermodynamic stability in solution. Ideally, the polymers utilized to prepare nano micelles should be biodegradable and/or biocompatible.

B] NANOPARTICLES

Nanoparticles are colloidal carriers with a size range of 10 to 1000 nm. For ophthalmic delivery, nanoparticles 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 nanocapsules or nanospheres. In nanocapsules, the drug is enclosed inside the polymeric shell while in nanospheres; the drug is uniformly distributed throughout the polymeric matrix. In the past 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. Nanoparticles represent a promising candidate for ocular drug delivery because of their small size leading to low irritation and sustained release property avoiding frequent administration. However, like aqueous solutions, nanoparticles may be eliminated rapidly from the precorneal pocket. Hence, for topical administration nanoparticles with mucoadhesive properties have been developed to improve precorneal residence time. Polyethylene glycol (PEG), chitosan, and hyaluronic acid are commonly employed to improve the precorneal residence time of nanoparticles.

C] NANO SUSPENSIONS

Nanosuspensions are colloidal dispersion of submicron drug particles stabilized by polymer(s) or surfactant(s). It has emerged as a promising strategy for the delivery of hydrophobic drugs. Ocular delivery provides several advantages such as sterilization, ease of eye drop formulation, less irritation, increase precorneal residence time, and enhancement in ocular bioavailability of drugs that are insoluble in tear fluid. The efficacy of nanosuspensions in improving the ocular bioavailability of glucocorticoids has been demonstrated in several research studies. Glucocorticoids such as prednisolone, dexamethasone, and hydrocortisone are widely recommended for the treatment of inflammatory conditions affecting anterior segment ocular tissues. The current therapy with these drugs requires frequent administration at higher doses which induce cataract formation, glaucoma, and damage optic nerve. Efforts have been made toward improving the ocular bioavailability of glucocorticoids by formulating them as nanosuspensions.

.D] LIPOSOMES

Liposomes are 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 unilamellar vesicles (10–100 nm), large unilamellar vesicles (100–300 nm), and multilamellar vesicles (contain more than one bilayer. For ophthalmic applications, liposomes represent ideal delivery systems due to their excellent biocompatibility, cell membrane-like structure, and ability to encapsulate both hydrophilic and hydrophobic drugs. Liposomes have demonstrated good effectiveness for both anterior and posterior segment ocular delivery in several research studies. Recent advancements in liposomal ocular drug delivery.

E] DENDRIMERS

Dendrimers are characterized as nanosized, highly branched, star-shaped polymeric systems. These branched polymeric systems are available in different molecular weights with terminal end amine, hydroxyl, or carboxyl functional groups. The terminal functional group may be utilized to conjugate targeting moieties. Dendrimers are being employed as carrier systems in drug delivery. Selection of molecular weight, size, surface charge, molecular geometry, and the functional group is critical to delivering drugs. The highly branched structure of dendrimers allows the incorporation of a wide range of drugs, hydrophobic as well as hydrophilic. In ocular drug delivery, few promising results were reported with these branched polymeric systems Poly (amidoamine) (PAMAM) dendrimers are widely employed.

F] CONTACT LENSES

Contact lenses are thin, and curved shape plastic disks that are designed to cover the cornea After application, the contact lens adheres to the film of tears over the cornea due to the surface tension. Drug-loaded contact lenses have been developed for ocular delivery of numerous drugs such as β-blockers, antihistamines, and antimicrobials. It is postulated that in presence of a contact lens, drug molecules have a longer residence time in the post-lens tear film which ultimately led to higher drug flux through the cornea with less drug inflow into the nasolacrimal duct. Usually, the drug is loaded into contact lenses by soaking them in drug solutions. These soaked contact lenses demonstrated higher efficiency in delivering drugs compared to conventional eye drops. It had a much higher bioavailability of dexamethasone (DX) from poly (hydroxyethyl methacrylate) (PHEMA) contact lenses in comparison to eye

drops. Indeed, more efficient than topical drops, these soaked contact lenses suffer from disadvantages of inadequate drug loading and short-term drug release. To overcome these obstacles, particle-laden contact lenses and molecularly imprinted contact lenses have been developed. In particle-laden contact lenses, the drug is first entrapped in vesicles such as liposomes, nanoparticles, or microemulsions and then these vesicles are dispersed in the contact lens material.

G] IMPLANTS

Intraocular implants are specifically designed to provide localized controlled drug release over an extended period. These devices help in circumventing multiple intraocular injections and associated complications. Usually, for drug delivery to posterior ocular tissues, implants are placed intravitreally by making an incision through minor surgery at pars plana which are located posterior to the lens and anterior to the retina. Though implantation is an invasive procedure, 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 the ability to circumvent the blood-retina barrier. Several implantable devices have been developed for ocular drug delivery, especially for the treatment of chronic vitreoretinal diseases. Ocular implants are available as biodegradable and non-biodegradable drug-releasing devices. Non-biodegradable implants offer long-lasting release by achieving near zero-order release kinetics.

ADVANTAGES AND DISADVANTAGES:

ADVANTAGES	**DISADVANTAGES**
Accurate dosing	Interference with vision
Absence of preservative	Occasional loss during sleep
Increase in shelf life due to absence of water	Movement around the eye

7. OCULAR DRUG DELIVERY SYSTEM IN THE TREATMENT OF PINK EYE SYNDROME

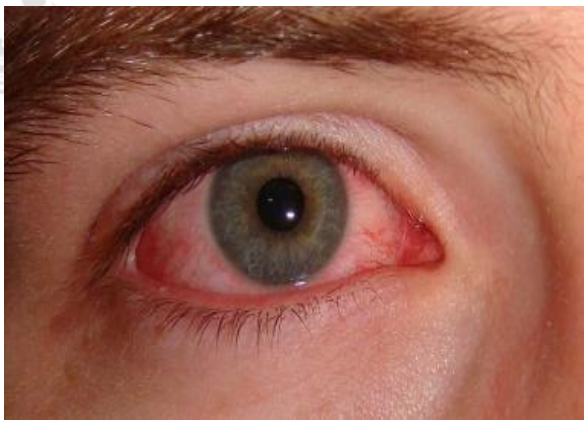
WHAT IS PINK EYE SYNDROME?

Conjunctivitis, also known as pink eye, is inflammation of the outermost layer of the white part of the eye and the inner surface of the eyelid. It makes the eye appear pink or reddish. Pain, burning, scratchiness, or itchiness may occur.

CAUSES OF PINK EYE SYNDROME

Conjunctivitis can be caused by a virus, bacteria, or by allergies. Bacterial and viral conjunctivitis are easily spread from person to person. Allergic conjunctivitis is not contagious. **Viral conjunctivitis** is the most common type of conjunctivitis. This type of pink eye is very contagious and often spreads through schools and other crowded places. It usually causes burning, red eyes with a watery discharge. Viral conjunctivitis is usually caused by the same virus that causes a runny nose and sore throat in people with the common cold.

Viral conjunctivitis is often associated with an infection of the upper respiratory tract, a common cold, or a sore throat. Its symptoms include excessive watering and itching. The infection usually begins in one eye but may spread easily to the other eye.



Viral conjunctivitis manifests as a fine, diffuse pinkness of the conjunctiva which may be mistaken for iritis, but corroborative signs on microscopy, particularly numerous lymphoid follicles on the tarsal conjunctiva, and sometimes punctate keratitis are seen.

VIRAL CONJUNCTIVITIS

Bacterial conjunctivitis is also very contagious. An infection from bacteria causes this form of pink eye. With bacterial conjunctivitis, you have sore, red eyes with a lot of sticky pus in the eye. Some bacterial infections, however, may cause little or no discharge. Sometimes the bacteria that cause pink eye are the same that cause strep throat.

Bacterial conjunctivitis causes the rapid onset of conjunctival redness, swelling of the eyelid, and a sticky discharge. Typically, symptoms develop first in one eye but may spread to the other eye within 2–5 days. Conjunctivitis due to common pus-producing bacteria causes marked grittiness or irritation and a stringy, opaque, greyish, or yellowish discharge that may cause the lids to stick together, especially after sleep. Severe crusting of the infected eye and the surrounding skin may also occur. The gritty or scratchy feeling is sometimes localized enough that patients may insist that they have a foreign body in the eye.

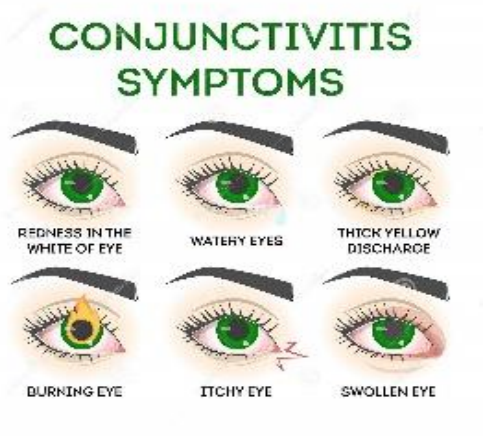
BACTERIAL CONJUNCTIVITIS

Allergic conjunctivitis is a type of pink eye that comes from an allergic reaction to pollen, animals, cigarette smoke, pool chlorine, car fumes, or something else in the environment. It is not contagious. The allergic pink eye makes your eyes very itchy, red, and watery, and the eyelids may get puffy.

The specific allergens may differ among patients. Symptoms result from the release of histamine and other active substances by mast cells, and consist of redness (mainly due to vasodilation of the peripheral small blood vessels), swelling of the conjunctiva, itching, and increased production of tears.

ALLERGIC CONJUNCTIVITIS

SYMPTOMS OF PINK EYE SYNDROME



- The feeling that something is in your eye, or a gritty sensation in your eye
- Red eyes
- Burning eyes
- Itchy eyes
- Painful eyes (this is usually with the bacterial form)
- Watery eyes
- Puffy eyelids
- Blurry or hazy vision
- Being extra sensitive to light
- Lots of mucus, pus, or thick yellow discharge from your eye symptoms

TREATMENT STRATEGIES FOR PINK EYE SYNDROME

If your conjunctivitis is caused by a viral infection, there are no specific treatments. Your body fights the virus on its own. Placing a cool, wet washcloth on your eyes can help make them feel more comfortable. If your pink eye is caused by a bacterial infection, your ophthalmologist may prescribe antibiotic eye drops, depending on how severe your symptoms are. Antibiotics do not treat an infection caused by a virus or by an allergy.

If your conjunctivitis is due to allergies, you might be told to use certain eye drops to help with the itchiness and puffiness. Sometimes conjunctivitis can be caused by a chemical or other substance in your eye. In this case, rinse the eye free of the substance. You might be told to use certain eye drops or ointment for the eyes.

8. CONCLUSION

Ocular drug carriers are of great importance in pharmaceutical technology and the ophthalmology area. The unique characteristics of the eye and the ocular barriers hinder ocular bioavailability since tear fluids wash off the topically applied solution of drugs. Thus, the design and development of novel and sufficient drug delivery systems for ocular diseases management are mandatory. Treatment of ocular diseases in an effective manner is a major challenge for scientists working in the field of ocular drug delivery because of the nature of the ocular diseases, the unique structure of the eye, and barriers present in the system; particularly the posterior ocular segments make the system unapproachable. Many attempts have been made to enhance ocular bioavailability by manipulating product formulation using factors, such as viscosity and the use of mucoadhesive polymers. These approaches are capable of increasing the corneal contact time and improving ocular bioavailability also. Therefore, it could be concluded that modern technology seems to be logically explored in various ways over the conventional approaches for the treatment of eye and eye disorders.

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