

# MUCOADHESIVE OCULAR NANOFORMULATIONS: ADVANCEMENTS IN DRUG DELIVERY FOR IMPROVED OCULAR THERAPY

## Abstract

Ocular drug delivery poses a significant challenge due to the intricate structure and protective barriers present in the eye. Traditional techniques, including systemic administration and topical eye drops, often have limited therapeutic efficacy and poor bioavailability. However, the emergence of mucoadhesive ocular nanoparticles has the potential to revolutionize ocular drug delivery by overcoming these challenges. Eye drops remain a popular non-invasive method of treating ocular ailments. Nevertheless, conventional eye drop formulations are associated with several limitations, such as rapid drainage from the eye, low bioavailability, and frequent administrations. Mucoadhesive nanoparticles present a promising solution to address these issues by enhancing drug retention and permeation in the eye. This chapter offers a comprehensive overview of recent developments in mucoadhesive ocular nanoparticles and their implications for ocular drug delivery. It discusses the anatomy and protective barriers of the eye that influence drug penetration and the need for innovative drug delivery systems. The chapter explores various natural and synthetic mucoadhesive polymers used in nanoparticle formulations and their interactions with ocular tissues. Additionally, it highlights the development and characterization of nanosystems, including micelles, liposomes, nanosuspensions, and nanogels, that incorporate mucoadhesive properties to enhance ocular drug delivery. The potential applications of mucoadhesive ocular nanoparticles in addressing ocular diseases affecting both the anterior and

## Authors

### **Shubhrat Maheshwari**

Faculty of Pharmaceutical Sciences  
Rama University  
Kanpur, Uttar Pradesh, India.

### **Ajeet Kumar**

Faculty of Pharmaceutical Sciences  
Rama University  
Kanpur, Uttar Pradesh, India.

### **Shubham Sharma**

Faculty of Pharmaceutical Sciences  
Rama University  
Kanpur, Uttar Pradesh, India.

### **Sayantana Dutta**

Faculty of Pharmaceutical Sciences  
Rama University  
Kanpur, Uttar Pradesh, India.

### **Jagat Pal Yadav**

Faculty of Pharmaceutical Sciences  
Rama University  
Kanpur, Uttar Pradesh, India.

### **Sonia Pandey**

Faculty of Pharmaceutical Sciences  
Rama University  
Kanpur, Uttar Pradesh, India.

posterior segments are discussed. Furthermore, the chapter emphasizes the importance of understanding the anatomical and physiological challenges in ocular drug delivery to design effective and safe drug delivery systems. Overall, this book chapter serves as a valuable resource for researchers, scientists, and pharmaceutical experts working in the field of ocular drug delivery. It provides insights into the recent advancements in mucoadhesive ocular nanoparticles and their potential implications in improving therapeutic outcomes and patient compliance for various ocular disorders.

**Keywords:** Ocular Drug Delivery, Bioavailability, Micelles, Liposomes, Nano-suspensions, Eyedrop, Mucoadhesive, Anterior, Posterior

## I. INTRODUCTION

The eyes are a vital organ that is directly exposed to external environmental factors making them susceptible to various stimuli, including pathogens. Ocular disorders are common among individuals and can occur more than once throughout their lifetime, despite the presence of a well-developed immune system in the eyes [1]. Pathogenic bacteria have the potential to cause ocular diseases that are infectious in nature, such as conjunctivitis and keratitis. These diseases tend to occur more frequently in situations that involve trauma, surgical procedures or conditions like dry eye. Cataracts, which are responsible for 40-60% of cases of blindness worldwide, develop early due to genetic mutations in specific genes that are associated with crystalline. Glaucoma, an optic neuropathy disease, can lead to irreversible blindness when it advances to certain stages, and is caused by elevated intraocular pressure. Vision impairment can also be caused by factors such as aging, diabetes and fungal infections. Ocular conditions, such as age-related macular degeneration, diabetic retinopathy, retinoblastoma and fungal keratitis, can present additional challenges [2]. The eyes possess several protective barriers, such as the corneal barrier, blood-ocular barrier, and eye blink and tear turnover.

The presence of various diseases can lead to impaired vision, which can have a significant impact on an individual's quality of life [3]. The protection afforded to the human eyes makes it challenging for drugs to reach the anteroposterior segments of the eye after topical application. This difficulty has led researchers to explore nanoparticle-mediated ocular drug delivery systems, with chitosan being a commonly employed polymer due to its mucoadhesive properties. Chitosan's success in this regard is attributed to the presence of amino groups that interact with sialic acid residues abundant in mucosal linings [4]. Various studies have investigated natural polymers for the development of nanoparticle-mediated ocular drug delivery systems, with chitosan being one of the most extensively researched [5]. Topical drug delivery is the favoured non-invasive technique for treating ocular ailments. However, it is imperative that it reaches the affected area, delivers adequate drug doses, and sustains them in the eye continuously. Eye drops have conventionally been the primary option for treating numerous anterior segment eye diseases including glaucoma, cataracts, dry eye syndrome, and inflammatory infections, and they account for roughly 90% of the global ocular drug market [6]. Besides eye drops, traditional ocular formulations, such as ointments, suspensions, lotions, etc., are widely available on the market, and they generally prolong drug retention time in the eye and enhance bioavailability. However, they also have some drawbacks. Ophthalmic ointments, being semisolid in nature, are prone to causing blurred vision and inaccurate dosage due to the differences in refractive indices of tears. For optimal effectiveness, it is recommended that patients apply the ointment prior to sleeping. However, suspensions are inherently unstable and their crystal structure can be altered by environmental factors, leading to changes in particle size and solubility. Furthermore, the presence of particles exceeding 10  $\mu\text{m}$  in solution can cause ocular irritation, resulting in increased tear secretion and rapid drug drainage which greatly diminishes bioavailability. This can lead to lower pharmacological effects post-delivery, necessitating increased dosage frequency and decreased patient compliance [7]. To address these challenges, ophthalmic formulations typically incorporate various additives such as permeation enhancers, viscosity enhancers, and cyclodextrins to enhance their therapeutic efficacy [8].

There are limitations to traditional medication delivery systems for ocular infections, which can affect vision preservation. Corneal ulcers are mainly caused by *Pseudomonas aeruginosa*, with Ceftazidime (CFT) being the most effective cephalosporin drug against it. However, the rapid degradation of Ceftazidime in aqueous solutions, leading to the opening of the lactam ring, is a significant challenge that prevents its commercial availability as eye drops. Several barriers limit the therapeutic efficacy of potent drugs available for ocular conditions. Conventional eye drops, for instance, may be wasted due to blinking and tear flow, resulting in minimal bioavailability (less than 5%) [9].

These systems are designed to enhance the medication's duration in the eye and improve its bioavailability. By using encapsulated medicine, its presence can be prolonged on the ocular surface. This is achieved by the nanoparticles adhering to the eye, thus reducing the rate of drug discharge due to their increased viscosity. Mucoadhesion is a unique form of bioadhesion that allows a substance to adhere to a biological surface containing mucous membranes or tissues. Specifically, mucoadhesion refers to the ability of a substance to form a sticky connection with the mucus layer covering a tissue, especially when considering specific biological surfaces such as epithelial tissue or the mucus layer [10].

Developing formulations for delivering drugs to the eye is a complex and fascinating task for experts in formulation and development, given the significant challenges presented by the human eye. The ultimate objective is to achieve a high degree of therapeutic efficacy while minimizing the risk of side effects. This critique will strive to provide a comprehensive analysis of recent advancements and techniques in ocular drug delivery, particularly focusing on mucoadhesive ocular nanocarriers [11]. These nanosystems have demonstrated potential in addressing ocular diseases affecting both anterior and posterior segments [12].

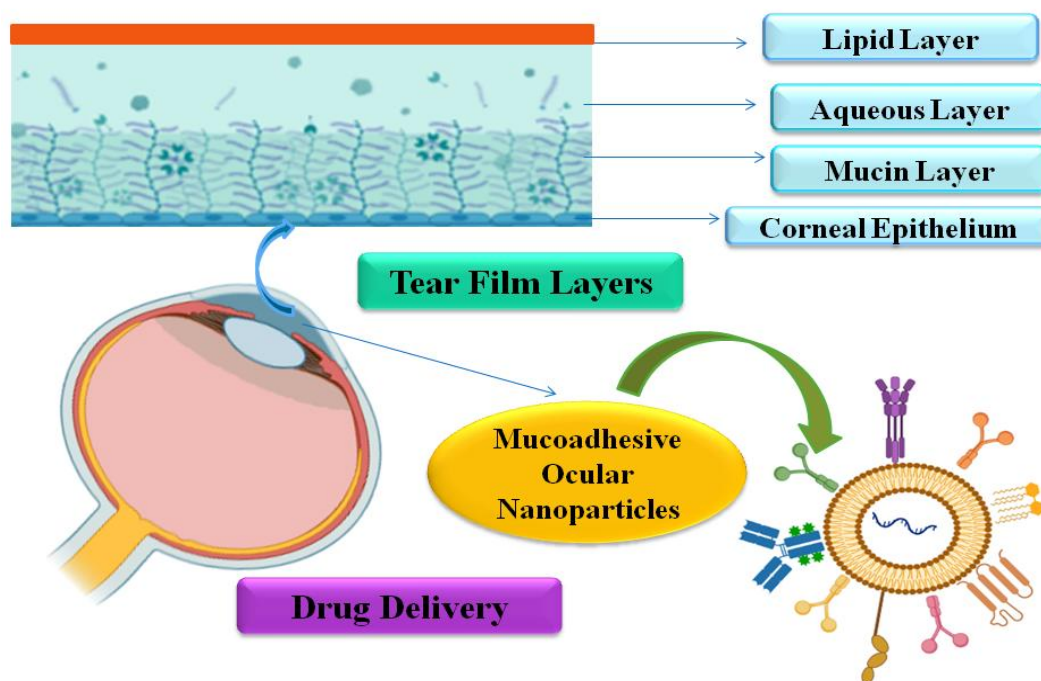
## II. ANATOMY

The ocular system is a delicate construct, and it is of utmost importance to take into account the unique attributes of ocular anatomy and physiology when administering topical medications. These attributes include the lacrimal film, mucus layer, and the impact of blinking-induced friction, which interact closely with the eye surface post-application, creating ocular barriers. The lacrimal film, which comprises a lipid and an aqueous layer, is a thin, transparent membrane that provides protection, humidification, and lubrication to the conjunctiva. While the lipid layer contains bacteriostatic agents and is important for the stability of the aqueous layer, it can lead to a loss of active agents upon frequent flushing and entrapment after topical administration. Meanwhile, the inner aqueous layer is the primary layer, containing enzymes and proteins that can metabolize and dilute active agents, leading to decreased bioavailability [13]. Excessive tear production post-application is responsible for poor drug retention [14].

In addition to the tear film, there exists a thick mucus layer covering the ocular surface [15]. This layer comprises water, mucin, and lipids, with the mucin component being particularly crucial in the formation of a gel-like structure that effectively entraps foreign material. The cornea, on the other hand, is a transparent tissue located in the front part of the eye, with dual roles of providing refraction and safeguarding the inner structures. It is an

essential component of the eye, functioning as a clear and circular boundary [16]. Predominantly made up of vascular connective tissue, the cornea has the capacity to protect the eye from harmful microorganisms, while also serving as the primary barrier to drug molecules attempting to gain entry into the eye [17].

In addition, the cornea is equipped with a tear buffer system that effectively regulates its pH, and any reduction in the quantity or quality of tear fluids may disturb the acid-base balance of the corneal surface, which could potentially worsen ocular diseases [18]. The iris, which is the pigmented part of the eye, acts as a gatekeeper that controls the amount of light that enters the eye. The pupil, located in the centre of the iris, adjusts its size according to the available light. The lens, a transparent structure, plays a crucial role in focusing light onto the retina. The ciliary body is composed of pigmented and non-pigmented ciliary epithelia, a stroma, and ciliary muscles [19]. The ciliary body contains capillaries that enable communication between the anterior and posterior sections of the eye. The vitreous humour, a gel-like connective tissue that lacks blood supply, can be found between the lens and retina [20]. It comprises mainly of hyaluronic acid, water, ions, and collagen and serves to maintain the eye's form and stability. The mucous membrane of the eye is composed of an outer epithelium layer, a substantia propria layer that houses nerves, blood vessels, and lymphatic vessels, and a submucosa layer that is connected to the sclera. The sclera, which extends from the cornea, is made up mainly of collagen and muco-polysaccharides. The retina, a thin layer of tissue, is composed of neural and glial cells covering the back of the eye. It generates electrical impulses that travel through the optic nerve to the brain [21].



**Figure 1:** The diagrammatic illustration representing the internal structure of the eye highlights the presence of three distinct layers constituting the tear film, namely the lipid layer, aqueous layer and mucin layer

### III. CONVENTIONAL FORMULATIONS FOR OCULAR DRUG DELIVERY

The delivery of drugs to patients through the administration of topical drops is an accepted practice [22]. This area is vital for its passive diffusion across the cornea. Nevertheless, to efficiently deliver ocular drugs with eye drops, it is essential to improve strategies, such as the use of iontophoresis ion-pair forming agents and cyclodextrins are employed. There is a large selection of ophthalmic products on the market, and around 70% of prescriptions call for traditional eye drops. Reasons might include the simplicity of production at a large scale, the high level of patient acceptance, the effectiveness of the therapeutic product, stability, and affordability [23-27].

**1. Topical liquid:** Topical drops are a highly convenient and non-invasive method of administering ocular drugs that is immediately effective and safe. Upon administration, the drug concentration in the eye decreases quickly, following an approximate first order. To address this issue, viscosity enhancers have been used to improve precorneal residence time and enhance corneal uptake, thus improving bioavailability [28]. However, certain investigations have revealed that permeation enhancers have a potential risk of local toxicity, necessitating further research to modify their effects and evaluate their safety. One approach to address this issue is by utilizing cyclodextrins as carriers for hydrophobic drug molecules in aqueous solutions, enabling effective drug delivery to the surface of biological membranes. Despite their advantages, viscosity enhancers and cyclodextrins do have a drawback of precorneal loss [29]. These traditional formulations persist to have a significant role in today's nanotechnology-based world and keep taking over the market. The adverse outcomes of these formulations, however, include ocular irritation, redness, inflammation, visual trouble and stability problems. Nonetheless, research efforts are currently underway to overcome these limitations [30].

- **Emulsions:** The application of emulsions as a method of formulation has been proven to offer numerous benefits in enhancing ocular bioavailability [31]. Among various options, emulsions are favoured due to their ability to cause less irritation and exhibit better ocular tolerance [32]. The study confirmed that difluprednate emulsion has the potential to be a suitable contender for treating anterior ocular inflammations. Carrier systems, such as emulsions, have been assessed for their ocular performance and bioavailability in delivering azithromycin [33]. Moreover, the emulsion formulation has been proven to augment the chemical stability of azithromycin at different pH levels in comparison to aqueous solutions. An alternative method for enhancing ocular bioavailability is through the use of emulsion as a carrier system by derivatizing active pharmaceutical ingredients (API). Several researchers have proposed the use of chitosan surface coating for this purpose [34]. Their findings indicate that chitosan surface coating can prolong the precorneal residence time of an API, leading to an increase in ocular bioavailability. In a particular study, castor oil and polysorbate-80 were used to create an oil-in-water (o/w) emulsion containing indomethacin, which was then coated with chitosan [35]. A study was conducted to compare the effects of chitosan-coated and non-coated indomethacin emulsions using topical drop instillation on male albino rabbits [36]. The concentration of indomethacin was measured in the cornea, conjunctiva, and aqueous humour an hour after the instillation of the emulsion [37].

- **Suspensions:** Non-invasive methods are preferred for drug delivery, and a suspension is one such ingredient. To enhance medication contact time and duration of action in comparison to drug solution, suspension particles gain more time to stay in the precorneal pocket. The time frame of the drug's function in suspension depends on the particle size [37]. The analysis of suspension settling studies revealed that the recently devised formulation exhibited a significantly low settling percentage of 3% over a period of 24 hours, in contrast to the existing TobraDex<sup>®</sup> product that demonstrated a much higher settling percentage of 66%. Study conducted on ocular distribution demonstrated that rabbits treated with TobraDex ST<sup>®</sup> exhibited higher concentrations of dexamethasone and tobramycin in their tissues compared to those treated with TobraDex<sup>®</sup>. Additionally, the new suspension formulation showcased greater efficacy against *Staphylococcus aureus* and *Pseudomonas aeruginosa* when compared to TobraDex<sup>®</sup>. Human clinical studies further confirmed the higher concentration of dexamethasone in aqueous humor in subjects treated with the new suspension formulation compared to TobraDex<sup>®</sup>. These findings collectively suggest that the recently devised suspension formulation may serve as a viable alternative to the marketed TobraDex<sup>®</sup> suspension, given its superior formulation characteristics, pharmacokinetics, bactericidal properties, and improved patient compliance [38].
- **Ointments:** Ophthalmic ointments represent a type of carrier system that has been developed for topical use. The ointments are composed of a semi-solid and solid hydrocarbon mixture that is dependent on biocompatibility and has a melting point at physiological ocular temperature. Through the use of ointments, ocular bioavailability is improved while drug release is sustained [39]. The effectiveness of TN-011 was assessed in two groups of rabbits, one normal and the other induced with MRSA infection. The latter group was also administered *Bacillus subtilis*. *In vivo* studies demonstrated that VCM concentrations in the MRSA-induced BS group were maintained above MIC levels, which would be highly beneficial to patients [40]. Eguchi and colleagues conducted a study in which they prepared four different ointment formulations of vancomycin with varying concentrations and evaluated their efficacy in a rabbit model of MRSA keratitis infection. Their findings indicated that 0.3% vancomycin ointment was adequate and effective in resolving corneal MRSA keratitis [41].

#### IV. LIMITATIONS IN CONVENTIONAL FORMULATIONS FOR OCULAR DRUG DELIVERY

Standard formulations such as eye drops, ointments, and gels have certain limitations, which include the aforementioned findings [42-43].

1. **Low Bioavailability:** Conventional formulations often suffer from poor bioavailability, which refers to the fraction of the administered drug that reaches the target tissues in the eye. Factors like tear dilution, drainage, and the protective mechanisms of the ocular surface can reduce the amount of drug available for absorption.
2. **Short Residence Time:** After administration, conventional formulations tend to have a short residence time on the ocular surface. Frequent blinking and tear production can

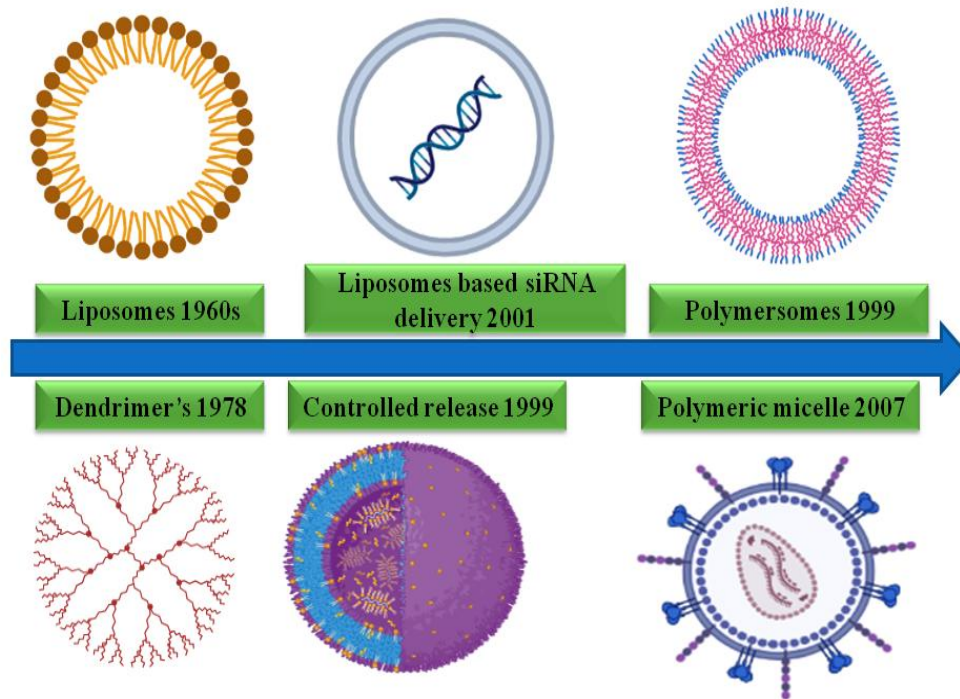
quickly wash away the drug, limiting its contact with the target tissues and reducing therapeutic efficacy.

- 3. Inconsistent Drug Absorption:** The ocular surface is heterogeneous, with variations in permeability and absorption rates. As a result, drug absorption can vary between individuals and even in different areas of the eye, leading to inconsistent therapeutic outcomes.
- 4. Difficulty in Targeting Specific Ocular Tissues:** Conventional formulations may have limited ability to target specific tissues within the eye. This lack of tissue specificity can result in suboptimal drug delivery to the intended site of action.
- 5. Irritation and Discomfort:** Some conventional formulations, particularly eye drops, can cause irritation or discomfort upon instillation, leading to potential non-compliance by patients.
- 6. Risk of Systemic Side Effects:** Ocular drugs delivered through conventional formulations can be absorbed into the bloodstream, leading to systemic side effects. This can be a concern, especially with long-term use.
- 7. Poor Patient Compliance:** Due to the need for frequent administration and potential discomfort associated with some formulations, patients may not adhere to the prescribed dosing regimen, impacting treatment outcomes.

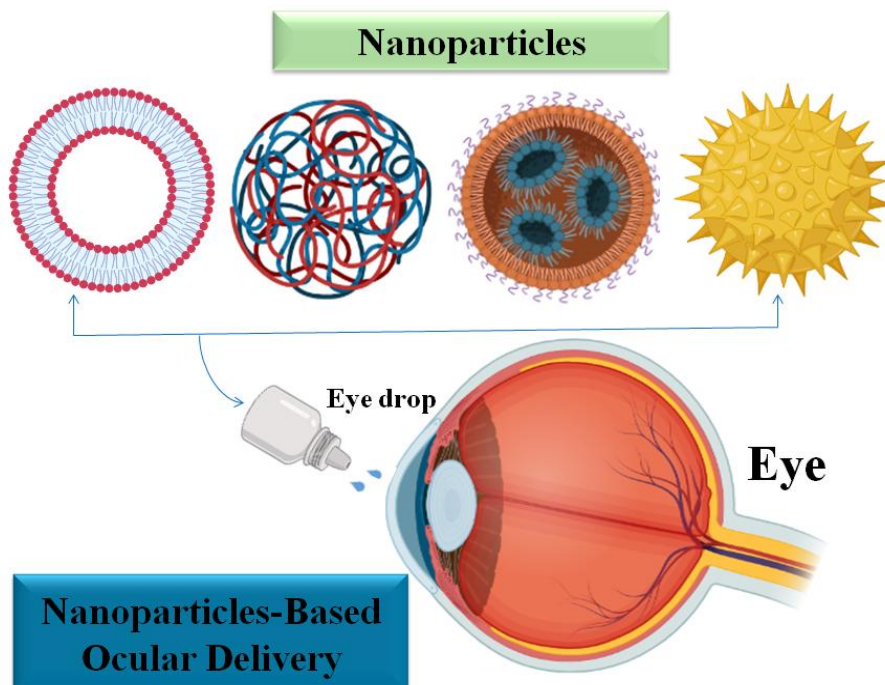
## V. NANO-FORMULATION-MEDIATED OCULAR DRUG DELIVERY SYSTEMS

Recent developments in technology have resulted in the creation of a variety of innovative methods for drug administration, as illustrated in table 1. Biodegradable and biocompatible lipids have emerged as promising materials for the development of lipid nanoparticulate systems, which enable precise drug delivery and targeting [44]. Lipids are solid colloidal particles with a size range of 1 to 1000 nm. Their small size and extended circulation in the bloodstream have made them a subject of significant interest in the realm of drug delivery and targeting.





**Figure 2:** The Diagrammatic Illustration Representing the History of Nanoparticles



**Figure 3:** The Diagrammatic Illustration Representing Nanoparticles Delivery

**Table 1: Recent Nano-formulations for Ocular Drug Delivery**

<b>Nanoparticles</b>	<b>Drugs for ocular delivery</b>	<b>Outcomes</b>	<b>Results</b>	<b>References</b>
Vesicular	Loteprednol etabonate	According to reports, the occlusive impact of SLN and NLC can present a promising avenue for more effective treatment by obstructing the pores in the corneal epithelium and preventing water loss.	SLN, NLC, and NE formulations exhibited corneal drug retention rates that were 2.05, 1.86, and 1.39 times greater, respectively, when compared to the marketed product.	45
Nanomicelles	Dexamethasone/glucocorticoid	A portable microfluidic system has been employed for the purpose of producing nanomicelles.	The nanomicelles that have been acquired are deemed to be both secure and efficient.	46
Cyclodextrin NPs	Fluoromethalone/corticosteroids	The formulation of a transparent nanoparticle has been achieved through the use of CD technology, all while avoiding the need for any organic solvents.	Encapsulated CD-NPs containing Fluoromethalone demonstrate superior efficacy in reducing dry eye symptoms compared to a commercially available preparation, despite having only one-fifth of the dosage.	47
Micelles	Apocynin/alkylphenyl ketones	The utilization of Polyvinylpyrrolidone VA64 micelles was effective in producing an ophthalmic solution of apocynin that was clear and transparent.	Micelles measuring 14nm in size displayed a notable tendency towards high entrapment efficiency, enhanced aqueous solubility, antioxidant capabilities, as well as corneal permeation.	48

Nanoparticle	Curcumin/antioxidant	The self-assembly of nanoparticles was achieved by utilizing Hydrophobin HGFII-his that was obtained from <i>S. cerevisiae</i> .	The utilization of Nanoformulation has resulted in a significant enhancement	49
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## VI. CHALLENGES IN NANOFORMULATIONS-MEDIATED OCULAR DRUG DELIVERY SYSTEMS[50-58]

Novel Drug Delivery Systems (NDDS), which are designed to improve drug delivery efficiency, efficacy, and patient compliance. While NDDS offers several advantages, it also faces certain challenges, including:

- 1. Irritation and Tissue Damage:** Some NDDS formulations may cause irritation or tissue damage at the site of administration. For example, certain intramuscular or subcutaneous injections can cause pain, inflammation, or local reactions. Overcoming this challenge involves optimizing the formulation's composition and selecting suitable excipients to minimize irritation.
- 2. Safety Concerns:** NDDS should be carefully evaluated for their safety profiles. Novel delivery systems may introduce new materials or carriers into the body, which could trigger immune responses or adverse reactions. Rigorous preclinical and clinical testing is essential to assess the safety and biocompatibility of these systems.
- 3. Drug Loading and Stability:** Achieving high drug loading in NDDS while maintaining drug stability is a challenge, especially for drugs with limited solubility or chemical stability. The formulation must strike a balance between drug loading capacity and maintaining the drug's integrity during storage and administration.
- 4. Manufacturing Complexity:** Some NDDS may involve complex manufacturing processes that require precise control over particle size, drug distribution, and release kinetics. Such complexities can increase the cost of production and introduce challenges in scale-up for commercial manufacturing.
- 5. Regulatory Approval:** Introducing novel drug delivery systems may require additional regulatory approval, as they may be considered new drug products rather than mere reformulations. The regulatory path can be more time-consuming and resource-intensive.
- 6. Pharmacokinetic Variability:** NDDS can alter drug release rates, absorption profiles, and tissue distribution. This variability can impact drug efficacy and may require personalized dosing adjustments for certain patient populations.
- 7. Targeting and Specificity:** Achieving targeted drug delivery to specific tissues or cells while avoiding off-target effects is a significant challenge. NDDS should be engineered to

enhance drug accumulation at the intended site and minimize systemic exposure to reduce side effects.

- 8. Biodegradability and Clearance:** For some NDDS, the body's clearance mechanisms must handle the carrier materials after drug release. Ensuring the biodegradability of carrier materials is critical to avoid long-term accumulation or potential toxicity.
- 9. Cost-effectiveness:** While NDDS offers promising advantages, it's crucial to balance these benefits with the overall cost of development and manufacturing. Cost-effectiveness is a significant consideration, especially in the healthcare industry.

## VII. ADVANTAGES OF OCULAR NANO DRUG DELIVERY [59-63]

1. Nanoparticles can be engineered to specifically target certain tissues or cells within the eye, allowing for more precise drug delivery and minimizing side effects.
2. Encapsulating drugs within nanoparticles can protect them from degradation and rapid clearance, extending their shelf life and improving stability.
3. Ocular nanoparticles may reduce the toxicity of certain drugs by minimizing their exposure to non-target tissues.
4. Nanoparticles can enhance the penetration of drugs across the ocular barriers, ensuring that therapeutic agents reach their intended site of action.
5. Controlled release from nanoparticles may reduce the frequency of administration, leading to increased patient compliance with the prescribed treatment.
6. Ocular nanoparticles are being investigated for the treatment of various eye diseases, including glaucoma, macular degeneration, diabetic retinopathy, and uveitis.
7. Nanoparticles can enhance the delivery of antibiotics to treat ocular infections, reducing the risk of microbial resistance.
8. Ocular nanoparticles are explored for delivering anti-inflammatory drugs to manage conditions like dry eye syndrome and inflammation after eye surgeries.
9. Nanoparticles can facilitate the delivery of genetic material for gene therapy to treat genetic eye disorders.
10. Nanoparticles can also be used as contrast agents for imaging techniques to aid in the diagnosis of eye diseases.

## VIII. MUCOADHESIVE FORMULATIONS-MEDIATED OCULAR DRUG DELIVERY SYSTEMS

Mucoadhesive ocular nanoparticles play a significant role in the current drug delivery system for ophthalmic applications. These specialized nanoparticles are designed to adhere to the ocular surface, specifically the mucus layer that covers the eye's cornea and conjunctiva. The mucoadhesive properties of these nanoparticles help prolong the residence time of drugs on the ocular surface, enhancing their bioavailability and therapeutic effects [64]. Here are some key aspects of mucoadhesive ocular nanoparticles in the current drug delivery system [65]:

- 1. Enhanced Drug Retention:** Mucoadhesive nanoparticles have the ability to adhere to the mucosal surfaces of the eye, which reduces drug clearance and washout. This prolonged

retention increases the contact time between the drug and the target tissues, leading to better drug absorption and therapeutic outcomes.

- 2. Improved Bioavailability:** By maintaining a longer presence on the ocular surface, mucoadhesive nanoparticles enhance drug penetration through the cornea and conjunctiva, overcoming the natural barriers to ocular drug absorption. This leads to improved bioavailability of drugs delivered via these nanoparticles.
- 3. Reduced Frequency of Administration:** The sustained release properties of mucoadhesive nanoparticles allow for less frequent dosing compared to conventional eye drops. This reduction in dosing frequency improves patient compliance and convenience.
- 4. Targeted Drug Delivery:** Mucoadhesive nanoparticles can be engineered to target specific ocular tissues or cells, allowing for localized drug delivery. Targeted drug delivery reduces systemic exposure and minimizes side effects.
- 5. Protection of Drugs:** Mucoadhesive nanoparticles offer protection to sensitive drugs from degradation and enzymatic activity in the ocular environment, ensuring the drug's stability and efficacy during its residence time.
- 6. Versatility:** Mucoadhesive nanoparticles can encapsulate various types of drugs, including hydrophilic and hydrophobic compounds. They can also accommodate combination therapy, where multiple drugs can be co-encapsulated, enabling synergistic therapeutic effects.
- 7. Non-Invasive Administration:** Mucoadhesive nanoparticles can be formulated into eye drops or ophthalmic gels, providing a non-invasive and patient-friendly route of administration for ocular drug delivery.
- 8. Ongoing Research:** Research in the field of mucoadhesive ocular nanoparticles is continuously advancing, exploring new materials, formulations, and targeting strategies to optimize drug delivery and therapeutic outcomes.

**Drug loading into mucoadhesive ocular nanoparticles:** Loading of drugs into mucoadhesive ocular nanoparticles is a crucial step in the formulation process [66]. It involves the incorporation of therapeutic agents (drugs) into the nanoparticle matrix to ensure their controlled and sustained release at the target site in the eye. Several techniques are utilized for drug loading in mucoadhesive ocular nanoparticles, including:

- 1. Encapsulation:** The most common method for drug loading involves encapsulating the drug within the nanoparticle core. During formulation, the drug is dissolved or dispersed in the liquid phase along with the polymer(s) used to construct the nanoparticles. As the nanoparticles form, the drug gets entrapped within the core.
- 2. Surface Adsorption:** Some drugs, especially hydrophobic ones, can be adsorbed onto the surface of the nanoparticles. The drug molecules adhere to the nanoparticle surface due to hydrophobic interactions or other forces.

- 3. Covalent Conjugation:** In certain cases, drugs can be chemically linked or conjugated to the nanoparticle matrix through covalent bonds. This covalent conjugation ensures stable drug association with the nanoparticles and controlled release.
- 4. Physical Entrapment:** For certain drug-loaded nanoparticles, the drug is physically entrapped within cavities or pores formed during the nanoparticle fabrication process.

## IX. POLYMERS INVOLVING MUCOADHESIVE NANO-FORMULATIONS

Nanoparticle formulations have the ability to adhere to the mucous that surrounds crucial absorptive zones within the human anatomy [67]. This adhesion can result in subsequent intermolecular cohesion and chemical interactions, which are some examples of chemical interactions. The intricate process of adhesion can be comprehended through various theories. One such theory, the electronic theory, elucidates adhesion by means of the attractive forces instigated by the distinct electronic structures of the components engaged. Conversely, the adsorption theory accentuates which culminate in materials adhering to the mucus layer and establishing an intimate connection with the mucosal surface [68]. So for the preparation of mucoadhesive nano-formulation different kinds of polymers are used.

- 1. Natural Mucoadhesive Polymers:** Numerous mucoadhesive polymers possess unique characteristics that differentiate them [69]. Chitosan, which is synthesized by bacteria and is negatively charged due to carboxylic acid groups, is a thick and dense polysaccharide. Starch, another natural polymer polysaccharide, is made up of glucose units and is commonly used as a mucoadhesive agent. Imaging scans have demonstrated extended retention time of up to 24 hours post vaginal administration with customized starch derivatives [70]. Amylopectin-based starch, in conjunction with PAA, has been posited for ocular delivery owing to its mucoadhesive potential, exhibiting consistent fluorescein concentration in the ocular cavity for up to 8 hours.

Pectin, a complex structure comprising homogalacturonan as a fundamental unit, is a natural anionic polysaccharide commonly employed in pharmaceutical formulations due to its thickening and gelling properties. Buccal mucosa has been found to have a heightened retention time of up to 5 hours for pectin [71]. Gellan gum, another anionic polysaccharide with mucoadhesive characteristics, has demonstrated greater mucoadhesive strength than non-modified gellan gum [72]. Gelrite<sup>1</sup>, which is a commercial derivative of gellan gum with low-acetyl properties, has demonstrated successful usage in delivering ocular antibiotics with prolonged therapeutic efficacy.

Additionally, carrageenans, which are linear sulfated polysaccharides obtained from edible seaweeds, are known for their mucoadhesive potential and are utilized as gelling or thickening agents in various commercial applications. Meanwhile, hyaluronic acid (HA) is a mucoadhesive polymer that has significant potential as it is characterized by lacking sulfate moieties, unlike other glycosaminoglycans [73]. Gelatine, a linear and water-soluble polypeptide derived from collagen, is also a mucoadhesive polymer commonly employed in the pharmaceutical sector to manufacture capsules, ointments, cosmetics, and tablet coatings. A derivative of gelatine, positively charged aminated gelatine, is useful as a tool for delivering mucoadhesives [74].

2. **Synthetic Mucoadhesive Polymers:** Chitosan, an essential member of the semi-synthetic mucoadhesive polymer cohort, exhibits solubility in aqueous acidic media when the degree of chitin deacetylation attains roughly 50%. Additionally, it possesses film-forming attributes. Its superior mucoadhesion on ocular, buccal, and vaginal mucosa render it a promising therapeutic option for dry X syndrome. Notably, an ocular gel containing chitosan demonstrated a precorneal clearance half-life of up to 10 minutes, in contrast to only 1.5 minutes for the control lacking chitosan. In addition, chitosan possesses the ability to remain on buccal mucosa for over 24 hours. Derivatized cellulose, which belongs to the group of semi-synthetic mucoadhesive polymers, is also a significant member. Cellulose ethers, such as methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and carboxymethylcellulose salts, are commonly used in the treatment of dry X syndrome. These cellulose ethers and esters are non-toxic and non-irritating, and some are listed as Generally Recognized As Safe (GRAS). Although it is difficult to make a definitive statement about mucoadhesive rankings due to the many possible modifications to partially synthetic polymers, CMC has been reported to exhibit enhanced mucoadhesion on the ocular surface for up to 43 minutes, dependent on viscosity [75].
3. **Semisynthetic Mucoadhesive Polymers:** The class of synthetic mucoadhesive polymers includes the third category, which encompasses compounds like PEG, also known as polyethylene oxide. Although PEG lacks specific functional groups such as carboxylic acid or thiol moieties that can interact with mucin components, it is still considered an "adhesion promoter" due to its facilitation of mucoadhesion via interpenetration. Despite its uncertain mucoadhesive properties, PEG eye drops have been found to have a longer ocular residence time than saline alone. PVA has a weak mucoadhesion, but its adhesive capacity can be improved through purifying freeze-thaw cycles. On the other hand, PAA, or carbomer, is an anionic polymer of acrylic acid that exhibits significant mucoadhesive properties by interacting with mucus glycoproteins and remaining localized to a specific site. This makes it a popular choice in oral mucoadhesive drug delivery [76].

The duration of ocular contact time for carbomer is dependent on their concentration, whereby a 2% gel results in an approximate 2.5-hour contact time. It has been observed that carbomer gel elastic properties are correlated with human ocular contact time. Furthermore, the combination of PAA, HPMC, and PEG has been found to be beneficial, as films containing these mucoadhesive remain on vaginal tissues for up to 6 hours. Additionally, synthetic mucoadhesives such as crosslinked carbomer derivatives like Noveon1 AA-1 Polycarbophil have been identified. Tablets composed of PAA derivatives have shown to possess the highest mucoadhesion force in comparison to other commonly used mucoadhesives [77].

4. **Passive Mucoadhesive Polymers:** Thiomers signify a new era of mucoadhesive polymers that differ from conventional polymers as they are capable of creating covalent bonds. Thiolated polymers, in particular, have shown enhanced mucoadhesive traits, and there are numerous thiomers obtainable. For instance, thiolated chitosan has exhibited a retention time of up to 50 hours and an adhesion period that is 26 times longer on vaginal mucosa compared to the unmodified polymer. Thiolated PAA has also emerged as a promising tool for mucoadhesion, with an increase in strength reported up to 2.3-fold.

Recently, thiolated carrageenan, xanthan gum, and gelatin have been developed and demonstrate potential for diverse applications. These polymers adhere to mucosal surfaces through disulfide exchange reactions, and preactivated thiomers offer increased stability against oxidation. Chitosan, also known as B (1,4) 2-amino-deoxy-D-glucose, is a polysaccharide that is sourced from chitin, which is one of the most abundant polysaccharides present globally. The substance has free amino groups in its chain, which results in a cationic characteristic of the substance. These unique properties include improved solubility in acidic solutions, as the free amino groups become protonated and contribute to the increased solubility at  $\text{pH} < 6.3$ . Antibacterial activity is another feature of chitosan, as it binds effectively to negatively charged biomacromolecules on cell walls, disrupting the transport of active molecules and bacterial metabolism [78]. The substance also has mucus adhesion properties because of the negative charge of the mucus layer, which leads to electrostatic interaction with chitosan. Furthermore, chitosan has numerous hydroxyls that aid in the formation of hydrogen bonds, which is vital for the interaction of chitosan with drugs.

## **X. ADVANCES MUCOADHESIVE OCULAR NANOPARTICLES**

Carbopols, a type of mucosal adhesive polyacrylic acid (PAA) polymers, possess favourable characteristics that allow them to prolong their stay in the eye. When applied, the polymer binds to the eye's surface and subsequently enhances the drug's accessibility, thereby increasing its availability [79]. A thermosensitive hydrogel, which includes chitosan and was formulated for the ocular administration of levocetirizine dihydrochloride as a model drug, exhibited an initial rapid release followed by a sustained release, thus significantly improving the drug's corneal permeation. Polymers have become increasingly utilized biomaterials in the field of drug delivery, owing to their desirable characteristics such as exceptional biocompatibility, easy biomimetic potential, and significant role in the progress of intelligent drug delivery. They facilitate efficient and precise delivery of therapeutic agents to the designated target site. Recently, pharmaceutical scientists have shown a growing interest in polymers due to the numerous advantages they offer, including extended residence and contact time with mucous/epithelial membranes, controlled drug release, reduced dosing frequency, simple preparation, and maintenance of prolonged drug release [80]. Bioadhesion refers to the attachment of polymers to a biological substrate, while mucoadhesion pertains to the attachment of a substance to the mucus layer, ultimately leading to better bioavailability [81].

## **XI. MUCOADHESIVE GELS**

Carbopols are categorized as a form of mucoadhesive poly(acrylic acid) (PAA) polymers that have advantageous properties in extending the drug's residence time in the eye. The adhesive characteristics of these polymers are responsible for the increase in drug bioavailability, as well as the heightened viscosity of the polymeric formulation [82]. For the purpose of achieving an improved corneal permeation and sustained fluconazole release, formulations were developed that contained either chitosan alone or combined with thermosensitive polymers such as poloxamer[83]. The hydrogel exhibited prompt liberation in the initial phase, followed by constant liberation and a substantial increase in the drug's penetration into the cornea. Alza presented the Ocusert during the mid-1970s, which is



deemed one of the earliest controlled-release ophthalmic delivery devices. The Ocusert efficiently liberated 20 or 40 µg/h of medication for up to a week from the cul-de-sac between the sclera and eyelid [84].

## **XII. POLYMERIC INSERTS/DISKS**

Various forms of ocular inserts have been created for the purpose of drug delivery. These include adherent poly(acrylic acid)-cysteine inserts, degradable inserts composed of polyethylene oxide, and soluble inserts such as PVA film [85]. *In vitro* testing demonstrated that the Eudragit RL-100 coating had the most effective drug permeability. Furthermore, ocular inserts containing ciprofloxacin hydrochloride were developed utilizing esterified gelatin with PVA. These inserts exhibited wettable and swellable qualities, as well as appropriate adhesion to reconstituted mucin. *In vitro*, the drug was released for up to 24 hours, and the inserts were discovered to be biocompatible. The inserts had equivalent qualities to the aforementioned type and sustained drug release for up to 48 hours. Finally, a cylindrical hydroxyethyl methacrylate inserts with Cyclosporine A were developed. These inserts showed zero-order drug release for approximately one month at therapeutic levels. The physical and chemical properties of the film were evaluated including swelling, adhesion, and physicochemical characteristics. All films showed optimal features. The film formulation with 0.5% Carbopol and 1% HPMC had the best film properties such as good adhesion, acceptable pH, and a reasonable drug release of 99% over a 12-hour period. To enhance the solubility and dissolution rates, acyclovir, which was poorly soluble, was incorporated into HPMC matrix by preparing binary systems with beta-cyclodextrin. The *in vitro* release profiles indicated consistent and controlled drug release, lasting up to 20 hours, with non-Fickian diffusion behavior. To treat keratoconjunctivitis sicca, ophthalmic inserts were developed containing epidermal growth factor (EGF) by employing various alginates with hydroxyethyl cellulose [86].

## **XIII. CONTACT LENSES**

Soft contact lenses, which consist of hydrogels made of poly-hydroxyethyl methacrylate (pHEMA), were initially invented in the 1960s. These lenses were also examined for their potential in delivering drugs to the eye during that time. Since then, there have been attempts to use soft contact lenses for both short-term and long-term drug delivery purposes. The conventional method for doing this involves immersing the pre-formed contact lens into a drug solution, which allows the drug to be absorbed into the polymeric lenses. Developing contact lenses for delivering drugs to the eye is a challenging task. There are several hurdles to overcome, such as ensuring proper drug loading, achieving a desired release rate for an extended period, maintaining optical clarity, ensuring patient comfort during prolonged wear, and ensuring biocompatibility. Additionally, prolonged use of contact lenses can increase the risk of microbial keratitis and dry eye syndrome. Furthermore, certain inflammatory conditions make it inadvisable to use contact lenses, which limit the applicability of this drug delivery system. The use of contact lens-based drug delivery systems is particularly challenging for geriatric patients [87].

#### **XIV. INTRAVITREAL IMPLANTS**

Drug delivery systems (DDSs) utilized for the posterior segment of the eye primarily comprise of polymeric depot systems that are directly implanted or injected into the vitreous. The fundamental aim of these systems is to attain a sustained drug release over an extended period. Intravitreal implants containing corticosteroids offer prolonged relief from ocular inflammation and are available in both biodegradable and nonbiodegradable forms. DX in polylactic acid/glycolic acid matrix is a biodegradable implant, while fluocinolone acetonide (FA) in a polyvinyl acetate/silicone laminate is nonbiodegradable. Additionally, even with low-dose administration, corticosteroids in the vitreous humor have been linked to the development of cataracts and heightened intraocular pressure (IOP) [89].

#### **XV. CONCLUSION**

In summary, the treatment of ocular ailments, particularly those affecting the posterior ocular segments, continues to be a daunting challenge for formulation scientists owing to the intricate anatomy and physiology of the human eye. Considerable efforts have been directed towards achieving non-invasive drug delivery methods. In the case of anterior drug delivery, several polymeric systems have been devised to prolong retention time and reduce the frequency of administration. These techniques display potential for treating conditions in the front part of the eye. Biodegradable and non-biodegradable polymeric implants have been researched for delivering drugs in long-term treatment of chronic vitreoretinal diseases affecting the posterior segments. These implants offer a potential solution for reducing intervention frequency and delivering prolonged treatment.

In the future, the focus is expected to remain on achieving ocular targeted delivery combined with intelligent drug delivery systems that respond to external environmental changes or disease-specific pathophysiological signals. Such advancements hold great promise as a potential direction in research. The employment of colloidal polymeric carriers and nanocomposites has emerged as a promising and potential solution for enhancing existing therapy for ocular disorders. These advancements might present a viable substitute to conventional drug delivery methods, which, in turn, can bring about newfound optimism for the effective management of ocular diseases.

In general, the current advancements in mucoadhesive ocular nanoparticles, as well as other inventive drug delivery techniques, indicate a positive projection towards overcoming the challenges that ocular diseases represent and improving patient outcomes in the field of ophthalmology. The continued study and collaboration between scientists, clinicians, and pharmaceutical industries will undoubtedly play an essential role in shaping the future of ocular drug delivery and advancing the treatment of ocular disorders.

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