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NANOTECHNOLOGY BASED - OCULAR DRUG DELIVERY SYSTEMS AND RECENT ADVANCES AND FUTURE PROSPECTS

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ABSTRACT

Ocular drug delivery is challenged by the eye's complex anatomy and physiological barriers, which impede effective treatment for prevalent disorders such as cataracts, glaucoma, age-related macular degeneration, and diabetic retinopathy. Conventional delivery methods, including eye drops and injections, often result in low bioavailability and rapid drug clearance.

This review examines the barriers to ocular drug delivery, categorizing them into precorneal, corneal, and blood-ocular barriers, while also exploring various dosage forms—liquid, semisolid, solid, and mixed—that aim to enhance retention and reduce side effects. Notably, nanotechnology presents innovative solutions through nanocarriers, such as liposomes, niosomes, and polymeric nanoparticles, which improve drug penetration, stability, and targeted delivery. Key factors for effective application, including pH, stability, size, and zeta potential, are discussed. The review underscores the potential of nanostructured platforms to enhance therapeutic outcomes in ocular treatments, highlighting the need for further research to optimize these technologies for clinical use.

Keywords: Ocular Drug Delivery, Corneal Permeability, Drug Release, Bioavailability, Pharmacokinetics, Transscleral Delivery, Bioadhesive Formulations, Gene Therapy, Personalized Medicine.

I. INTRODUCTION

The eye is a very delicate organ with a complex physiology. It consists of two segments: Anterior and Posterior. visual impairment resulting from variety of disorders generally has a substantial impact on quality of life. worldwide cataracts are the primary cause of blindness. Contract complication account for between 40 and 60 percent of blindless worldwide [1].

The eye is the most significant sensory organ in the human body, accounting 80% of all sensory input[2]. Mutations in a, ß, and γ crystalline and the corresponding genes cause early cata- tract development[3]. Ocular tissues are enclosed anatomically by both dynamic and static barriers [4].

Further restricting a place of substances from the systemic circulation are the blood-retina barriers (BRB) and blood-aqueous barriers (BAB)[5].

Also, fungus infections, diabetes, and ageing are all linked to visual impairment. Ocular illnesses include retinoblastoma, diabetic retinopathy (DR), age-related macular degeneration (AMD), and fungal keratitis. According to a recent study, there are roughly 196 million AMD sufferers, 92.6 million DR patients, and 76 million glaucoma sufferers [1].

For most eye conditions, medication therapy is the main course of treatment[6]. Even though there are numerous powerful medications available to treat the majority of ocular ailments, their therapeutic efficacy is hampered by a number of ocular barriers, including tear film, corneal, conjunctival, and blood-ocular barriers. Blinking and tear flow waste conventional eye drops. Their bioavailability is therefore reduced to fewer than 5% [7].

One of the main areas of current study is how to deliver medications to target eye tissues at the desired therapeutic dose without injuring healthy tissues[8].The goals of ocular drug delivery systems (ODDS) are to:

(A) Overcome ocular barriers to deliver medications to target eye conditions;

(B) Enhance medication stability and treatment efficacy;

(C) Extend drug retention period and lower dosage frequency;

(D) Allow for the use of multiple drug combinations; and

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(E) Enhance patient adherence and lower adverse event rates associated with medication [9,10].

Conventional delivery techniques, including topical eye drops, intracameral, conjunctival and scleral, intravitreal, retrobulbar, and systemic administration, are commonly used in medical departments and have produced specific therapeutic effects [11]. As was previously indicated, though, the availability of ocular barriers presents an essential barrier to therapies in terms of getting to the intended spot and remaining there for sufficient time. Because of this, these treatments' bioavailability is frequently restricted and usually less than 5% [11]. The stroma, endothelium, and epithelium include the cornea. The epithelium only permits lipophilic, small-molecule drugs through. However, hydrophilic medications can flow through the stroma [8].The endothelium allows hydrophilic medications and macromolecules to enter the aqueous humour selectively while maintaining the transparency of the corona. Compared to the cornea, the conjunctiva has less of an effect on drug absorption; at present certain macromolecular nanomedicines, peptides, and oligonucleotides completely pass through these tissues to reach the deep layers of the eye. Blood-ocular barriers stop foreign substances from entering the bloodstream. They are the blood-retinal barrier (BRB) in the posterior portion of the eye and the blood-aqueous barrier (BAB) in the anterior segment [13].

The field of ocular medication delivery has advanced significantly with the introduction of nanotechnology, supplying new therapeutic approaches for ocular illnesses [11,12]. When compared to conventional drug administration, nanocarriers have a number of benefits, such as the ability to get past ocular barriers, promote transcorneal permeability, extend the time that a drug is in the body, decrease drug degradation, lower the frequency of doses, increase patient compliance, achieve sustained/controlled release, target specific drugs, and deliver genes[14].Ocular formulations are intended to be applied on the anterior surface (topical route) of the eye, delivered intraocularly (inside the eye), periocularly (subtenon or juxtascleral), or in combination with ocular devices [15].

Nanomicelles, Nanoparticles (NPs), Nanoemulsions (NEs), Microemulsions, Tiny particles, Dendrimers, Liposomes, Niosomes, Nanowafers, and Microneedles (MNs) are examples of novel drug carriers [16].They have a little residence period and are used to administer medication to the anterior portion of the eye [8]. Hydrophobic medications can be delivered by ocular suspensions and emulsions, although vision impairment is a potential side effect. Semi-solid ointments and gels for the eyes may significantly lengthen the amount of time that people spend there. Solid dose forms can be utilized to sustain residence duration (therapeutic contact lens), distribute water-sensitive medications (powder), and give zero order release models (insert) [15]. To achieve and maintain an optimum medication concentration with the least amount of the active therapeutic component, effective ocular absorption requires both appropriate corneal penetration and effective precorneal residence duration. Innovative technologies known as nanosystems have been developed to overcome ocular barriers, protect the drug from the biological environment, extend the drug's residence time, and enhance corneal absorption through biological barriers [10].

It is critical to characterize the included nanosystems to make sure they can carry out the necessary task. Characterization can be done in a variety of ways, including by measuring pH, stability, size, zeta potential, potential interactions, and other crucial ex-vivo and in-vivo assessments [13].

II. OCULAR DISEASE

a) Cataract

b) Glaucoma

c) Age-related macular degeneration

d) Conjunctivitis

e) Diabetic retinopathy (DR)

f) Dry eye disease

g) Fungal keratitis

Diagrammatic representation for ocular disease:-

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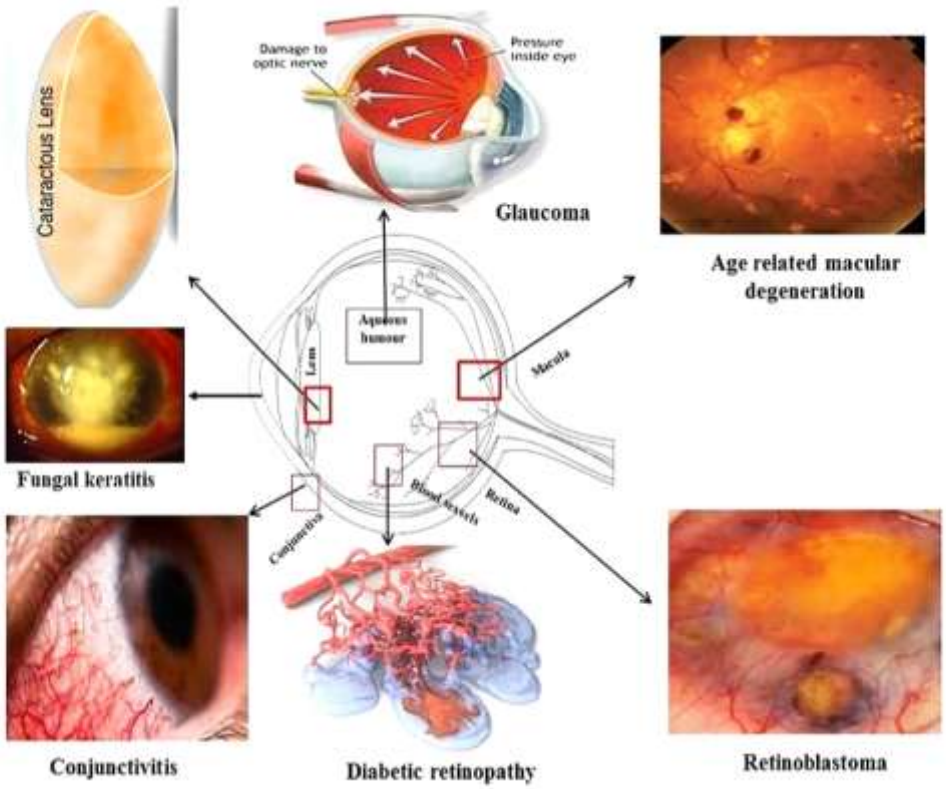

a) Cataract:-Worldwide, cataracts are the most common cause of vision loss. Approximately 40–60% of blindness worldwide is a result of cataract complications [1] .One definition of a cataract is the development of darkness or cloudiness in the lens of the eye. The risk factors include exposure to UV light, diabetes, bad nutri- tion, genetic determinism, and smoking. Cataract could be divided into three type:

a] Cortical

b] Nuclear

c] Posterior subcapsular

The clearness and transparency of lens is regulated by crystallin protein.Changes in α, β, and γ crystallin and its related genes are the cause of early cataract development. Currently, the treatment option is surgical extraction of the opaque lens; however, early anti-cataract drug use may reduce the need for surgery [42].Some the anti-cataract medications include metformin, lanosterol, resveratrol, and curcumin [43].

b) Glaucoma:-After cataracts, glaucoma is the second most common cause of blindness world wide. It is an eye condition that causes progressive vision loss [17].Blindness results from the retinal ganglion cells death and the optic nerve's axon's gradual degradation [18].It is frequently linked to an increase in intraocular pressure (IOP) as a result of abnormal aqueous humour formation or blockage [19].Age, race, diabetes, heredity, nearsightedness, migraines, and retinal vascular calibre are risk factors.[1].It is projected that by 2040, there will be 111.8 million people suffering from glaucoma [20].Open angle and closed angle glaucoma are the two forms of the disease. There are no symptoms associated with open angle glaucoma. Instead, it is characterised by a growing optic disc cupping and visual field, which raises the risk of aqueous humour draining through trabecular meshwork. On the other hand, the elevated pressure that results from the obstruction of outflow routes characterises a closed angle [18].Topical anti-glaucoma drugs are typically used as the first line of treatment. However, because to the substantial precorneal loss and minimal corneal penetration, topical treatment has a bioavailability of less than 5% [21,22,23].Additionally, frequent ocular delivery results in a decrease in patient compliance. As a result, using nanotechnology is essential to effectively administer medication, enhance bioavailability, and preserve the efficacy of anti-glaucoma medications [24].

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c) **Age-related macular degeneration:-**One of the primary causes of vision loss in developing nations is AMD. It occurs more than others in people who are older than 50 [18].AMD causes about 8.7% of blindness on an international scale [25].AMD affected around 196 million individuals in 2020, and by 2040, that figure is predicted to rise to 288 million [26].The following are risk factors: advanced age, smoking, poor diet, elevated blood pressure, and immobility. AMD currently has no known cure, however suitable treatment can stop its development [27].Clinically it divides into early and late AMD. The symptoms of early AMD comprise of changes in retinal pigmentation and medium-sized stone fruit. Neovascular (also known as wet or exudative) or non-neovascular (also known as atrophic, dry, or non-exudative) late AMD is characterised by the possibility of central vision loss and legal blindness [28].High dosages of antioxidant vitamin supplements and zinc can prevent the development of disease from its early stages to its advanced stages [29].Anti-vascular endothelial growth factors (VEGF) can be injected intravitreal (IVT) to treat neovascular AMD, but this procedure is still painful and uses drugs like bevacizumab (Bev), afibercept, etc [30].

d) **Conjunctivitis:-** It is basically the conjunctival tissue getting inflamed. All ages, races, and genders are affected.can be divided as either infectious or non-infectious. Microbiological infections cause infectious conjunctivitis, whereas allergens and irritants cause non-infectious conjunctivitis [40].Conjunctivitis is characterised by redness, pain, tears, and increased secretions from the eyes. Approximately 40% of people worldwide suffer from allergic conjunctivitis [41].

e) **Daibetic retinopathy (DR):-** One specific vascular problem associated with both forms of diabetes mellitus is diabetic retinopathy. After 20 years of diabetes, retinopathy affects all type I diabetic individuals and about 60% of type II diabetic people. DR develops as a result of inflammation and oxidative stress caused on by hyperglycaemic diseases rise of pro-inflammatory mediators. In the USA, it is the third most common cause of blindness. The first and second causes of blindness are cataract and corneal blindness. It can be prevented with early diagnosis, effective treatment, and control of blood pressure and glucose [31].It comes in two types: Proliferative and Non-Proliferative, and both eventually cause the retina to deteriorate more and more. These days, vitrectomy, laser photocoagulation, and medication are used to treat diabetic retinopathy. Laser photocoagulation prevents blindness by sealing blood vessels that are leaking, but also leaves a laser scar. A vitrectomy is a surgical operation used to remove blood and vitreous gel from leaking capillaries in the back of the eye; however, this procedure only temporarily stops the blood leakage and does not stop it from happening again [1].Clinically, retinal circulation can be enhanced and vitreous haemorrhage and retinal neovascularisation can be prevented if laser treatment is administered on time. However, in order for treating macular oedema and enhance vision in patients with the condition, anti-VEGF injections are typically required [32].

f) **Dry eye disease:-** Dry keratoconjunctivitis, were also referred to as dry eye disease, is a multifactorial ocular surface disorder [33].Tear film instability, hypertonicity, inflammation, injury to the ocular surface, and nerve paraesthesia are its defining characteristics [34].DED symptoms include pain, soreness, reduced vision, foreign body sensation, and ocular irritation. DED has a major negative impact on patients' quality of life, makes psychological stress, and causes a significant financial strain on people [35,36].Local secretagogues, corticosteroids, immune suppressants, and artificial tears are common medication therapies. However, there are adverse effects that include glaucoma, elevated intraocular pressure, limited patient compliance, and ocular pain [37].

g) **Fungal keratitis:** Since a healthy cornea would not permit any fungal infection, fungal keratitis only develops in corneas that have sustained trauma. Various fungi, including Candida albicans, Candida glabrata, Candida tropicalis, Candida krusei, and Candida parapsilosis, are the cause of it [38]. Systemic risk factors include diabetes, HIV positive, and leprosy; ocular risk factors include trauma, contact lenses, previous corneal surgery, and topical corticosteroids. Refractive error, corneal ulceration, and stromal infection are the outcomes of fungal keratitis. mRNA expression may change as a result of ocular inflammation [39].

Barriers to ocular drug delivery:

Daigramatic representation for physiological barrier:

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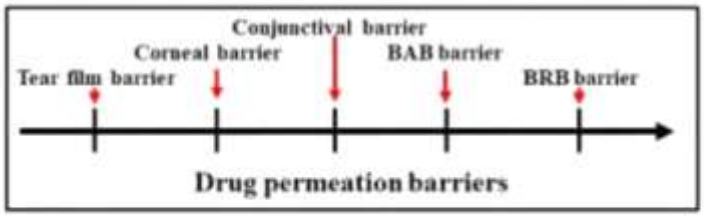

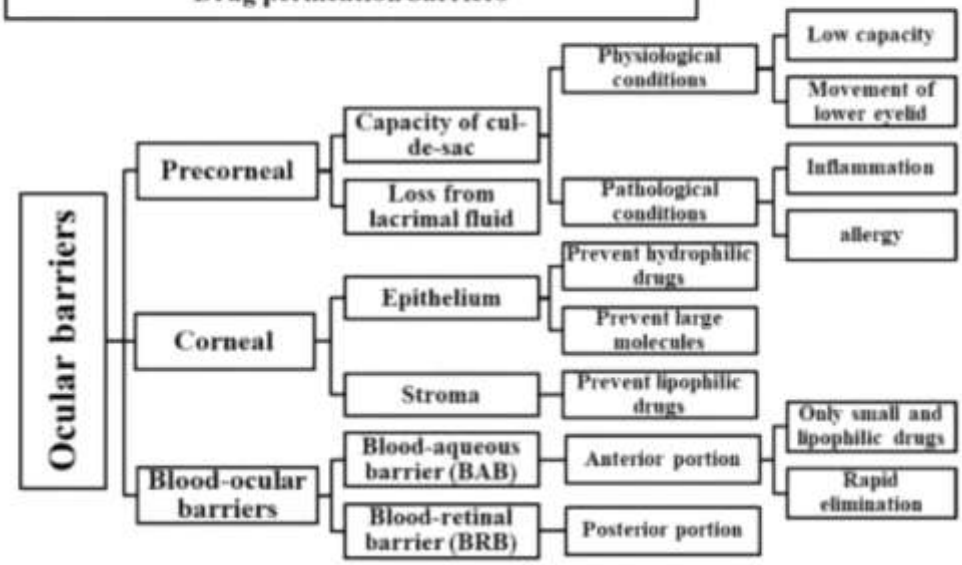

1) Precorneal Barriers

2) Corneal Barriers

3) BloodOcular Barriers

1) Precorneal Barriers:

a. Capacity of cui-de sac:-Palpebral and bulbar conjunctiva meet in the lower eyelid's cul-de-sac, which is located there, as is the upper eyelid's larger recess. In humans, a cul-de-sac are able to hold a maximum of 30 µL. This capacity would drop to 70–80% if the lower eyelid moved to its normal position. Additionally, the cul-de-sac's capacity would be reduced by ocular inflammation and allergic reactions [13].The medication's concentration in the eye would be lowered due to cul-del-sac's poor capacity, which would decrease its therapeutic effect.

b. Loss of Drug from Lacrimal Fluid:-One of the main Barriers in the precorneal region is the administration of ocular solution outflow. Drug loss from the lacrimal fluid may occur from lacrimation, drainage of the solution, and ineffective absorption in the conjunctiva [44].Other barriers to drug absorption would come from protein binding and drug metabolism [13].

2) Corneal Barriers:

The stroma, endothelium, and epithelium make up its division. The epithelium is made up of tightly packed cells arranged in five to seven layers. Stroma is a thick layer composed of water. Large molecules and hydrophilic medicines are blocked by the epithelium, while lipophilic medications are blocked by the stroma [44].The endothelium protects the cornea's transparency and gives hydrophilic medications and macromolecules targeted entry into the aqueous humour. In general, the degree of ionisation, hydrophobicity, charge, and molecular weight of the medicine all affect corneal penetration. As a result, the rate-limiting stage for drug transfer from the lachrymal fluid into the aqueous humour is known as transcorneal permeation [13].

3) BloodOcular Barriers:

They stop foreign substances from entering the bloodstream. They are divided into two categories: blood-retinal barrier (BRB) and blood-aqueous barrier (BAB). The anterior BAB region of the eye blocks several chemicals from entering the intraocular environment. BAB facilitates the transport of tiny and lipophilic medicines. Compared with hydrophilic and bigger molecules, these medications are excreted from the anterior

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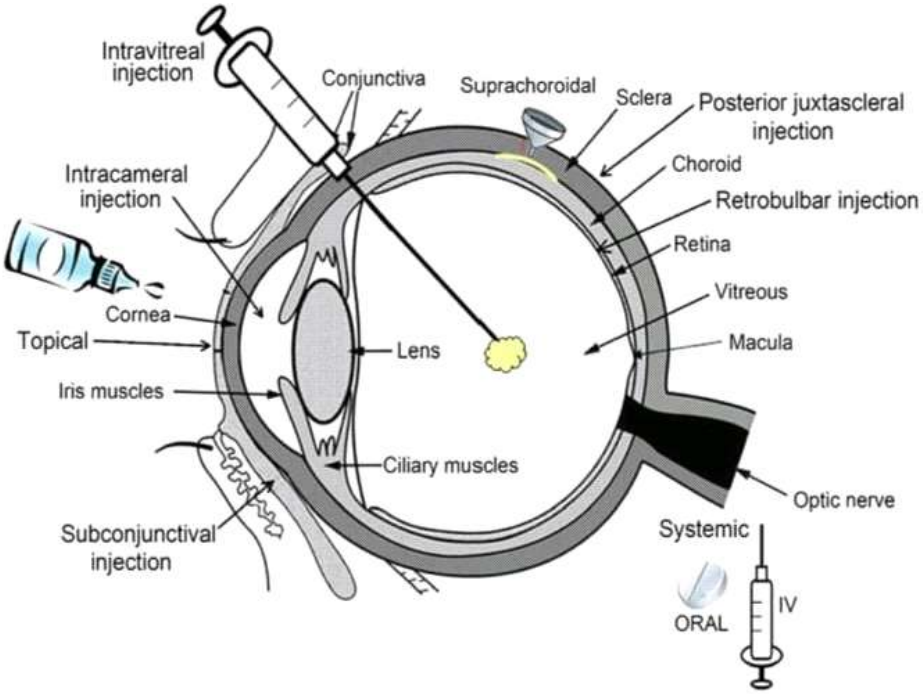
compartment more quickly [13]. Water, hazardous substances, and parts of plasma are kept out of the retina by BRB [45].

Routes for Ocular Drug Delivery:

Daigramatic representation for Routes for Ocular Drug Delivery:-



1. Topical Administration
2. Intracameral Injections
3. Intravitreal Injections/Implants
4. Juxtascleral Injections
5. Retrobulbar Injection
6. Subconjunctival Injection
7. Systemic circulation

1. **Topical Administration:-** The most popular simple method of administering medicines to the eyes is applied topically [46].However it is a non-invasive method, its short residence period and insufficient corneal penetration result in limited bioavailability (<5%) [7].

Its benefits over systemic administration include:

(a) Being comparatively non-invasive.

(b) Reducing the drug's systemic negative effects.

(c) Being reasonably simple for patients to administer [47,48].

Because of this, ophthalmic solutions are the first line of treatment for a variety of eye conditions, including glaucoma, allergies, DED, inflammation, and infection.[49]Topical therapy is inappropriate for elderly and disabled people [15].When terconazole was administered topically as bilosomes, there was improved medication penetration and safety [50].

2. **Intracameral Injections**:- The anterior region of the eyeball or the vitreous cavity are the two sites where an antibiotic is injected during intracameral injections [51].This local delivery strategy first-passes metabolism with some systemic medicines and prevents negative effects. It also stays away from the BAB, conjunctiva, and cornea at the same time [52].So intracameral injections make it properly simple and effective to administer medication to the anterior segment of the eye [53,54].Nevertheless, medication cannot be administered to the posterior chamber of the eye through the anterior chamber. At the same time, medications in the anterior chamber typically need to be rearranged, diluted, sterile, prepared specifically without preservatives, and administered at the right quantities and strengths [55].

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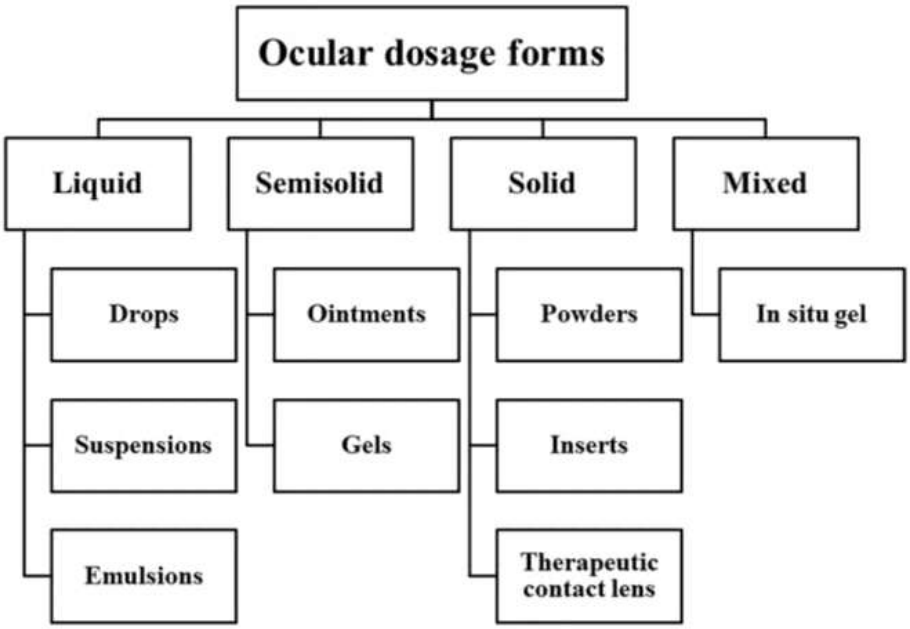
3. **Intravitreal Injections/Implants:-**When treating ocular illnesses in the eyeball, intravitreal injection is the recommended mode of medication delivery in the posterior segment of the eye [56].After IVT injections, free medicines can be rapidly eliminated due to vitreous fluid turnover [57].Good therapeutic outcomes involve many IVTs, which may have undesirable side effects such retinal detachment, eye infection, endophthalmitis, and increased intraocular pressure [58,59].A single intravitreal injection of vitamin E/poly-lactic-co-glycolic acid microspheres containing neurotrophic factor produced from glial cell lines is one innovative method for treating glaucoma. For six months, this method offered a lasting release. After intravitreal injection of polymer-free dexamethasone dimer implants, comparable outcomes were seen [60].
4. **Juxtascleral Injections:-** Injections into the posterior portion of the body are used to treat It is applied in the management of diabetic-related conditions, trauma, and cystoid macula oedema. Juxtascleral injections of anecortave cortisone, which demonstrated prolonged release for six months in the choroid and retina, are a novel therapy option for AMD [61].For the purpose of treating retinal genes, effective trans-scleral microneedles have been developed to deliver adeno-associated viruses [62].
5. **Retrobulbar Injection:** To administer the drug into the retrobulbar space behind the globe, the retrobulbar method involves administering a needle through the orbital fascia and eyelid. Compared to intravenous administration, retrobulbar injection of amphotericin B had greater antifungal efficacy [63].Chloropromazine injections retrobulbarly are used to treat blinding pain in the eyes [64].
6. **Subconjunctival Injection:-** When topical treatment results in very little medication penetration into the anterior region of the eye, subconjunctival injection is commonly applied. For the treatment of uveitis, subconjunctival injections of steroids synthesised as PEGylated liposomes demonstrated anti-inflammatory efficacy that persisted for at least one month, specifically targeting the necessary ocular tissue [65].When brinzolamide was administered as PLGA nanoparticles by subconjunctival injection, the IOP was successfully managed for 10 days [66].
7. **Systemic circulation**:-Systemic administration is an additional drug delivery technique that includes parenteral and oral dosage. At this point, endophthalmitis, increased intraocular pressure, and uveitis have been treated with antibodies, antibiotics, and carbonic anhydrase inhibitors administered systemically [66-70].However, frequent administrations are necessary to achieve the desired therapeutic effect because of ocular barriers and tight junctions of the retinal pigment epithelium, which allow only 1% to 2% of the drug to reach the retinal and vitreous regions. This may lead to systemic side effects and poor patient compliance [71-73].

Dosage form:

Classification of ocular dosage form



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1. liquid dosage form
a) Eye drop
b) Eye suspensions
c) Eye emulsion
2. Semisolid dosage form
a) Eye gel
b) Eye ointment
3. Solid dosage form
a) Eye powder
b) Ocular insert
c) Therapuetic contact lens
4. Mixed dosage form
a) In situ gel

1. Liquid dosage form:

a. Eye drop:- The medicine is injected into the front portion of the eye. Easy administration and well known equilibrium are two of their benefits. Nevertheless, their drawbacks include a short retention period (less than five minutes), low bioavailability, and severe adverse effects brought on by repeated high-concentration administration [74] .Numerous nanosystem platforms have been created for tackling their shortcomings. The mucoadhesive nanosystem of cyclosporine had been replicated by means of poly (D-L-lactone)-b-dextran. The formulation method used was nanoprecipitation. The final product showed improved permeability, drug retention, and tiny particle size [75]. The antibacterial hesperetin micellar system's formulation exhibited small tiny particles, high percentage entrapment efficacy, increased penetration, and improved efficacy [76].

b. Eye suspensions: Ocular suspensions are aqueous solvent-based dispersions of hydrophobic drugs. Because of the drug's retention in the conjunctival cul-de-sac, their contact time is increased. During the preparation phase, the tear fluid's particle size, solubility, and dissolution rate are crucial[77].Particles smaller than 10 µm are often more soluble, dissolve more quickly, and have lower surface retention. Particles larger than 10 µm, however, may cause eye irritation and lead to tears[78]. One drawback of ocular suspension is its lack of stability. Since the particles are likely to cluster together and are difficult to disperse, they cannot be kept in the freezer. Additionally, alterations in crystallinity during medication storage can impact the drug's solubility and bioavailability. Another possible side effect of its administration could be impaired eyesight. Posaconazole was administered more effectively in the eyes in a polymer system containing xanthan gum and carbopol 974P by utilizing a high pressure homogenizing process. This resulted in improved stability, longer retention times, and antifungal activity[79].

c. Eye emulsion: When stabilizers or surfactants are added, a biphasic system becomes solubilized and becomes an emulsion. Hydrophobic medications can be delivered by eye emulsions, and oil-in-water (O/W) emulsions have reduced ocular irritation, longer contact times, and higher bioavailability[80] .Dexamethasone acetate and polymyxin B sulfate were delivered more effectively through the cornea thanks to the creation of a nanoemulsion using high-pressure homogenization. To improve ocular adherence, a positive charge inducer was used. The final formula had improved retention time, decreased particle size, and increased stability [81]. The triamcinolone acetonide microemulsion was created using the water titration method. It revealed reduced particulate matter and enhanced permeability[82].

2. Semisolid dosage form:

a. **Eye gel:-** Gels for the eyes are a semisolid dose form with a large amount of water. Their viscosity gives them improved absorption and retention time. Even with gels' high water content, visual impairment is still possible. Ocular gels could be made using a variety of polymers, including carboxymethyl cellulose, hydroxypropyl methylcellulose, polyacrylic acid, and acrylic acids[83].A proniosomal gel containing curcumin was prepared using the coacervation process, which effectively reduced the particle size and

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improved the anti-inflammatory action[84]. The creation of phytantriol-based lyotropic liquid crystalline gel, which was achieved by the vortex method, revealed an increase in the ex vivo permeability and retention time of pilocarpine[85].

a. **Eye ointment:-** Mineral oil and white petroleum are the ingredients of eye ointments, which are semisolid dosage forms. Because they obstruct eyesight, they are only applied to the lower eyelid at night. They are frequently utilized by younger patients. Their anhydrous nature makes them a suitable option for medications that are moisture-sensitive and lipophilic. When compared to solutions, they are more bioavailable and have a longer retention period[86].Approved in 2019 for the treatment of herpetic keratitis, Avaclyr® is an eye ointment that contains the antiviral acyclovir. Lotemax® containing the anti-inflammatory loteprednol etabonate is another. They both displayed improved drug release and corteal penetration[87].

3. Solid dosage form:

a. Eye powder:- These are water-sensitive medication dose forms in sterile, solid form. Cefuroxime, moxifoxacin, and voriconazole are administered as injectables through intracameral injection. Voriconazole is reconstituted in water, whereas cefuroxime and moxifoxacin are reconstituted in saline. After reconstitution, cefuroxime and voriconazole solutions remain stable for a period of seven days. On the other hand, the moxifoxacin solution lasts f**or** 24 weeks[88,89].

b. Ocular insert:- Ocular inserts have a zero order drug release model and are a solid dosage form made of biodegradable polymers. They have several benefits, such as a prolonged residence duration, sustained drug delivery, constant release, and fewer side effects[90].The process of electrospinning was used to create nanofibers filled with triamcinolone acetonide. They displayed less adverse effects, systemic absorption, and particle size reduction[91].Additionally, when its insert was implanted, prolonged bimatoprost activity over several months was demonstrated[92].

c. Therapuetic contact lens:-According to recent studies, a therapeutic contact lens's sustained residence time and close contact with the cornea can increase bioavailability by more than 50%[93].They stay in the eye ten times longer than regular eye drops[94].They also shorten the time between doses, the amount needed, and the amount absorbed by the body[95].There are numerous methods for enclosing the medication inside contact lenses, including soaking, ion ligation, molecular imprinting, and the use of nanoparticles[74,96,97].Protein attachment, ion and oxygen permeability, medication loss during fabrication or storage, transmittance, and lens edema are some of the issues that prevent their clinical usage[15].The encapsulation process was used to prepare the Dexamethasone contact lens. It demonstrated 200-fold medication preservation in the retina comparable to that of standard eye drops[98].Chips containing either timolol, bimatoprost, or hyaluronic acid have been utilized to lessen fast medication release[93].

4. Mixed dosage form:

a. In situ gel: These are low viscosity polymeric solutions. When they came into touch with tear fluid, they transformed into pseudo-plastic gels. When opposed to basic solutions, they have a longer contact duration [99].Based on the transition properties, in situ gel can be classified as temperature, ionic, or pH sensitive[100].Ciprofoxacin in situ gel containing hydroxypropyl methylcellulose and ion-sensitive sodium alginate demonstrated extended drug release and improved residence time[101].Hydrocortisone butyrate's thermosensitive in situ gel demonstrated prolonged medication release without burst release[102]. Ketorolac tromethamine's thermosensitive in situ gel demonstrated enhanced mucoadhesive qualities and a 12-hour drug release duration[103].

Nanostructured platform:

1. liposomes
2. niosomes
3. nanoemulsion
4. Nanomicelles
5. Polymeric nanoparticles
6. solid lipid nanoparticles

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7. Nanostructured lipid carriers
8. Nanocrystals
9. Dendrimers
10. Cubosomes
11. Olaminosomes
12. Bilosomes

1. **liposomes**:-Liposomes are increasingly used in ocular drug delivery due to their ability to improve bioavailability and target specific tissues in the eye. They can encapsulate both hydrophilic and lipophilic drugs, enhancing stability and reducing toxicity.

Advantages of Liposomes for Ocular Delivery:-

1. Improved Drug Absorption: Liposomes can enhance the permeation of drugs across the corneal epithelium.
2. Sustained Release: They provide a controlled release mechanism, prolonging drug action.
3. Targeted Delivery: Liposomes can be designed to target specific cells or tissues in the eye, improving therapeutic efficacy.
4. Reduced Side Effects: Encapsulation in liposomes can reduce the systemic exposure and associated side effects[104-106].

liposomes are used to treat some ocular diseases are as follow :-

1. **Dry Eye Disease:-**Liposomes can encapsulate lubricating agents or anti-inflammatory drugs to provide relief in dry eye conditions. They help to stabilize tear film and reduce evaporation[150].
2. **Glaucoma:-**Liposomes can be used to deliver intraocular pressure-lowering agents. Their sustained release properties can enhance adherence to therapy[151].
3. **Retinal Diseases:-**In diseases like age-related macular degeneration (AMD) and diabetic retinopathy, liposomes can facilitate targeted delivery of anti-VEGF agents or steroids directly to retinal tissues[152].

2. **Niosomes:-**Niosomes, non-ionic surfactant-based vesicles, are gaining attention for ocular drug delivery due to their unique properties, such as improved drug stability and prolonged release. They are particularly useful for delivering both hydrophilic and lipophilic drugs to the eye.Advantages of Niosomes for Ocular Delivery:

1. Enhanced Stability: Niosomes are generally more stable than liposomes, reducing the risk of drug degradation.
2. Improved Bioavailability: They facilitate better penetration through the corneal barrier.
3. Controlled Release: Niosomes can provide a sustained release of drugs, improving therapeutic outcomes.
4. Reduced Irritation: Being less toxic than traditional formulations, niosomes can minimize ocular irritation.

Applications: Niosomes have been investigated for delivering anti-inflammatory agents, antibiotics, and antiglaucoma drugs. Their versatility makes them suitable for treating various ocular conditions[107-109].

Niosomes are used to treat some ocular diseases are as follow :-

1. **Glaucoma:-**Niosomes have been developed to deliver timolol, a common glaucoma medication, enhancing its bioavailability and prolonging its therapeutic effect[153].
2. **Dry Eye Disease:-**Niosomal formulations have been explored to deliver lubricating agents like hyaluronic acid, providing longer retention time on the ocular surface and enhancing relief from dry eye symptoms[154].
3. **Age-related Macular Degeneration (AMD):-**Research is ongoing into the use of niosomes for targeted delivery of anti-VEGF (vascular endothelial growth factor) agents, aiming to improve efficacy while minimizing systemic side effects[155].

3. **Nanoemulsion:-**Nanoemulsions are a promising drug delivery system for ocular applications due to their ability to enhance drug solubility, stability, and bioavailability. They consist of oil, water, and surfactants, forming a stable emulsion with droplet sizes typically in the range of 20-200 nm.

Advantages of Nanoemulsions for Ocular Delivery:

1. Improved Permeability: Nanoemulsions enhance drug penetration through the corneal barrier.
2. Sustained Release: They allow for prolonged drug release, reducing the frequency of administration.

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3. Enhanced Drug Solubility: They can solubilize poorly water-soluble drugs, improving their therapeutic effects.
4. Reduced Irritation: Nanoemulsions can minimize ocular irritation compared to traditional formulations.

Applications:- Nanoemulsions have been explored for delivering various ocular therapeutics, including anti-inflammatory agents, antibiotics, and antiglaucoma medications[110-112].

Nanoemulsion are used to treat some ocular diseases are as follow :-

1. **Glaucoma:** Nanoemulsions can improve the delivery of antiglaucoma drugs, increasing intraocular pressure control.
2. **Dry Eye Disease:** They help in delivering lubricants and anti-inflammatory agents effectively.
3. **Retinal Disorders:** Nanoemulsions facilitate the delivery of drugs to the posterior segment of the eye[156-158].
4. **Nano micelles:** Nano micelles are surfactant-based colloidal carriers that can enhance ocular drug delivery. They are typically composed of amphiphilic molecules, allowing them to encapsulate both hydrophilic and lipophilic drugs, improving solubility and stability.

Advantages of Nanomicelles for Ocular Delivery:

1. Enhanced Drug Solubility: Nanomicelles can solubilize poorly water-soluble drugs, increasing their bioavailability.
2. Targeted Delivery: They can be engineered to target specific tissues in the eye, improving therapeutic efficacy.
3. Sustained Release: Nanomicelles provide controlled release profiles, reducing the frequency of administration.
4. Reduced Ocular Irritation: They are less irritating compared to conventional eye drops.

Applications:-Nanomicelles have been investigated for delivering various drugs, including anti-inflammatory agents, antibiotics, and antiglaucoma medications[113-115].

Nano micelles are used to treat some ocular diseases ae as follow :-

1. **Cataracts:-**Nano micelles can deliver anti-cataract drugs effectively, improving solubility and penetration into the lens[159].
2. **Age-Related Macular Degeneration (AMD):**Targeted delivery of anti-VEGF therapies via micelles can improve treatment outcomes in AMD[160].
5. **Polymeric nanoparticles:** Polymeric nanoparticles (PNPs) are emerging as a versatile platform for ocular drug delivery, offering numerous advantages for enhancing drug efficacy and bioavailability.

Advantages of Polymeric Nanoparticles for Ocular Delivery:

1. Biocompatibility: Many polymers used in PNPs are biocompatible and biodegradable, minimizing toxicity.
2. Controlled Release: PNPs can provide sustained drug release, reducing the frequency of dosing.
3. Enhanced Stability: They protect encapsulated drugs from degradation, improving stability and shelf life.
4. Targeted Delivery: PNPs can be modified to target specific tissues or cells in the eye, enhancing therapeutic outcomes.
5. Improved Permeability: Their small size allows for better penetration across ocular barriers.

Applications: Polymeric nanoparticles have been used for delivering anti-inflammatory drugs, antibiotics, and therapeutics for conditions like glaucoma and retinal diseases[116-118].

Polymeric nanoparticles (PNPs)are used to treat some ocular diseases ae as follow :-

1. **Glaucoma Treatment:** Polymeric nanoparticles can deliver anti-glaucoma medications, improving ocular bioavailability and providing sustained release[161].
2. **Age-Related Macular Degeneration (AMD):** Targeted polymeric nanoparticles can deliver therapeutic agents directly to retinal tissues, enhancing treatment efficacy[162].

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6. **Solid lipid nanoparticles:** Solid lipid nanoparticles (SLNs) have gained attention for ocular drug delivery due to their ability to enhance drug solubility, stability, and bioavailability while minimizing toxicity. They provide a controlled release mechanism, improve penetration through the corneal barrier, and can be formulated to target specific ocular tissues.

Key Advantages of SLNs in Ocular Drug Delivery:

1. Enhanced Drug Solubility: SLNs can encapsulate lipophilic drugs, improving their solubility in aqueous environments.
2. Sustained Rlease: The lipid matrix allows for a controlled and prolonged release of the drug, reducing the frequency of administration.
3. Biocompatibility: Made from biocompatible lipids, SLNs are generally well-tolerated in ocular applications.
4. Targeted Delivery: SLNs can be modified to enhance targeting to specific ocular tissues, improving therapeutic efficacy.
5. Reduced Side Effects: By localizing drug delivery, SLNs can minimize systemic side effects[119-122].

Solid lipid nanoparticles (SLNs) are used to treat some ocular diseases ae as follow :-

1. **Glaucoma Treatment:**SLNs can be used to deliver antiglaucoma medications effectively, improving intraocular pressure management while minimizing systemic absorption.
2. **Retinal Diseases:**SLNs can encapsulate drugs for conditions like age-related macular degeneration (AMD) and diabetic retinopathy, allowing for targeted delivery to the retina and prolonged drug release.
3. **Anti-inflammatory Treatment:**SLNs can carry anti-inflammatory agents to manage ocular inflammation associated with conditions such as uveitis or allergic conjunctivitis, reducing irritation and enhancing bioavailability.
4. **Antibiotic Delivery:**In cases of bacterial infections, SLNs can be utilized to deliver antibiotics directly to the site of infection, improving therapeutic outcomes while minimizing systemic exposure.
5. **Gene Therapy:**SLNs are being explored for delivering genetic material to treat inherited ocular diseases, enhancing the delivery of therapeutic genes directly to retinal cells[163-166].

7. **Nanostructured lipid carriers:** Nanostructured lipid carriers (NLCs) are an advanced formulation for ocular drug delivery, offering enhanced stability, improved drug loading capacity, and controlled release profiles. They combine solid lipids and liquid lipids, enabling better encapsulation of both hydrophilic and hydrophobic drugs.

Key Benefits of NLCs in Ocular Drug Delivery:

1. Improved Drug Solubility: NLCs enhance the solubility of poorly water-soluble drugs, increasing their bioavailability in ocular tissues
2. Sustained Release: The lipid matrix facilitates a prolonged release of the drug, which can enhance therapeutic effects and reduce administration frequency.
3. Enhanced Penetration: NLCs can improve drug penetration through the cornea and into the ocular tissues.
4. Biocompatibility: Formulated from biocompatible and biodegradable lipids, NLCs are suitable for ocular applications.
5. Targeted Delivery: Modifications to the lipid carriers can allow for targeted delivery to specific ocular sites [123-126].

Nanostructured lipid carriers (NLCs) are used to treat some ocular diseases ae as follow :-

1. **Glaucoma Treatment:** NLCs can deliver anti-glaucoma medications, improving intraocular pressure management through enhanced bioavailability and sustained release[167].
2. **Age-Related Macular Degeneration (AMD):** NLCs can encapsulate therapeutic agents like antioxidants and anti-VEGF drugs, enhancing their delivery to the retina[168].

8. **Nanocrystals :-**Nanocrystals have emerged as a promising approach in the design of ocular drug delivery systems, aiming to improve the solubility, bioavailability, and therapeutic efficiency of drugs administered to the eye. These tiny crystalline particles, typically ranging from 10 to 1000 nm in size, allow poorly soluble drugs to be delivered more effectively.

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Key Features of Nanocrystals for Ocular Drug Delivery:

1. **Enhanced Solubility:** Nanocrystals increase the surface area of drugs, improving their solubility in the aqueous environment of the eye. This is especially important for drugs with poor water solubility.
2. **Increased Bioavailability:** Nanocrystals can enhance the bioavailability of ocular drugs by promoting better absorption through the corneal and conjunctival barriers.
3. **Sustained Release:** Nanocrystals can be engineered for prolonged drug release, reducing the frequency of administration and improving patient compliance.
4. **Stability:** Nanocrystal formulations tend to be physically stable over time, which is important for maintaining consistent drug performance.
5. **Minimal Irritation:** Due to their small size and reduced need for surfactants or other stabilizing agents, nanocrystal formulations often cause less irritation to ocular tissues compared to other formulations.

Challenges: Sterility: As with all ocular formulations, ensuring sterility is a challenge, particularly when scaling up production.

Stability: While physically stable, nanocrystal formulations can suffer from chemical stability issues, depending on the drug being used[127-129].

Nanocrystals are used to treat some ocular diseases ae as follow :-

1. **Glaucoma Treatment:** Nanocrystal formulations can deliver anti-glaucoma medications effectively, ensuring sustained release and improved therapeutic efficacy[169].
2. **Retinal Diseases:** Nanocrystals can be utilized for targeted delivery of therapeutics for retinal disorders like age-related macular degeneration (AMD), improving drug distribution to the retina[170].
9. **Dendrimers:** Dendrimers are highly branched, nanoscale macromolecules that have shown promise in ocular drug delivery due to their unique structure, which allows for high drug loading and controlled release. Their properties can enhance solubility, stability, and bioavailability of therapeutic agents for ocular conditions.

Key Advantages of Dendrimers in Ocular Drug Delivery:

1. High Drug Loading Capacity: The branching structure allows for multiple functional groups, enabling the attachment of various drugs.
2. Controlled Release: Dendrimers can be designed to release drugs in a controlled manner, improving therapeutic efficacy.
3. Enhanced Bioavailability: Their nanoscale size can facilitate better penetration through the corneal barrier.
4. Targeted Delivery: Dendrimers can be modified with targeting ligands to improve specificity to ocular tissues.
5. Biocompatibility: Many dendrimers are designed to be biocompatible, minimizing toxicity in ocular applications [130-133].

10. **Cubosomes:** Cubosomes are nanostructured drug delivery systems that can enhance the bioavailability of ocular medications. These lipid-based carriers form cubic phase structures, providing a high surface area for drug loading and controlled release. Their ability to encapsulate both hydrophilic and lipophilic drugs makes them particularly suitable for ocular applications.

Key Advantages of Cubosomes in Ocular Drug Delivery:

1. Enhanced Stability: Cubosomes are more stable than conventional liposomes, which is beneficial for maintaining drug efficacy in the ocular environment.
2. Sustained Release: The cubic structure allows for a gradual release of the drug, which can prolong therapeutic effects and reduce dosing frequency.
3. Improved Bioavailability: Their small size and ability to penetrate biological membranes can enhance drug absorption in the eye.
4. Biocompatibility: Cubosomes are made from biocompatible lipids, minimizing potential toxicity.

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Recent Studies:

1. In Vitro Studies: Research has shown that cubosomes can effectively deliver drugs like anti-inflammatory agents and antibiotics to ocular tissues, demonstrating improved permeation compared to traditional formulations.
2. In Vivo Models: Animal studies have indicated that cubosome formulations result in higher drug concentrations in the aqueous humor and cornea, suggesting better therapeutic outcomes.
3. Formulation Development: The formulation parameters, such as lipid composition and surfactant type, play a crucial role in the physicochemical properties and performance of cubosome systems[134-136].

Cabooses are used to treat some ocular diseases ae as follow:

1. **Anti-Inflammatory Treatments:-**Due to their ability to deliver anti-inflammatory drugs, cubosomes are being explored for treating conditions like uveitis and other inflammatory ocular diseases. They help in targeting the site of inflammation while minimizing systemic side effects[171].
2. **Glaucoma Therapy:-**Cubosomes can enhance the efficacy of glaucoma medications by facilitating sustained release and increasing ocular retention time, potentially improving patient compliance[172].
3. **Retinal Disease Treatment:-**Researchers are investigating cubosomes for delivering therapeutics to treat retinal diseases, such as age-related macular degeneration (AMD), leveraging their ability to penetrate the retinal barrier[173].

11. **Olaminosomes:** Olaminosomes are innovative lipid-based nanocarriers that have shown promise in ocular drug delivery due to their unique structure and properties. These vesicular systems can enhance the solubility and bioavailability of poorly water-soluble drugs, making them suitable for treating various ocular conditions.

Key Advantages of Olaminosomes in Ocular Drug Delivery:

1. Enhanced Drug Loading: Olaminosomes can encapsulate a range of hydrophilic and lipophilic drugs, improving the loading efficiency.
2. Sustained Release: They provide a controlled release profile, which can prolong therapeutic effects and improve patient compliance.
3. Increased Penetration: Their small size facilitates penetration through ocular barriers, enhancing drug absorption in the cornea and other tissues.
4. Biocompatibility: Olaminosomes are typically composed of biocompatible lipids, minimizing the risk of toxicity[137-139].

12. **Bilosomes :-** Bilosomes are innovative lipid-based nanocarriers that can enhance ocular drug delivery. They consist of a bilayer structure that incorporates bile salts, improving the solubility and bioavailability of poorly water-soluble drugs. This feature makes them particularly effective for ocular applications.

Key Advantages of Bilosomes in Ocular Drug Delivery:

1. Improved Drug Solubility: Bile salts in bilosomes enhance the solubility of hydrophobic drugs, allowing for higher drug loading.
2. Enhanced Penetration: The unique composition facilitates better penetration through ocular barriers, increasing drug absorption in the cornea and other tissues.
3. Sustained Release: Bilosomes can provide controlled and prolonged release of the drug, which can enhance therapeutic effects and improve patient adherence.
4. Biocompatibility: The natural components of bilosomes reduce the risk of irritation and toxicity, making them suitable for ocular use.

Recent Studies and Applications:

1. Formulation Development: Research has focused on optimizing bilosome formulations for various ocular drugs, showcasing improved stability and efficacy compared to conventional delivery systems.
2. In Vitro and In Vivo Studies: Studies demonstrate that bilosomes can significantly increase drug concentrations in ocular tissues, providing better therapeutic outcomes for conditions like glaucoma and dry eye syndrome.

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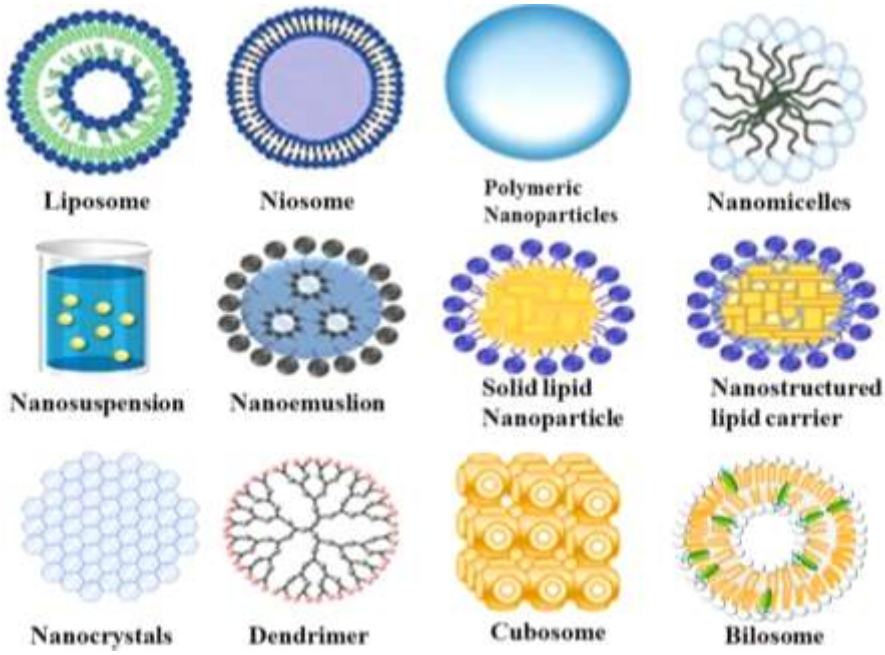
3. Mechanistic Insights: Investigations into the mechanisms of action have shown that bilosomes enhance drug permeability and retention in ocular tissues[140-142].

Bilosomes are used to treat some ocular diseases ae as follow :-

1. **Enhanced Ocular Drug Delivery:-**Bilosomes can improve the bioavailability of both hydrophilic and lipophilic drugs by facilitating their absorption across the corneal barrier, making them effective for treating various ocular conditions[174].
2. **Treatment of Intraocular Inflammation:-**Bilosomes can effectively deliver anti-inflammatory agents, which are crucial for managing conditions like uveitis and postoperative inflammation, improving therapeutic outcomes while minimizing systemic side effects[175].
3. **Glaucoma Therapy :-**The sustained release profile of bilosomes can improve the effectiveness of glaucoma medications, potentially increasing intraocular pressure management and patient compliance[176].
4. **Retinal Disease Treatment:-**Bilosomes are being studied for their ability to deliver therapeutics directly to the retina, potentially addressing conditions like diabetic retinopathy and age-related macular degeneration (AMD)[177].
5. **Gene Delivery Applications:** Bilosomes can also be explored for ocular gene therapy, providing a means to deliver genetic material to retinal cells for treating inherited retinal disorders[178].

Daigramatic representation of nanostructured platform:-



Recent advance in ocular drug delivery system:

Recent advances in ocular drug delivery systems have focused on improving bioavailability and patient compliance while minimizing side effects. Here are some key developments:

1. **Nanoparticle Systems:** Nanoparticles, including liposomes and solid lipid nanoparticles, enhance drug solubility and penetration into ocular tissues. They can provide sustained release and targeted delivery, improving therapeutic outcomes.
2. **Microneedle Technology:** Microneedles allow for pain-free delivery of drugs into the anterior chamber of the eye. This method bypasses barriers associated with conventional eye drops and improves bioavailability.
3. **Intraocular Implants:** Biodegradable implants provide a long-term drug release mechanism directly in the eye, reducing the need for frequent administration. These systems are particularly useful for chronic conditions like glaucoma and retinal diseases.
4. **Hydrogel Systems:** Smart hydrogels that respond to environmental stimuli (pH, temperature) have been developed for controlled release. They can improve residence time on the ocular surface.

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5. **Transscleral Delivery:** Techniques that facilitate drug diffusion across the sclera (the white part of the eye) are being researched. This route can target the posterior segment of the eye effectively.
6. **Ocular Inserts:** Sustained-release ocular inserts that adhere to the conjunctiva or cornea provide prolonged drug delivery, reducing the frequency of administration.
7. **Bioadhesive Formulations:** Mucoadhesive polymers are used in formulations to enhance retention on the ocular surface, improving the bioavailability of topical medications.
8. **Gene Therapy Approaches:** Advances in gene delivery systems are being explored for the treatment of retinal diseases, providing potential for long-term therapeutic effects[143-146].

III. FUTURE PROSPECTS OF OCULAR DRUG DELIVERY SYSTEM [ODDS]

The future prospects of ocular drug delivery systems (ODDS) are promising, driven by advancements in technology, materials science, and a deeper understanding of ocular pharmacokinetics. Here are some key trends and developments:

1. **Nanotechnology:** Nanoparticles and Nanosuspensions: These can improve drug solubility and bioavailability. They enable targeted delivery and prolonged retention in ocular tissues.
2. **Nanocarriers:** Liposomes, solid lipid nanoparticles, and dendrimers enhance drug stability and facilitate controlled release.
3. **Microneedle Arrays:-**These minimally invasive devices can deliver drugs through the cornea, bypassing barriers associated with traditional methods like eye drops. They offer precise dosing and improved patient compliance.
4. **Implantable Drug Delivery Systems:-**Sustained-release implants: These can provide long-term drug release, reducing the need for frequent administration. They are particularly beneficial for chronic conditions such as glaucoma and macular degeneration.
5. **Smart Contact Lenses:-**Incorporating sensors and drug reservoirs, these lenses can monitor ocular conditions and release medications in response to specific stimuli, offering personalized treatment options.
6. **Thermal and Chemical Enhancements:-**Iontophoresis and Sonophoresis: These methods use electrical or ultrasonic waves to enhance drug penetration through the corneal barrier.
7. **Permeation enhancers:** New compounds are being researched to temporarily increase corneal permeability for better drug absorption.
8. **Gene Therapy and Biologics:-**Advances in gene therapy provide potential for treating genetic ocular diseases through direct delivery of therapeutic genes. Biologics, such as monoclonal antibodies, are also being explored for targeted treatment.
9. **Regulatory and Market Trends:-**Increased investment in ocular therapeutics, along with supportive regulatory frameworks, is accelerating the development of innovative delivery systems.
10. **Personalized Medicine:-**The integration of patient-specific data and AI can lead to tailored therapies that optimize drug delivery based on individual needs and responses[147-149].

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[136] Recent Advances in the Application of Cubosomes for Ocular Drug Delivery"* - This paper reviews recent findings and technological advances in cubosome formulations specifically for eye care.

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[139] Recent Advances in Nanocarrier Systems for Ocular Drug Delivery"* - This paper highlights the advancements in nanocarrier technology, with a focus on olaminosomes and their role in enhancing drug delivery to the eye.
[140] Bilosomes: A Promising Drug Delivery System for Ocular Applications"* - This article reviews the structure, advantages, and potential applications of bilosomes in ocular drug delivery.
[141] Nanocarriers for Ocular Drug Delivery: A Comprehensive Review"* - A detailed review that includes discussions on bilosomes and their comparative effectiveness with other delivery systems.
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