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Review Paper

Advances In Ocular Drug Delivery: A Review

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ABSTRACT

The intricate anatomical and physiological barriers of the eye, such as tear turnover, nasolacrimal drainage, corneal epithelial tight junctions, and restricted permeability to posterior ocular tissues, make ocular medication administration extremely difficult. With less than 5% of the supplied dose reaching intraocular tissues, conventional ophthalmic formulations including eye drops and ointments have poor precorneal residence duration and low bioavailability, requiring frequent dosing and decreasing patient compliance. Many sophisticated drug delivery techniques, such as nanoparticles, liposomes, niosomes, nanosuspensions, microemulsions, dendrimers, and in situ gelling systems, have been developed to get around these restrictions. These innovative technologies provide continuous and controlled medication release, increase corneal contact duration, improve drug penetration, and lessen systemic side effects. Combining the benefits of nanocarriers with stimuli-responsive sol–gel transition mechanisms as pH-, temperature-, and ion-triggered gelation, nanoparticle-loaded in situ gels have become a promising approach. This method reduces the frequency of dose, increases ocular bioavailability, and lengthens the duration of drug residency. Ocular anatomy, the shortcomings of traditional administration methods, methods to improve bioavailability, and current developments in novel ophthalmic formulations are all highlighted in this review. Although more research is needed to address stability, large-scale production, safety, and regulatory considerations, advanced ocular drug delivery systems offer a potential platform for improving therapeutic efficacy in the treatment of both anterior and posterior segment ocular diseases

INTRODUCTION

Because of its complex anatomical and physiological composition, the human eye is a unique organ composed of its biologically autonomous functions. Its wide range of shapes makes the development of drug delivery systems for it even more challenging. The primary problem with the conventional ocular medication administration technique, which uses eye drops, is that they are rapidly and extensively

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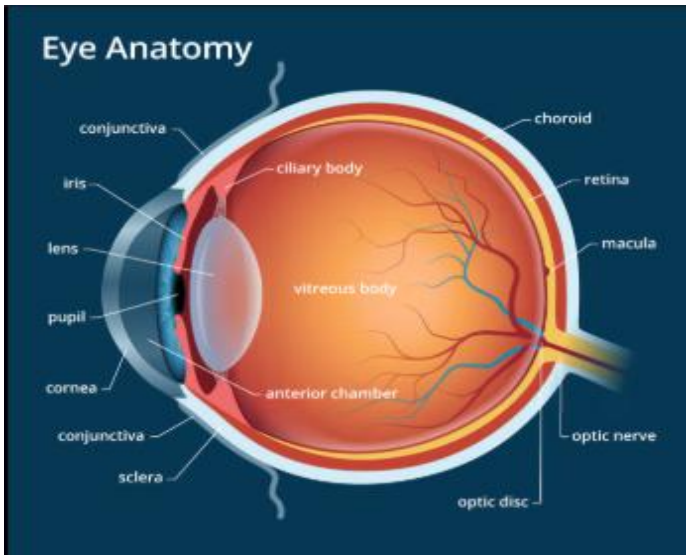
evacuated from the eye, leading to a considerable loss of medicine [1, 2]. Only a small amount of medication can enter the internal tissues of the eye due to the corneal layer of eye drops [3, 4]. According to a general classification, there are two ways to administer medications to the eyes: anterior and posterior portions. Traditional medicine administration options for vision-threatening ocular illnesses include eye drops and suspensions and ointments, are not suitable for the best course of treatment [5]. Diseases affecting the anterior portion of the eye are the sites of action for over 90% of the ophthalmic formulations on the market, which are sold as eye drops [6]. The posterior portion of the eye cannot be reached by topical medication delivery using traditional methods Because of the flow of tears and lachrymal nasal drainage, formulations such as eye drops and ointments are rapidly swept away from the eye region when administered into the cul-de-sac. Frequent dosage is necessary to establish a therapeutic effect since the majority of the drug is drained away and only a little quantity reaches the site of action. The retina, vitreous humour, and choroid make up the posterior portion of the eye. Diseases affecting these areas can be treated with implants, intravenous and intravitreal drug delivery systems, or periocular medication administration, all of which require high drug concentrations. The posterior region of the eye is often a target for locating medications using innovative techniques for ocular drug delivery [7]. The purpose of this review and this study's novelty is to draw attention to the more recent advancements in pharmaceutical ophthalmic formulations, including the creation of in situ gels, nanoparticles, liposomes, nanosuspension, microemulsion, ocular inserts, and so forth, and their advancements in resolving issues with the current conventional dosage forms while simultaneously enhancing the drug's bioavailability and sustained release at the intended site [8].

1.1Structure of eye:



The eye is composed of three primary components:

i. The eye
ii. The orbit of the eye socket
iii. Adnexal, or accessory structures.

The eyeball: Also known as the globe, the eyeball is the primary component of the eye. Each sphere-shaped eye has a diameter of roughly 2.5 cm (1inch) [6]. There are many blood arteries in the eyeball. The eyeball's inside is packed with mostly with vitreous humour, a transparent, jelly-like fluid. The posterior (rear) region of the eye is filled with vitreous fluid. It aids in maintaining the eye's shape and supporting the inside tissues. An exterior, middle, and inner layer (from the outside to the inside of the eye) make up the structure of the eyeball, which is collectively referred to as the wall of the eye

Outer layer: The cornea and sclera make form the fibrous tunic, which is the outermost layer or covering of the eye's wall.

Sclera: The sclera is the strong, white connective tissue that covers much of the outside of the eyeball**.** The white part of the eye, known as the sclera, acts as a protective layer The blood vessels and optic nerve Go through the back of the eye's sclera. The sclera is where the muscles that regulate eye movement are attached.

Cornea: The transparent, dome-shaped layer that that allows light to enter the eye at the front. The cornea covers the iris and pupil. It is devoid of blood vessels.

Middle Layer: The middle layer of the ocular wall the vascular tunic is the term for it. Three major pieces make up the uvea: Iris: The thin, muscular, colourful portion of the eye is called the iris. It is situated at the anterior, or front, of the eye. between the cornea and lens the white part of the eye, known as the sclera, acts as a protective layer The blood vessels and optic nerve Go through the back of the eye's sclera [9]. The amount of light entering the eye is altered by the iris opening and closing the pupil, which is the tiny central opening.

Choroid: The retina receives oxygen and nutrients from the choroid, a thin layer of tissue that is home to numerous tiny blood veins. There are numerous pigment-producing cells called melanocytes in the choroid [10]. These cells aid in reducing reflections in the eye and absorbing extra light.

Ciliary body: Directly behind the iris is the ciliary body. and protrudes from the choroid. The ring of muscle tissue is what aids in eye focus. It modifies the lens's shape so that it can concentrate on close or distant things [11]. Aqueous humour, the transparent fluid in the front of the eye, is produced by cells found in the ciliary body. between the lens and cornea.

Inner Layer: The layer that is closest to the eye's wall consists of the neural tunic or retina. The thin layer of cells at the rear of the eye is called the retina, and it functions similar to a camera's film. It is composed of nerve cells. that are light-sensitive [12]. The optic nerve, which transmits information between these cells and the brain, from the brain to the eye, which enables vision

Lens: The inner portion of the lens is a clear structure. of the eye, which is situated immediately behind the iris and cornea. To enable the eye to focus on objects, the lens undergoes a shape shift. Light beams are focused on the retina by the lens [13].

Orbit: The orbit, often known as the eye socket, is a hollow bowl. composed of the connective tissues around the eye and the bone that makes up the skull, which houses the eye. The eye is protected and cushioned by the bone and connective tissues. The eyeball's muscle attachments make it Go in various directions [14]. These tiny muscles attach to the orbit is bones in the back and the sclera close to the front of the eye. Nerves, lipids, blood arteries, and various connective tissues are also found in the orbit.

Structures for accessories: The adnexal accessory the eye's structures include the conjunctiva, eyelids, Lachrymal (tear) and caruncle glands, auxiliary components of the eye.

Eyelids: The folds of skin that cover and shield the eye are called palpebrae [15]. The glands in the eyelids create an oily secretion that covers the tear layer and keeps the tears from evaporating and the eyelids from sticking together. These muscles raise and close the eyelids.

1. The anterior (front) and posterior (rear) lamellae of the eyelid are described.
2. A layer of fatty tissue called skin makes up the anterior lamella. muscle Fiber layer and connective tissue. It controls the quantity of light that enters the eye and aids in eye protection. 3. A layer of muscle

makes up the posterior lamella The palpebral conjunctiva and the tarsal plates. Two thick, densely connected plates make up the tarsal plates. tissue inside the upper and lower eyelids that support and aid in the formation of the eyelid.
4. Eyelashes emerge from the eyelid's margins.

Conjunctiva: The conjunctiva is a clear membrane Mucous membrane. The gastrointestinal (GI) tract, nose, mouth, lungs, airways, vagina, and other bodily cavities are lined by a thin, moist layer of tissue. That lines the inner surface of the eyelids and the Outer surface of the eye. Mucus is secreted by the conjunctiva. To maintain moisture and lubricate the eyeball [16]. Bulbar Conjunctiva is the part of the conjunctiva that covers the Front, outer surface of the eyeball. 1. The anterior (front) and posterior (rear) lamellae of the eyelid are described. 2. A layer of fatty tissue called skin makes up the anterior lamella. muscle Fiber layer and connective tissue. It controls the quantity of light that enters the eye and aids in eye protection. 3. A layer of muscle makes up the posterior lamella. Mucus is secreted by the conjunctiva. To maintain moisture and lubricate the eyeball. Two thick, densely connected plates make up the tarsal plates. tissue inside the upper and lower eyelids that support and aid in the formation of the eyelid. 4. Eyelashes emerge from the eyelid's margins. Conjunctival forniceal is the loose fold that joins the membrane of the conjunctiva. that forms the conjunctiva along the inside of the eyelid. membrane that envelops the eye. Tarsal or palpebral the portion of the conjunctiva that covers the inside of the eyelids is called the conjunctiva [17]. The plica is a little fold of conjunctiva tissue located in the inner corner of the eye, adjacent to the caruncle.

Caruncle: The caruncle is the little, pinkish area of the inner canthus, or innermost corner of the eye, which houses the conjunctival tissue and sebaceous glands that produce perspiration and oil.

Lacrimal gland: The almond-shaped gland in the top, outer corner is the lacrimal gland, also known as the tear gland. of every eye to assist, the lacrimal gland secretes tears. Maintain the lining of the eyelids and the surface of the eye Lubricated and moist [18]. Tears lessen friction, prevent infection by clearing the eye of dust and dirt. Lacrimal canaliculi, or tiny lacrimal ducts Tears are drained from the lacrimal gland using small, holes (lacrimal punctum) in each eyelid's inner corner.

Function:

1. The organ that collaborates with the brain to give us the ability to see is the eye. It works like a camera.
2. The eye's primary job is to gather light and convert it into electrical impulses that are transmitted to the brain [19].
3. Even if one eye becomes blind, we can still see. most of what was previously seen. Light first travels through the cornea when it enters the eye.
4. The Iris then modifies the amount of light entering the eye after it has passed through the pupil.
5. After that, the light passes through the lens of the eye. Light beams are focused by the lens onto the retina, where they are converted into a signal that the optic nerve then sends to the brain.

1.2 Ocular Drug Delivery Systems' Benefits [20]

1. A more precise dosage. To get past the side effects of conventional systems' pulsed dosage.
2. to continuously and regulatedly dispense medications.
3. To extend the corneal contact time in order to improve the drug's ocular bioavailability. This is achievable. by efficient adhesion to the ocular surface.
4. To prevent loss to other eye tissues by providing targeting within the ocular globe.

5. To get beyond defense mechanisms such as conjunctival absorption, lacrimation, and drainage.
6. To make the patient more comfortable, encourage better compliance, and enhance the medication's therapeutic efficacy.
7. To improve the delivery system's housing.
8. The patient can administer them with ease.
9. They absorb quickly and cause fewer systemic and ocular negative effects.
10. Patient compliance is higher with an ocular drug delivery device.

1.3 Ocular Drug Delivery System Drawbacks [21]

1. The drug solution is only in the eye surface for a brief period of time.
2. Its bioavailability is low.
3. Illustrates the drug's fragility after dissolution.
4. Preservatives must be used.

1.4 Ocular Drug Delivery Limitations [21]

1. In an emergency, the dosage form cannot be stopped.
2. Vision interference.
3. Placement and removal are challenging.
4. Occasional loss while rubbing your eyes or sleeping.

2.Approaches to improve ocular bioavailability

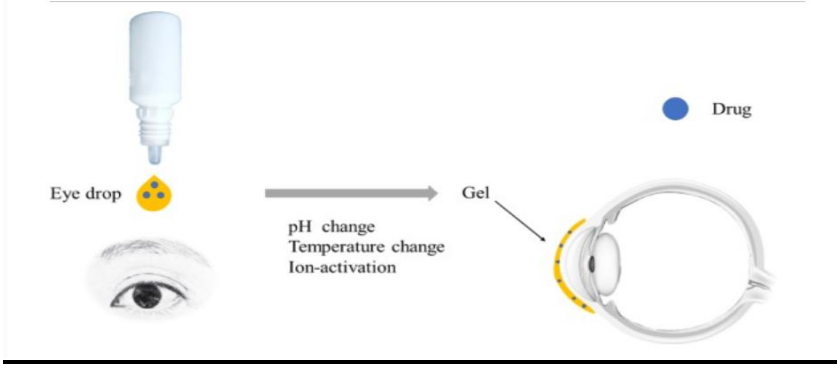
- **Use of viscosity enhancers**

Because of their ability to increase viscosity and, consequently, the drug's penetration into the anterior chamber of the eye by decreasing the rate of elimination from the preocular area, which increases precorneal residence time and transcorneal penetration, viscosity-increasing polymers are highly preferred additives in ophthalmic formulations. However, their effects on improving bioavailability in humans are negligible. Polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), methylcellulose, hydroxylethylcellulose, hydroxylpropyl methylcellulose (HPMC), and hydroxypropyl cellulose are a few examples of polymers [21]. In their study of tropicamide solution, Saettone et al. (1984) used PVA, HPMC, and PVP solution. At concentrations that produced the same viscosity of 20 cst, PVA was found to be the most effective of all. This is likely because of PVA's adhesive properties and its capacity to increase the thickness of the precorneal tear film [21]. As the vehicle spreads over the ocular surface with each eye blinking, Saettone et al. (1982) found that the retention of the drug in the precorneal tear film is not solely due to the vehicle's viscosity but also to the vehicle's surface spreading properties and a polymer's ability to use water [22].

- **Penetration enhancers**

The corneal epithelial membrane is crucial for permeability. Therefore, the transport property around the cornea can be improved by increasing its permeability [29, 30]. Chelating agents, preservatives (such as benzalkonium chloride), surfactants, and bile acid salts are examples of agents with these characteristics; nevertheless, their local toxicity prevents their application in the production of ophthalmic formulations [31, 32].

- **Gel formulation**

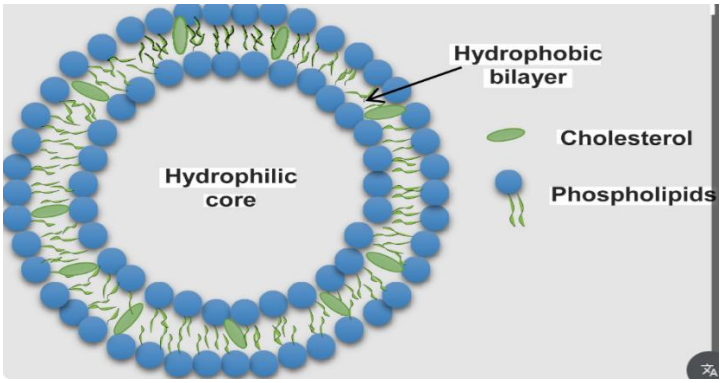


Gels exhibit stiffness in the steady state and are known to be highly diluted crosslinked systems. Although gels are typically liquids, their three-dimensional cross-linked structure within the liquid causes them to behave like solids [23–25]. Conversely, if the gels have a very high viscosity, they will not be able to increase bioavailability; instead, they will regulate the release, resulting in a lower dosage frequency of once daily. Even clouded eyesight and matted eyelashes are caused by the extremely thick fluid, which significantly reduces patient compliance. While hydrogel or swellable water-insoluble polymers create regulated drug delivery systems, viscosity-building agents such PVA, polyacrylamide, Poloxamer, HPMC, carbomer, polymethylvinylether, maleic anhydride, and hydroxylpropylethylcellulose are added to aqueous gel [26].

- **Prodrug formulation**

Many formulation qualities can be enhanced by the production of prodrugs, making them appropriate for enhancing drug permeability through the cornea. It involves altering the chemical structure to provide the active moiety new properties, such as selectivity and site specificity [27]. This is explicable. Timolol, epinephrine, phenylephrine, and pilocarpine are a few examples of formulations that have been created as prodrugs. Other prodrugs that have seventeen times greater corneal permeability include dipiverine, diester of pivalic acid, and epinephrine. In contrast, epinephrine has six hundred times greater lipophilicity at pH 7.2. Therefore, a small amount of the medication solution (dipiverine) covers the entire eyeball and has a therapeutic effect that is identical to that of epinephrine. Dipiverine 0.1% eye drops have only minimal action by decreasing intraocular pressure with a considerable reduction of negative effects when compared to typical eye drops that contain 2% epinephrine [28].

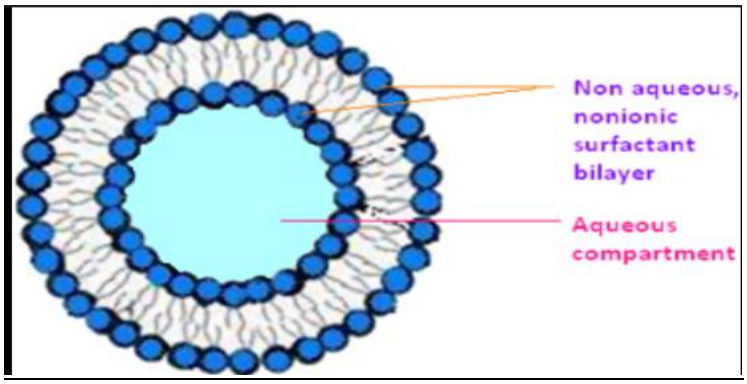
- **Liposomes**



Liposomes are tiny vesicles made up of one or more concentric lipid bilayers that are separated by aqueous buffer or water compartments. Because liposomes have close contact with the corneal and conjunctival surfaces of the eyes, they are frequently utilized in ocular formulations to facilitate drug absorption

through the ocular route. able to be raised [33]. Phosphorylcholine, stearylamine, and different concentrations of lecithin or cholesterol, as well as Ldipalmitoyl-phosphatidylcholine, can be used to manufacture liposomes [34–37]. The properties of this kind of delivery system—biocompatibility, biodegradability, amphiphilia, and relative toxicity—are the main reasons for its benefits [34, 35, 38]. Its benefits also include sustained drug release and delivery of the medication to the intended spot or site-specificity. Liposomes are typically made for medications with medium to high molecular weights, poor solubility, poor absorption, and a decreased partition coefficient [39]. When creating an ocular delivery system, the surface charge of liposomes must be taken into account. Positively charged liposomes are found to be preferentially captured by negatively charged corneal surfaces, whereas neutral or negatively charged liposomes are not. Acyclovir, pilocarpine, acetazolamide, chloramphenicol, and ciprofloxacin are the active pharmaceutical substances employed in liposomal ophthalmic formulations, according to the number of studies that have been published [36, 37].

- **Niosomes**



Both hydrophilic and hydrophobic drugs are transported via niosomes, which are bi-layered, chemically stable nanocarriers made of nonionic surfactants. They do not have the same issues as liposomes, which are made of highly unstable phospholipids, are costly, chemically unstable, and prone to oxidative destruction [34, 35, 40, 41]. Thus, niosomes offer many advantages. Because they are nonimmunogenic, biodegradable, and biocompatible, they extend the contact time. between the drug and the cornea, increasing the drug's bioavailability

- **Nanoparticles/nanospheres**

The medication is dissolved, entrapped, encapsulated, or adsorbed in these polymeric colloidal particles, which range in size from 10 nm to 1 nm [43]. It is made up of many biodegradable materials, such as metals, lipids, phospholipids, and natural or synthetic polymers. Drugs can be prepared in a variety of methods to create nanoparticles, such as by adhering to the surface of biodegradable polymers or integrating with the matrix. Polylactics (PLAs), polycyanoacrylate, poly (D, L-lactides), and natural polymers such chitosan, gelatine, sodium alginate, and albumin are examples of nanoparticles that are utilized to deliver drugs to ocular tissues. Nanoparticles have been utilized as medication delivery vehicles for ocular illnesses for the past ten years or so, with encouraging outcomes One particular kind of nanoparticle is a tiny capsule with a central cavity. encased in solid matrix spheres and a polymeric membrane, which are referred to as nanospheres and nanocapsules, respectively. According to Marchal et al. (1993), the drug (betaxolol, carteolol) present in the oily core of the nanocapsules diffuses into the cornea more quickly than it does in the nanospheres, which is why the nanocapsules have a superior effect [44]. According to several publications, the mucoadhesive feature of

the nanocapsules increases their efficiency by exhibiting a rise in residence length and biological reactions [45]. Thus, these can reduce the frequency of dosing and increase the bioavailability of medications at the ocular location. According to a 1995 study by Alonso et al., the poly-e caprolactone nanoparticles containing cyclosporine have superior corneal absorption compared to the drug's oily solution [46].

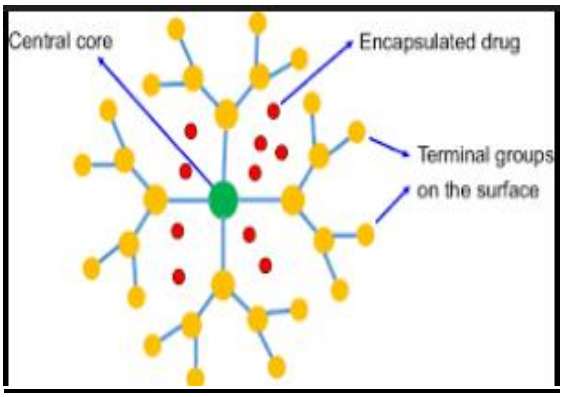
- **Nanosuspension and nanodispersions**

For medications that are poorly soluble in water, nanosuspensions are created. suspended in an appropriate dispersion media at nanoscale sizes. This technology can be effectively used to drug moiety that generates high-energy crystals that are insoluble in hydrophilic or organic (lipophilic) environments. Inert polymeric resins are being used to make polymeric nanoparticle suspensions, which can be essential drug delivery vehicles with the ability to enhance drug release and bioavailability. These kinds of carriers can be utilized as inert carriers. Because ophthalmic medications do not irritate the cornea, iris, or conjunctiva. A polymeric nanoparticle dispersion with flurbiprofen (FLU) as the active ingredient and the polymers eudragit RS 1001 and RL 1001 is an example of such a carrier. Morsi et al. (2015) described the production of alginate chitosan nanodispersions for better transcorneal penetration and sustained drug delivery [47, 48].

- **Microemulsion**

Microemulsions are stable water-in-oil dispersions made possible by the use of surfactant and co-surfactant in combination to reduce interfacial tension. Microemulsion improves ocular medication absorption and reduces the frequency of administration. This dosage form's strong thermodynamic stability, smaller droplet size (around 100 nm), and transparent appearance are its main features. Pilocarpine as a drug, lecithin, propylene glycol, PEG 200 as a surfactant or co-surfactant, and isopropyl myristate as the oil phase comprise the microemulsion formulation described by Ansari et al. (2008).

- **Dendrimers**



Recently, dendrimers—symmetric structures composed of repeating branched molecules encircling a central core—have been proposed as topical ocular drug delivery methods [50]. Poly(amidoamine) (PAMAM), PLL, polypropylenimines (PPI), and phosphorous dendrimers are often employed dendrimers for ocular system administration. These serve as carriers for nucleic acid-based medications, mostly in ocular delivery systems [51], but they are also occasionally utilized for low molecular weight medications that can be lipophilic (antiglaucoma) or hydrophilic (antibiotics) [52–58]. As per the approaches that have been published, altering the carrier's surface by techniques like acetylation or PEGylation can improve its function while also lowering its toxicity factors [53, 54, 59]. Therefore, the benefits of employing dendimers as drug carriers for topical applications are prolongation of the therapeutic effect, increased drug absorption, and improved drug residence duration in the pre-corneal region [52, 55, 57, 58].

- **In situ forming gel**

In the early 1980s, researchers discovered the novel idea of in situ gel. The primary purpose of in situ gel medication delivery to the ocular system is to increase

viscosity in order to reduce drug drainage from the cornea. When applied, the pourable gels are liquid, but when they approach the eye's cul-de-sac, they go through a phase change and become visco-elastic gels that cause a reaction. to alter the environment, which will immediately increase the drug's bioavailability. The main drawbacks of in situ gels Are they impacted by ions, pH, or temperature? Compared to traditional eye drops, Bazzaz et al. (2018) found that in situ gelling systems offer a more effective and prolonged medication action [60].

3.IN SITU GELLING SYSTEM APPROACHES:[61]

The different methods for the in situ gelling system are:

- In situ gel systems that are affected by temperature
- In situ gel systems with pH induction
- Systems that are ion-activated

3.1 Temperature-triggered in situ gelling system: The most widely researched class of environment-sensitive polymer systems in drug delivery research are likely temperature-sensitive in situ gels. Polymers in this gelling system are liquid at room temperature (20–25°C) and gel at physiological temperature (35–37°C) [62]. When the ambient temperature rises, an ideal temperature-triggered gelling polymer solution should turn into gel while remaining liquid below its low critical solution temperature (LCST) and up to its upper critical solution temperature (UCST). Increased micellar aggregation (entanglement of the polymeric network) and progressive polymer desolvation are seen The phase transition temperature for an ideal temperature-triggered in situ gelling solution should be higher than room temperature (25°C) so that it can be applied to the eye and gelled at precorneal temperature (35°C) without affecting tear fluid dilution, even at concentrations as low as 5% w/v[63,64,65].

3.2 pH-triggered in situ gelling systems: These are solutions, such cellulose acetate phthalate and Carbopol, that change into the gel phase when exposed to the lachrymal fluid's pH [65]. The backbone of pH-sensitive polymers is made up of either weakly acidic or basic groups that, in reaction to a change in pH, either release or receive free protons. Electrostatic, hydrophobic, and hydrogen bonding interactions occur at a particular pH, which causes inter-diffusion and a conformational shift in the polymer that causes swelling. Therefore, pH 30 triggers the sol to gel transition.

3.3 In situ gelling system activated by ions: When exposed to the ionic concentration of the tear fluids, the viscosity of the solution in the ion-triggered in situ gelling system increases [65]. Another name for it is osmotically induced gelation. Ion-sensitive polymers can increase the duration of medication retention by crosslinking with cations (monovalent, divalent) found in lacrimal fluid on the surface of the eye [66].

CONCLUSION

The distinct anatomical and physiological barriers of the eye impede drug penetration and lower the bioavailability of traditional ophthalmic formulations like eye drops and ointments, making ocular medication delivery extremely difficult. Nanoparticles, liposomes, niosomes, microemulsions, dendrimers, and in situ gelling systems are examples of recent developments in ocular drug delivery systems that have demonstrated encouraging potential in extending drug residence time, boosting ocular bioavailability, and offering sustained drug release. Compared to traditional dosage forms, these innovative methods assist lower the frequency of doses and increase patient compliance. Nanoparticle-loaded in situ gels have become one of the most successful advanced technologies for improving ocular medication delivery. To address concerns about stability, safety, large-scale production, and regulatory approval, more

research is necessary. All things considered, sophisticated ocular drug delivery devices offer a viable strategy for raising the therapeutic efficacy of ocular therapies.

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