Modern Approaches in Nanotechnology for Ocular Diseases

Nusratfatema Shaikh*[1], Prof. Randhawan B.B [2], Arya Shaligram[3], Shravan Yadav[4], Adesh Zende[5], Dhanashri Avhad[6], Aarati Shinde[7], Archana Garudkar[8]

Students[1,3,4,5,6,7,8] Assi. Professor[2]

Arihant College of Pharmacy, Kedgaon, Ahilyanagar – 414005.

ABSTRACT:

Nanotechnology encompasses the study, processing, and application of various functional materials, tools, and systems, as well as the manipulation of substances at the nanoscale. A specific application of nanotechnology is "nanomedicine," which involves its use in the detection, management, prevention, and monitoring of a wide range of diseases. Research in this field can potentially accelerate disease treatment and drug development.

In cases involving ocular diseases, medications delivered through eye drops must traverse several ocular barriers to reach the posterior segment of the eye. Nanotechnology offers significant advantages for these treatments. It can effectively address the limitations of conventional ocular delivery methods, which often suffer from poor therapeutic efficacy and possible side effects due to invasive surgery or systemic exposure.

KEYWORDS: Nanotechnology, ocular diseases, nano-based drug delivery systems, nanocarriers.

INTRODUCTION:

The study, design, synthesis, operation, and application of diverse functional materials, tools, and systems, as well as the manipulation of substances at the nanoscale (1–100 nm), are all included in the field of nanotechnology. The ability to work at the molecular level, atom by atom, to develop a massive structure and a new molecular organization is the essence of nanotechnology, according to the National Nanotechnology Initiative. (1) The discovery of treatments for many ocular conditions, such as diabetic retinopathy, age-related macular degeneration (AMD), glaucoma, cataracts, and uveitis, has involved extensive preclinical and clinical research during the past ten years. (2)The World Health Organization (WHO) estimates that over 2.2 billion people worldwide suffer from vision impairment due to ocular illnesses, which have a significant impact on both eyesight and quality of life. Ocular illnesses have a significant influence on patient's vision and quality of life around the world. (3) Numerous nanotechnology-based approaches, such as bioadhesive enhancement, sustainable release, stealth function, selectively targeted distribution, and stimulus-responsive release, have been developed to manage eye disorders. (4) To deliver medications to the intended eye tissues, ocular drug

delivery systems (ODDS) are made to: (1) get past ocular barriers; (2) increase drug stability and treatment effectiveness; (3) extend drug retention time and decrease dosage frequency; (4) allow for multiple drug combinations; and (5) enhance patient adherence and lower drug-related adverse events. [5]

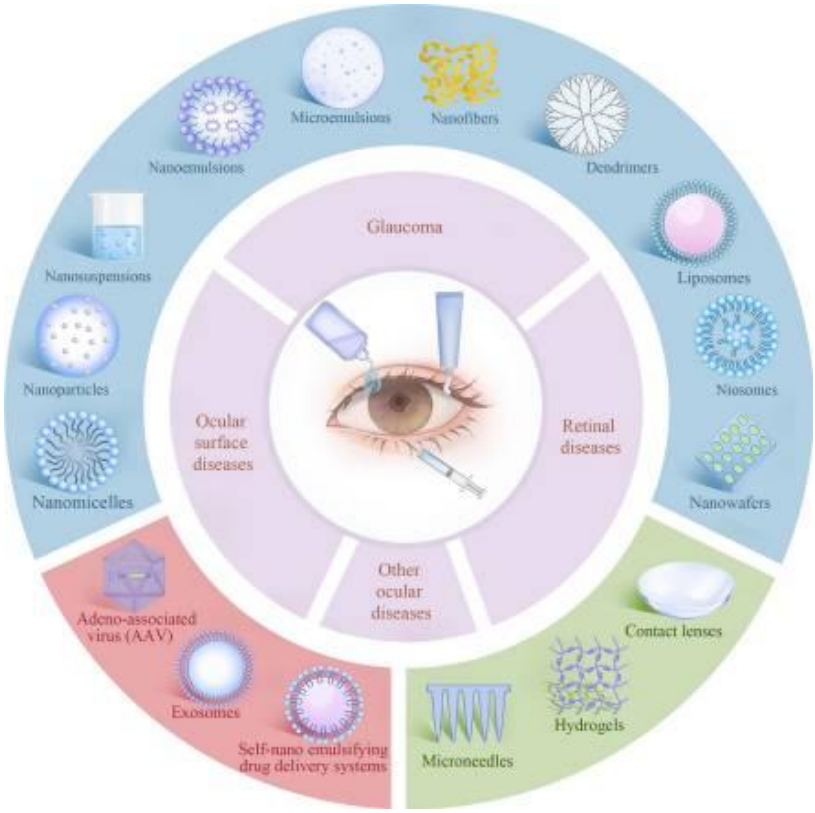

Fig Representation Ocular Drug Delivery System [5]

ANATOMY OF EYE:

Depending on the lens, the eyeball's anatomical structure can be separated into anterior and posterior segments. The anterior segment consists of: the cornea conjunctiva, iris, ciliary body, aqueous humor, and lens; while The posterior segment consists of: the sclera, retina, choroid, and vitreous body. [5]

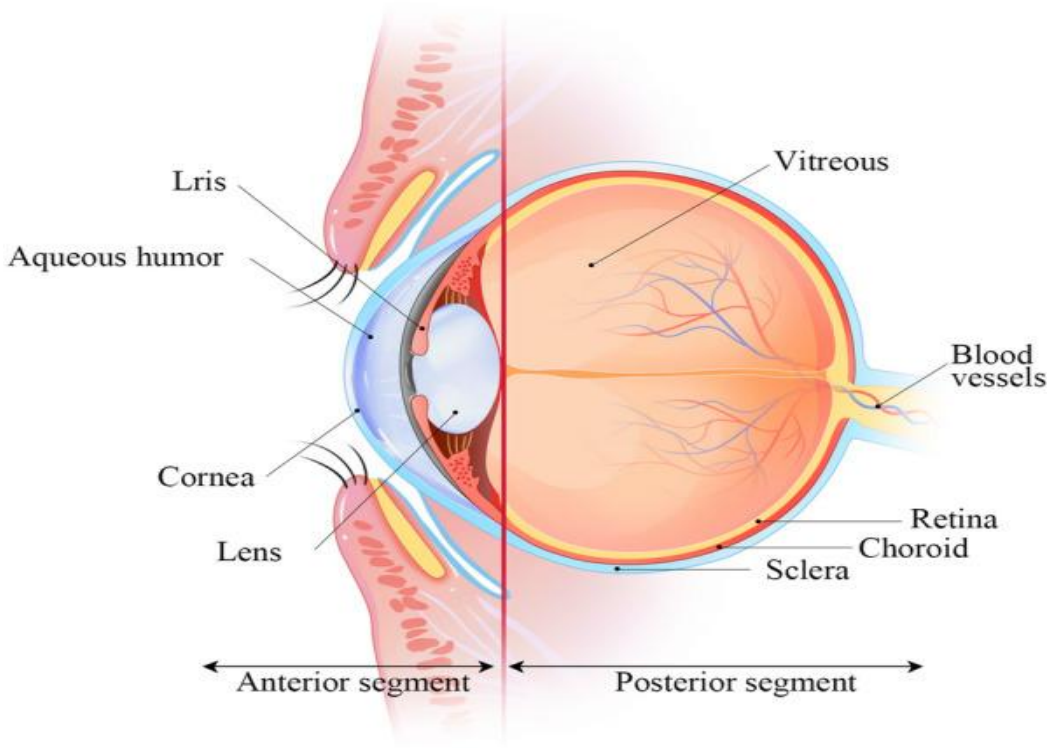

Fig Anatomical Structure of Eye [5]

The eye is among the human body's most complicated organs [6]. It can also be distinguished into three layers: the outer, middle, and inner layers.

The outer layer comprises the sclera and cornea, and the middle layer consists of the Iris, ciliary body, and choroid. In contrast, the inner layer consists of the retina, aqueous, vitreous, and lens. [6]

DRUG ADMINISTRATION: ADVANTAGES AND DISADVANTAGES

To reach the posterior segment in clinical practice, various administration routes for ophthalmic drug delivery are frequently employed. Topical application, conjunctival and scleral application, intracameral administration, intravitreal injection, retrobulbar injection, and systemic routes are the primary traditional routes of administration. [5]

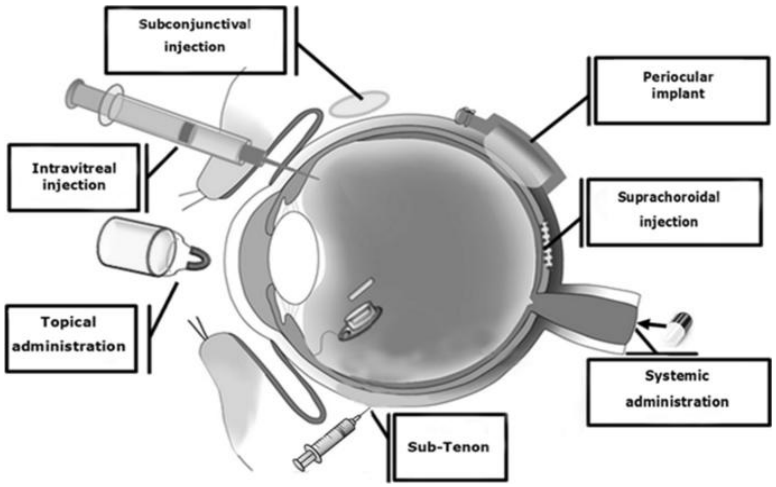

Fig. Various Delivery Routes for Ocular Administration [2]

Sr. No.	Routes of Drug Administration	Advantages	Disadvantages
1.	Systemic	Incredibly effective at treating systemic and ocular disorders at the same time. High drug stability, high patient compliance, and the availability of numerous pharmaceutical forms without the need for stringent sterile conditions. [2]	Low bioavailability, systemic toxicity from high dosage, and blood ocular barriers. [5]
2.	Periocular implant	Localized drug delivery, reduced complications, improved patient comfort, and safety, and less invasiveness compared to intraocular implants. [2]	Requires surgery, it is blocked by certain static barriers (choroid, RPE, and sclera), and is removed by lymph and blood flow in the surrounding tissues. The device's final burst stage causes the remaining

			medication to release uncontrollably. [2]
3.	Intravitreal injection	Achieving sustained drug levels, minimal systemic side effects, quick therapeutics (vitreous humor), and avoiding the blood-retinal barrier. [2]	Drug toxicity, invasiveness, poor patient compliance, retinal detachment, cataract endophthalmitis, and bleeding. [5]
4.	Topical route	Painless, non-invasive, simple to administer, patient compliance, localized drug effects, and reduced systemic drug circulation. [5]	Corneal barrier, high dosage, low bioavailability, dilution, and efflux. [5]

OCULAR DISEASES:

There are currently over 500 different types of eye diseases recognized, including dry eye disease (DED), diabetic retinopathy, macular degeneration, and glaucoma. As the population ages and eye usage patterns change, the prevalence of ocular diseases is gradually rising. These conditions have a significant impact on people's health and quality of life, which highlights how urgently effective interventions are needed. Without a doubt, medication therapy is essential in the treatment of numerous eye conditions. [5]

GLAUCOMA: After cataracts, glaucoma, an eye condition marked by progressive vision loss, is the second most common cause of blindness worldwide. One of the key characteristics of glaucoma is high intraocular pressure (IOP). [5] Defects in the central and peripheral visual fields result from glaucoma's damage to the optic nerve and retinal nerve fiber layer. [7] The primary goal of current treatment is to slow or lessen subsequent visual loss by lowering intraocular pressure. [5]

DIABETES RETINOPATHY: Diabetic retinopathy (DR) is the most common side effect of diabetes mellitus (DM) and the primary cause of blindness and vision loss in people of working age. [8] It is a chronic

consequence of diabetes. In extreme situations, retinal detachment may gradually show up as ocular floaters, blurred vision, distorted vision, and even partial or total blindness. (5)

DRY EYE DISEASE: Dry eye disease is a multifactorial ocular surface condition also referred to as dry keratoconjunctivitis. It is distinguished by hypertonicity, inflammation, and tear film instability. Artificial tears, local secretagogues, corticosteroids, and immunosuppressants are examples of common medication treatments. (5)

NANOTECHNOLOGY:

Drug delivery based on ocular nanotechnology is a specialized technique that uses nanoscale carriers or systems to precisely deliver therapeutic agents to the eye. These carriers decrease side effects, increase solubility and stability, prolong release, and deliver medications to the intended location. (3) To maximize drug bioavailability, extend contact time, and minimize the need for eye removal, new eye nano-systems with various shapes and properties were created. (1) Among the most popular nanotechnology-based ocular delivery systems are nanocapsules, nanohydrogels, nanoliposomes, nano micelles, niosomes, cubosomes, and nanoparticles (NPs), which provide certain advantages over existing diagnostic and therapeutic techniques. (2) The use of nanotechnology in ophthalmology has advanced along with its development in medicine and surgery. (1) The creation of nanocarriers has several benefits, such as lowering drug degradation, achieving sustained/controlled release, boosting transcorneal permeability, extending drug residence time, decreasing dosage frequency, improving patient compliance, drug targeting, and gene delivery. (5)

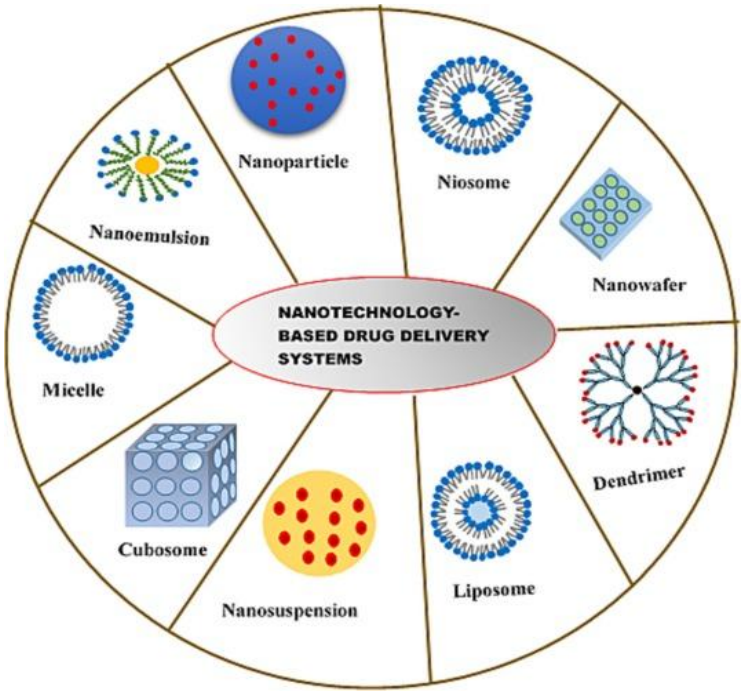

Fig Nanotechnology-Based Ocular Drug Delivery Graphical Representation [5]

NANO-SUSPENSIONS:

Nano suspensions are colloidal dispersions in which a surfactant helps evenly distribute the hydrophobic phase throughout the aqueous medium. [1] Pure drug nanoparticles and stabilizers make up nanosuspensions (NSs), which usually have an average diameter of less than 1 µm (usually between 200 and 500 nm). They improve drug solubility in both aqueous and organic environments by being formulated in either aqueous or non-aqueous liquid phases. [3] Aqueous dispersions of hydrophobic medications are made and delivered to the intraocular tissues using nanosuspensions. [9] A carrier material is not necessary for nanosuspension, in contrast to traditional matrix-framed nanosystems. It is typically stabilized by polymers or surfactants and contains 100% pure drug nanoparticles. They offer the benefits of longer residence time, longer-lasting drug release, and improved solubility. [5] NSs are being researched in the field of ocular drug delivery to treat a variety of eye disorders, including uveitis, diabetic retinopathy, macular degeneration, and glaucoma. [3] The drug is dissolved or bound within the structure, or it is encapsulated or captured within the structure by binding to the matrix. When treating immune disorders that impact vision, nanoparticles offer the advantages of better local delivery of macromolecules and low water solubility molecules like cyclosporine or glucocorticoids. Prednisone, dexamethasone, hydrocortisone, and other corticosteroids, for instance, have been delivered via nanosuspension. [1]

NANO-EMULSIONS:

A nanoemulsion is a transparent or translucent material with sizes between 20 and 500 nm that is kinetically stable but thermodynamically unstable. [5] Nanoemulsions (NEs) are emulsions made up of two immiscible liquids, typically oil and water, that are kept stable by an amphiphilic surfactant. [3] NEs are classified into three main categories based on the dispersed phase system: (1) water-in-oil (w/o) NEs, (2) oil-in-water (o/w) NEs, and (3) bi-continuous NEs. [5] Ophthalmic NE formulations have shown improved ocular drug bioavailability, longer pre-corneal retention times, improved penetration of ocular tissues, and stable drug levels in the eye. [3] NEs, which are based on nanotechnology, are frequently employed as noninvasive, affordable drug delivery methods and are readily scalable for commercial manufacturing. Additionally, NEs offer extended anterior corneal retention time, sustained drug release, high penetration ability, improved ocular bioavailability, and simple sterilization improvement when compared to conventional drug delivery methods. Additionally, it can be used to treat a variety of eye conditions, including glaucoma, herpes simplex keratitis infection, fungal keratitis, and DED. [5] Due to their small droplet sizes, which provide stability and rheology control, NEs have a wide range of uses in biomedicine. [3] Although the formulation elements of microemulsion and nanoemulsion are similar, their stability is different. Nanoemulsion is thermodynamically unstable, but microemulsion is thermodynamically stable. [9]

MICELLES (NANOMICELLES):

Micelles, which are colloidal drug delivery systems, spontaneously form in a solution when the polymer/surfactant concentration is higher than the critical micellar concentration (CMC). [9] Polymers, surfactants, and multi-ion composite nano micelles are the three types of micelles. Nanomicelles are self-assembling colloidal dispersions with a hydrophilic shell and a hydrophobic core that are nanoscale (particle size typically between 5 and 100 nm). [3] Polymer micelle formation is driven by hydrophobic interactions, hydrogen bonds, electrostatic interactions, etc. [5] When hydrophobic medications are ready to be given to the anterior segment of the eyeball, nano micelles enable their dissolution and create clear aqueous preparations. [1]In an aqueous solution, positive micelles function as efficient transporters of hydrophobic medications, whereas reversed micelles can be used to deliver hydrophilic medications. [9] Hydrophobic drugs are encapsulated, dissolved, and delivered by positive micelles, while hydrophilic drugs are encapsulated and delivered by reverse nano micelles. [5] Cyclosporine is one of the medications used in this nanotechnology. It is safe, quick, and effective in treating keratoconjunctivitis sicca, according to a phase III clinical trial. [1] A hydrophobic and effective immunosuppressant medication used to treat dry eye disease is cyclosporin A. [9]

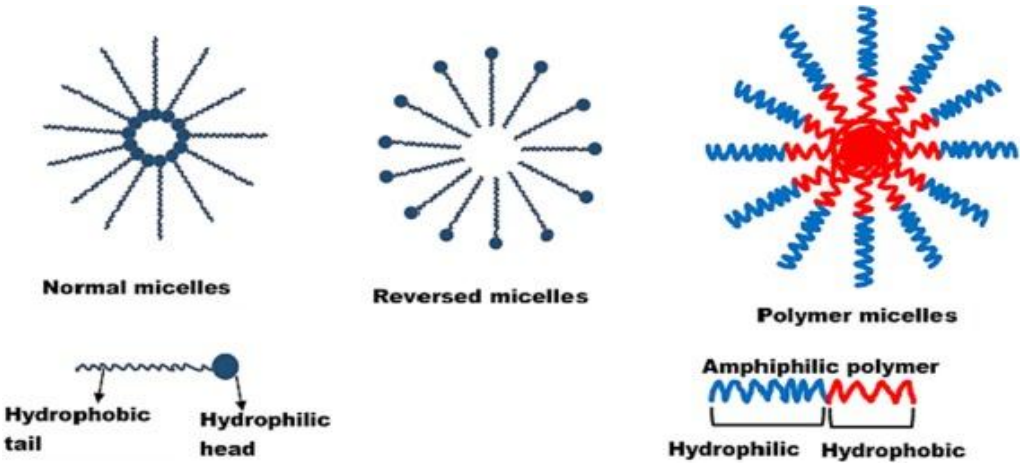

Fig. Structure of normal reversed, and polymer micelles [9]

NANOPARTICLES:

Due to their ability to target medications to particular ocular tissues and get past physiological barriers, nanoparticles ranging in size from 50 to 400 nm are frequently used in the delivery of therapeutics to the anterior eye. [9] NPs are carriers of colloidal drugs. They are primarily separated into lipid and polymer nanoparticles. Lipids, proteins, and natural or synthetic polymers like albumin, sodium alginate, chitosan, polylactide-coglycolide (PLGA), polylactic acid (PLA), and PCL make up the NPs used in ocular preparations. [5] Depending on the material and manufacturing process, they can be spheres, rods, tubes, or irregular shapes. Unlike micelles, they might or might not have a core-shell structure. [3] With the benefits of (a) being smaller and less irritating; (b) offering better absorption and improving intracellular penetration; and (c) targeted delivery to desired tissues, NPs have been used extensively to deliver drugs to the targeted tissue in the eye up to this point. [5] NPs can be classified according to their morphological structure as either nanospheres or nanocapsules. As nanospheres are made of solid polymers, nanocapsules are made up of an oily core surrounded by a thin polymeric envelope that is about 5 nm thick. Both hydrophilic and hydrophobic medications can be encapsulated in NPs. Lipid-based nanoparticles used in drug delivery include solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). [3]

NIOSOMES:

Niosomes are non-ionic surfactant vesicles with two layers that can capture both lipophilic and hydrophilic drugs. [1] The use of nonionic surfactants makes them biocompatible and low toxicity. They therefore have a lot of potential to be great ocular drug delivery carrier systems. [9] Niosomes can readily interact and pass through the tear film barrier to reach the cornea or conjunctival tissue because of their hydrophilic surface. [1] Niosomes

are non-immunogenic and biodegradable. [5] Although niosomes and liposomes share structural and functional similarities, in some aqueous solutions they are made up of non-ionic amphiphilic molecules. [3] Niosomes have been tested as antibiological and anticholinergic substances. [1] Physical instability, low drug loading, encapsulated drug leakage, and high production costs are some of the issues that restrict the use of niosomes in drug delivery. The potential of hyaluronic acid-modified niosomes to improve tacrolimus's ocular bioavailability and transcorneal permeability was investigated. After corneal transplant surgery, the immunosuppressive medication tacrolimus is used to lower the risk of graft rejection. [9]

LIPOSOMES:

Liposomes are lipid vesicles with a central water compartment diameter of 0.025 to 10 µm that are made up of one or more phospholipid bilayers. They can contain hydrophilic or lipophilic medications, which are frequently used to treat retinal disorders. ([5] Liposomes can be classified as small monolayer vesicles (10 and 100 nm), large monolayer vesicles (100 and 300 nm), and multimembrane vesicles with multiple phospholipid double chains based on their size and number of double chains. [1] Liposomes are of great interest because of their biodegradability and biocompatibility. Furthermore, liposomes can be used to deliver ocular medications with a high molecular weight and low solubility. [9] Liposomes can contain hydrophilic or lipophilic medications in their lipid bilayer or aqueous core, respectively. Targeting ligands or polymers can be added, and surface molecules, size, and lamellarity can be changed to improve specificity for particular cells or tissues. [3]

DENDRIMERS:

Dendrimers are monodisperse macromolecules. [1] A small molecule is surrounded by an inner cavity made up of several reaction end groups. There are several repeated terminal groups in its tree branch structure. [1]

With multiple functional groups on their surface and a three-dimensional structure, dendrimers are highly branched nanoscale polymer structures that are adaptable and biocompatible for a range of uses. [3] These are symmetrical, hyperbranched, nanoscale (usually 2–100 nm) structures that resemble trees or stars and have repeating molecules encircling a central core. They are highly effective at conjugating drugs, encapsulating them, and functionalizing surface groups. [5] Furthermore, dendrimers can be thought of as accurate models of globular proteins. Because of their size scale, electrophoresis, systematicity, and other bionic characteristics, they are referred to as "artificial proteins." [1] Certain dendrimers have innate biological characteristics, such as cytotoxic effects on cancer cells while preserving healthy cells or antifungal or antibacterial effects. [3]

Subconjunctival carboplatin for retinoblastoma and intravitreal injection of fluocinolone acetoacetate for retinitis pigmentosa are two medications created with this technology. [1]

CUBOSOMES:

A continuous, highly distorted lipid double chain with two disjoint and consistent waterways makes up the cube's structure. The cube has a larger surface area and can encapsulate a variety of hydrophilic, hydrophobic, and amphiphilic molecules in comparison to the basic liposome structure. [1] Amphiphilic lipids in water self-assemble to form liquid crystalline cubic phase nanoparticles known as cubosomes. The diameters of their particles range from 100 to 300 nm. [9] This nanoparticle is linked to the use of dexamethasone in eye drops, suggesting a greater drug availability in aqueous humor. [1] Hydrophobic drugs can be effectively delivered by cubosomes. They are not very effective at capturing hydrophilic medications, though. [9]

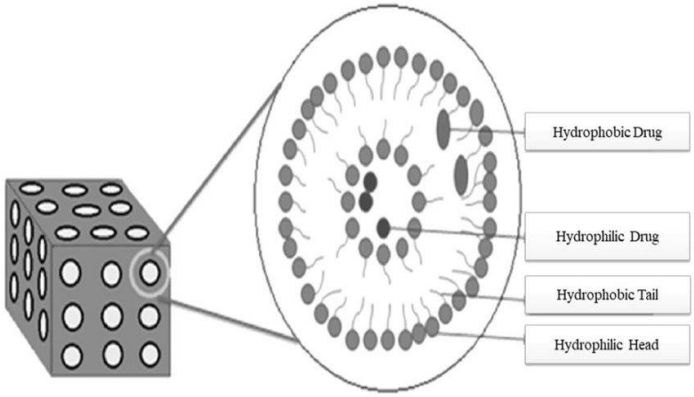

Fig. Structure of Cubosomes [10]

NANOWAFERS:

With just a fingertip, nano wafers transparent membranes or discs that are nanosized and loaded with medication can be applied to the surface of the eye. [9] By releasing the medication gradually, these nano reservoirs enhance the drug's absorption into the surrounding eye tissue. After the required amount of time for drug release, the nano wafer dissolves. PVA is an appropriate non-immunostimulatory polymer for the production of ocular nano wafers. [3] The drug's retention period on the ocular surface is extended and drug absorption is facilitated by the nanowafers' gradual release of the drug. [5]

CHARACTERIZATION OF NANOTECHNOLOGY-BASED DRUG DELIVERY SYSTEMS:

The term nanotechnology describes the treatment of structures at the nanoscale level, which is proportionally equivalent to peptide drugs and ranges in size from 1 to 100 nm. [5] To create efficient delivery systems, it is crucial to optimize various formulation and process parameters as well as characterize the physicochemical and biological characteristics of nanocarriers. [9] Their therapeutic efficacy in the ocular pathological environment is closely linked to their fundamental physicochemical characteristics, including size, zeta potential, refractive index, pH, retention, viscosity, osmolality, surface charge, hydrophobicity, and biodegradability. [5]

Particle Size and Polydispersity Index (PDI): Two important characteristics of nanocarriers that significantly influence their physical stability are particle size and polydispersity index (PDI). [9] Photon correlation spectroscopy or dynamic light scattering are the primary methods used to estimate these parameters. [5] This is a quick, sensitive, and user-friendly method. [9]

Refractive Index (RI): Abbe's refractometer measures the refractive index for determining the water content, salinity, and sugar concentration of soft contact lenses. In general, the tear RI ranged from 1.340 to 1.360. Therefore, a RI value of less than 1.476 is advised for ocular formulations. [5]

Zeta Potential (ZP): Another crucial feature of nanoformulations is zeta potential. Due to its influence on the stability and interaction of nanocarriers with biological systems, it is one of the most researched parameters. [9] It is one of the most researched parameters and is based on the electrophoretic motion of particles in an electric field. [5]

Stability: When creating nanocarriers, stability problems like creaming, flocculation, Ostwald ripening, coalescence, and precipitation are crucial obstacles. [5] Physical instability may arise from lipid modification brought on by a shift in lipid crystallinity in lipid nanoformulations. [9] The centrifugation test, freeze-thaw cycle, heating-cooling cycle, high-temperature storage, and short-term stability (3 months) can all be used to estimate the stability of various nanosystems. [5] By examining changes in particle size, zeta potential, and entrapment efficiency during storage, these instability issues can be tracked. [9]

Other Characterization May Include:

- pH
- Retention
- Surface morphology
- Osmolarity

- Safety/ biocompatibility
- Viscosity

CHALLENGES AND FUTURE PROSPECTS:

Drug delivery is extremely difficult in the eye due to its many and intricate physiological barriers, which is why different innovative delivery systems have been developed. Few of these novel drug delivery systems have been effectively marketed as nano-based systems, despite the large number of studies on their potential for treating various ocular conditions. [9] Due to the eye's numerous and complex physiological barriers, drug delivery is very challenging. For this reason, several creative delivery systems have been created. Despite the numerous studies on the potential of these innovative drug delivery systems to treat a variety of ocular conditions, few of them have been successfully marketed as nano-based systems. [2] There are still several obstacles to overcome in the development of innovative ocular drug delivery systems, despite some progress. These include the complexity of manufacturing procedures and technology, which restricts the clinical application of ocular drug delivery systems based on nanotechnology. [5] Future studies should also look into designing safer nanoformulations for drug delivery to the anterior eye segment that can deliver biologics (such as genes and peptides) as well as small molecules. These formulations should be highly stable, less toxic, and efficiently deliver the drug with improved pharmacokinetic and pharmacodynamic properties. [9] More work should be done in the future to create innovative non-invasive ODDS that can pass through ocular barriers, extend the duration of drug release, and maintain therapeutic concentration at the lesion sites. However, it is important to optimize the nanocarriers' size, zeta potential, refractive index, safety, stability, pH, surface tension, and osmotic pressure. [5] Future developments in a conventional nanoscale clinical drug delivery system must focus on the disease's diverse manifestations, including its etiology and pathogenesis. [2] In conclusion, there is no denying the benefits of new drug delivery techniques for ocular applications, and clinical practice will soon employ these advanced nanocarriers more frequently. [5]

REFERENCES:

1) An article by Arley Gomez, Marcela Gomez, and others, "Application of Nanotechnology in ophthalmology: Where are we?" from ResearchGate-2022 publication.

2) An article by Mehrdad Afarid, Shirin Mahmoodi, and Roghayyeh Baghban, on "Recent Achievements in Nano-based Technologies for Ocular Diseases Diagnosis and Treatment", from Journal of Nanobiotechnology (Article no. 361, Aug.2022) of the website springer nature.

3) An article by Li-Ching Liu, Yi-Hao Chen, and Da-Wen Lu, on "Overview of Recent Advances in Nano-based ocular Drug Delivery", from International Journal of Molecular Sciences-2023.

4) An article by Yuhua Weng, Juan Liu, Shubin Jin, and others, on "Nanaotechnology-based strategies for the treatment of ocular diseases", from the website ScienceDirect published in 2016.

5) An article by Shiding Li, Liangbo Chen, and Yao Fu, on "Nanotechnology-based ocular drug delivery systems: recent advances and prospects", from National Library of Medicine of Journal of Nanobiotechnology July edition- 2023.

6) An article by Colin E. Willoughby, Diego Ponzin, and others, on "Anatomy and physiology of the human eye", from Clinical and Experimental Ophthalmology 2010 on the website of an online library. Wiley.

7) An article by Isabella V. Wagner and others on "Updates on diagnosis and management of Glaucoma" from the National Library of Medicines website Pubmed Central.

8) An article by Martina Kropp on “Diabetic Retinopathy as the leading cause of blindness and early predictor of cascading complications- risks and mitigation”, from EPMA Journal edition Jan-2023.

9) An article by Adaeze Linda Onugwu and others, on "Nanotechnology-based drug delivery systems for the treatment of anterior segment eye diseases”, from the Journal of Controlled Release of website ScienceDirect.

10) A diagram of the structure of cubosomes from an article by Dhadwal Avantika and others on "Cubosomes: A Novel Carrier for Transdermal Drug Delivery" from ResearchGate.