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Nanoparticles as therapeutic agent for ophthalmic biomedical applications

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Abstract

Nanoparticles are very ultrafine particles, with potential applications in biomedical sciences. The use of nanoparticles in ophthalmology is new approach nowadays. The vital nanoparticles possibilities for the ophthalmology are AuNPs and AgNPs. In this review, issues will be deliberated about the application of nanoparticles which includes laser-heated nanoparticles for ophthalmology, and ophthalmic drug delivery. One approach is using gold nanoparticles, as they have several properties and applications in diagnosis and therapy tools. In the case of a healthy eye, the vitreous humor is made up of a large network of collagen and the polysaccharide (glycosaminoglycans) hyaluronic acid etc. But during some disease cases like an increase in age, diabetes, and myopia, the number and size of these protein clumps may change inside the vitreous. In such cases, these may disrupt the normal vision of the eye. The clumped collagen fiber can be removed by using nanoparticles. These nanoparticles will remain immobile at the position in the vitreous humor, where they are injected. When coated with a layer of hyaluronic acid, the nanoparticles allow them to travel and cluster on collagen bundles. Using nanoparticles, a specific medication can be administrated to a specific area of the eye, resulting into potential therapeutics in ophthalmology.

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Introduction

A nanoparticle is a very small particle whose size ranges between nearly 1 to 100 nm. This term is occasionally applied for bigger particles nearly up to 500 nm, or fibers which are less than 100 nm in only two directions. Nanoparticles are not visible by the human naked eye, and they can show various physical and chemical properties to their larger material equivalents. Nanoparticles (NPs) and nanocarriers, nanosystems are gaining recognition as a highly promising medicinal approach to treating ocular illnesses such as AMD, diabetic retinopathy, and glaucoma [1-3]. Metallic NPs such as Au, Fe, Ag, Pt, Pd, and Cu, their alloys, and oxides are synthesized in a green manner. The catalytic actions of various nanoparticles have been shown in numerous kinds of literature relating to the degradation of organic substances, including insecticides, phenolic compounds, and dye. They are employed in catalytic procedures related to environmental remediation, including cleansing polluted water. Also, Colorimetric findings of hazardous metal ions and theragnostic (therapeutic and diagnostic) appliances have both employed AuNPs as molecular sensors [4].

It has been discovered that visual acuity impairments impact over 285 million individuals globally, and various measures have been taken to safeguard the patient. When AuNPs are functionalized with molecules on their surface, they display a range of optical and biological features related to composition, thickness, organization, and conformation, all of which define their attributes [5]. Nanotechnology faces different challenges including AuNP aggregation in the circulation [6]. It is found that healthy and malignant cell lines do not demonstrate any harmful effects when the concentration is lower (20 g/mL) and the size is approximately 20 nm and their usage has enabled researchers to investigate the interactions between different NPs and cells. Then, nanotechnology is used to learn about cellular processes [7], antimicrobial properties [8], and an antioxidant defense response [9]. Further Different functionalized AuNPs can be employed as a drug, gene, or protein transporter, as well as in biomedical applications [10]. Furthermore, AuNP ligands such as polymers and proteins provide a chemical environment that aids the nanoparticle's internalization into the cytoplasm, nucleus, or over the membrane [10].

Currently available treatments

Eye drops: Nowadays, ocular drops are the most used medication delivery method, because it is effectively acceptable by the patient as well as for their economically important aspect. Drugs that are readily liquefied drips are adsorbed in the eyes in one or more ways. The corneal pathway, which comprises the cornea and aqueous humor, is the most common way. The intraocular and conjunctiva routes are both available which include sclera, conjunctiva, retina, choroid, and vitreous humor. Because of the corneal barrier and several pre-corneal variables, only around 5% of all medications delivered have a chance to enter the aqueous humor [11]. Therefore, the negative effect of eye drops is that they must be given regularly to keep therapeutic medication concentrations stable. Most eye drops are beneficial in curing illnesses of the cornea, iris illnesses, and glaucoma. Yet, eye drops are not very effective in curing certain diseases such as posterior eye disorders-intraocular malignancies, and retina illnesses, even while taking regular doses [12]. The blood-retinal barrier impedes the drug's translocation from the bloodstream to the retina. The ocular barrier is composed of thin connections between retinal capillary endothelial cells and Retinal Pigment Epithelium (RPE) [13].

Topical injection: Intravitreal injection is the most widely utilized among the numerous topical injections. Generally, a solution can be injected directly into the vitreous cavity of the eye with no irritation [14]. Intravitreal injections can help treat a variety of posterior eye problems by acting as an effective route of delivery. The vitreous, on the other hand, has a variety of drug distribution patterns due to its gel-like nature. The dispersion of the medicine in the vitreous humor region of the eye is strongly influenced by the molecular weights of the drug and the various pathophysiological circumstances [15]. It has been proven that microscopic molecules disperse fast in the vitreous body, while straight molecules having a molecular weight farther than 40 kDa or globular molecules with a molecular weight of more than 70 kDa can survive in the vitreous body for prolonged periods. Hyaluronan (glycosaminoglycan) is one of the most significant conformations in the vitreous humor of the human eye. It tends to interact with the positively charged cationic nanoparticles through the electrostatic interaction, causing the build-up of nanoparticles as well as lowering drug delivery effectiveness. Intravitreal injections are an invasive procedure that must pierce all three layers within the eye and can result in several complications, including iritis, retinal separation uveitis, cataract, endophthalmitis, and hemorrhage internal part of the eye [16]. Ophthalmic formulation already available provides weak bioavailability as they have lacrimation tear dilution and conjunctival absorption, as they are not permeable for corneal epithelium, also cause irritation of eyes, redness in the eyes, and visual impairments [13]. So, to overcome this problem nanotechnology came to light.

Types of nanoparticles for ocular delivery

Nanotechnology improves the bioavailability, solubility, and retention time of a drug so this increases the benefits from conventional ophthalmic formulations. Nanosystems used in ocular drug delivery are nano micelles, nanoparticles, liposomes, and nanocrystals. Nanoparticles can be classified into two categories: nanospheres and nanocapsules. Nanospheres are classified as matrix systems wherein medication is equally distributed throughout the matrix or adsorbed on the surface. They range in size from 100 to 1000 nm and have a compact nucleus surrounded by a high-density polymer. In vesicular systems known as nanocapsules, the interior of the carrier may be different from the exterior polymeric sheath. Typically, a medication is dissolved within the core of a particle, however, it can also be adsorbed onto the particle's nucleus [13]. Nanoparticles can be made in various shapes and sizes depending upon their practical implementation in different progress in the field of ophthalmology. Materials used to make NPs include organic biopolymers as well as inorganic, metallic, and semiconductor materials. Polyacrylates, poly alkyl cyanoacrylates, and polycaprolactam are some of the most used biomaterials. NPs may also be created in a variety of charges, shapes, and other physicochemical properties. The physicochemical features of NPs are not just useful in terms of the type of medicine that can be loaded. Nanoparticles influence cellular uptake and intracellular transportation as well. Furthermore, additional qualities, such as interaction with plasma protons, are dependent on the physicochemical property. Nanoparticles enhance the contact time of drugs with ocular tissue and enhance bioavailability. Nanoparticles have a small size and achieve sustained release without irritation so no need for frequent drug introduction [13].

First-generation nanoparticles: The first generation of nanoparticles was made up of polymerized matrices called nanoparticles and nanocapsules and stained release in the precorneal area was achieved. The first controlled release formulation was developed by Smith Kline and French in 1952. They release drugs through many methods including dissolution, diffusion, osmosis, and ion exchange (Figure 1) [17,13].

Second-generation nanoparticles: This is based on zero-order release kinetics and is better than FGN because it maintains the drug concentration in the blood. SGN was nearly like nanocapsules, but with augmented hydrophilicity (more water soluble) coupled with a covering polymer. After extensive studies, it came out that zero-order release doesn't maintain a sustainable release of drugs in the blood (Figure 1) [17,13].

Third-generation nanoparticles: The surface structure of third-generation NPs is functionalized through the adhesion of lectin or antibodies, among other moieties that can be targeted. Positively charged nanoparticles penetrate the cell membrane (Figure 1) [17,13].

The bioactive molecule loaded with nanoparticles can trans-

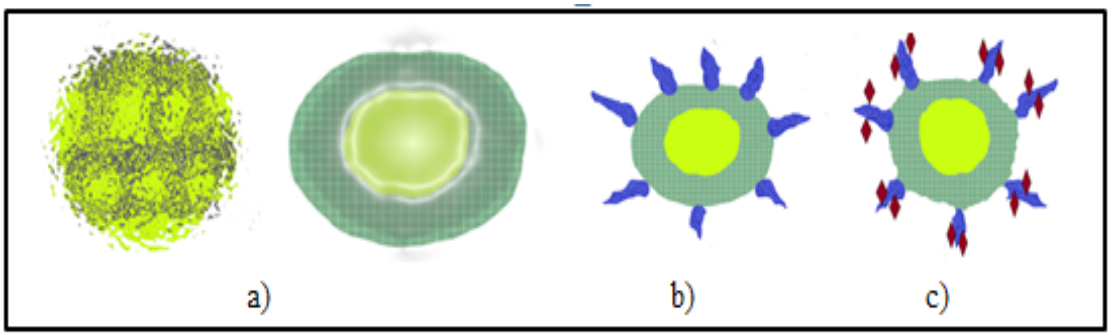

Figure 1: Type of nanoparticles in Ocular delivery a) 1st generation NPs b) 2nd generation NPs c) 3rd generation NPs.

Table 1: Nanosystem for treating and diagnosis of ocular diseases [15].

Formulation	Material type	Payload size (nm)	Size (nm)	Functions	Clinical stage
Nano wafer	Polymer	Axitinib	500	In smaller dosages as a commercial eye drop	Preclinical
Nano particle	Polymer	Flurbiprofen, Dexamethasone sodiumphosphate	200-300 100-500	Improved anti-inflammation impact in animal model after topical treatment of the formulation	Preclinical
	Chitosan	Gene	200	Higher efficiency	Preclinical
Hydrogel (virgan)	Polymer	Ganciclovir	-	For Herpes simplex virus infection treatment with a topical medication	In market
Nanosuspension	Polymer	Diclofenac	105	Increased penetration and retention in ocular tissues.	Preclinical
Hydrogel	Polymer	Diclofenac	-	The micelle supramolecular hydrogel enhances medication bioavailability by extending the retention duration on the corneal surface	Preclinical

verse epithelial and cell membranes via employing distinct internalisation routes. The physical and chemical features of nanocarriers are now known to determine their internalization pathway. Internalization of nanoparticles can be done by diverse pathways like clathrin, clathrin-mediated endocytosis, caveolin-mediated endocytosis, caveolin-independent endocytosis, etc. They target all mammalian cells and their vesicle size varies from 60 nm to 10 µm, and is degraded by endosomal and lysosomal route [18]. RPE cells (retinal pigment epithelial cells) are critical for human eyesight. RPE is important not just for maintaining the blood-retina barrier but also for the pathophysiology of several retinal diseases [19]. CD44 (a membrane receptor) is overexpressed on the RPE cell surface, and consequently, it can be utilized as a target for treatment. Drugs coated with Hyaluronic Acid (HA) are capable of being taken up by RPE cells by the receptor (CD44) mediated endocytosis mechanism and due to this high drug delivery and expression efficiency could achieved [20].

Types of nanosystems for ophthalmic issues

The process of nanotechnology appears to present new estimations in the administration of ophthalmic ailments, confirming low-down eye irritation and enlightening drug bioavailability or refining ophthalmic tissue compatibility [18]. Innumerable nanosystems are formed to carry their cargo into both the frontal and subsequent latter part of the eye. These nanosystems are primarily fabricated by using both natural and synthetic polymeric raw materials. A wide range of colloidal systems including liposomes, micelles, niosomes, in situ hydrogels, and dendrimers are available (Table 1,4). Additional models, having implants, nanoparticles, and contact lenses with nanoparticles, along with other delivery are also operated to carry the medication to the interior region of the eye using suitable paths. Several ways are available for drug delivery into the eye for ocular anterior diseases including nano wafer, hydrogel, nanosuspension, etc. [21]. Among them nano wafer is more efficient compared to the eye drop and drug loaded nano wafer is non-toxic and could treat corneal neovascularization [15].

Role of nanotechnology in opthalmology

Clearance of floaters in the eye using nanotechnology: Eye floaters can be of various sizes and shapes. Some people perceive little specks or dots, while others detect a thread or web in their eye floater. Others view them as transparent little bubbles. Most human eyes are a mix of forms and sizes. When staring at a blue sky or a blank wall, eye floaters are most noticeable. They can change their position when the eye moves, often with a delayed response [22]. When a person notices a floater in the eye, at that time he/she believes that they can visualize a floating object moving within the eye. But they are formed when a solid mass casts a shadow on the retina of the eye, and they are appropriately viewed as shadows. The vitreous humor of our eye is a very delicate and transparent hydrogel. This is a substance found between the lens and the retina. It takes up almost 80% of the eye's volume. It is made up of an extracellular matrix and is found between the retina and the lens. One of the biggest portions of the eyeball is made up of 98 to 99 percent water with just 0.1 percent macromolecules, mostly glycosaminoglycans like hyaluronan and collagen fibers [23]. Collagens are the most important macromolecules, forming a delicate network of heterotypic fibrils (types II, V/XI, and IX) and seem to keep the gel structure [22]. The vitreous contains collagens of many kinds, including II, V, and X. The vitreous humor works as a mechanical regulator for the eye, acting as

an absorbent medium and safeguarding the lens and retina due to its elastic qualities. The vitreous humor of the eye liquefies (softens) as it ages, resulting in a diminished ability to function as a shock absorber. This process leads to various issues, such as retinal detachment and vitreous hemorrhage. Vitreous floaters are produced due to the aggregation of minuscule collagen fibers in the vitreous, resulting in the formation of shadows on the retina [22]. It appears as floaters to the patient. Posterior Vitreous Detachment (PVD) is the primary cause of vitreous floaters in the field of ophthalmology. It causes detachment of the posterior hyaloid face from the retina. Often this condition is not visually threatening [24]. Those patients who show signs and symptoms of vitreous floaters should undergo evaluation by an ophthalmologist. A sudden surge in floaters, characterised by little black spots and lines that drift across one's field of vision, is a typical indication of vitreous humour detachment. Floaters are caused by the detachment of the vitreous humour, which leads to the formation of new shadows on the retina due to the presence of collagen bundles. Distinguishing between the presence and absence of ocular floaters is a straightforward task. We can easily discriminate between the eye floaters and the eye without floaters [25]. The difference between them is described in following Figure 2.

The treatment for vitreous floaters can be done by surgery to remove the vitreous portion of the eye. An ophthalmologist can remove the vitreous through a small incision (vitrectomy) followed by replacing it with a solution that can help our eye maintain its proper shape. However, the drawback of surgery may not remove all the floaters of the vitreous, and new floaters can be produced after surgery so the destruction of all the collagen clumps can be done by using gold nanoparticles followed by a laser-heated process.

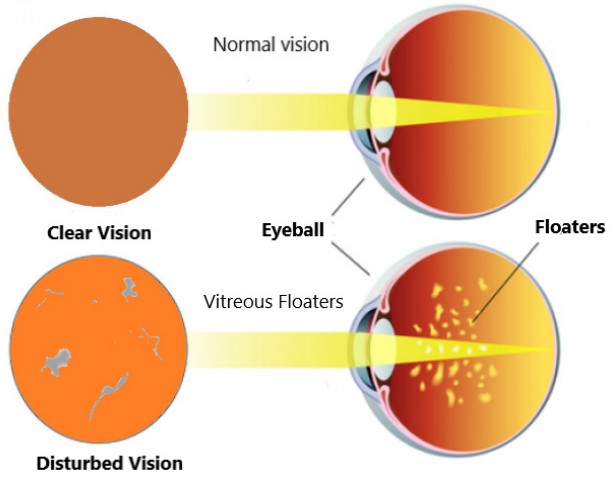

Figure 2: Difference between healthy eyeball and Floater eyeball.

Laser-heated nanoparticles: The human eye is discovered to have a nearly spherical complicated structure made up of multiple separate tissues. There are three levels to the eye's tear film (the mucus layer, the oily lipid layer, and the aqueous layer). Its pH is almost 7.4 on average. The cornea, which serves as a barrier for different topical medication absorption, the retina, which serves as a barrier to macromolecules, and the sclera, which serves as a barrier for macromolecule diffusion, are all present in the eye [23,26]. The most common neurodegenerative pathology in the eye occurs at the retinal point, it can damage either the outer retina (as seen in age-related macular degeneration) or the inner retina (as observed in glaucoma). Floaters can be produced due to clumping of collagen which is an age-related pathology. It is found that only 38% of patient's laser treatment is useful to eliminate their symptoms, and the procedure followed carries risks of damage to the lens or retina. The gold nanoparticle as a better solution was first found by Stefaan C. De Smedt of Ghent University. The eye is split into three portions in anatomical terms: the anterior chamber, the vitreous chamber, and the posterior chamber [23]. At the rear of the eyeball is the vitreous chamber. It is the biggest chamber of the eye, accounting for around 80% of the eye's volume. Vitreous humor is a fluid-like gel that is made up of 98-99 percent water and contains trace quantities of hyaluronic acid, glucose, anions, cations, and collagen. In a normal person, the collagen fibers are distributed throughout the vitreous humor. The main role of this collagen is they are essential to maintain transparency and to provide the biomechanical prerequisites necessary to maintain the shape and provide strength. Through aging, the eyeball of the person (88-year-old) shows many collagen strands that turn out to be floaters and disrupt vision. Other than that, various reasons like myopia, aging, and diabetes can all increase the number and size of these protein clumps inside the eyeball, which disrupt normal vision. All this collagen clumping can be removed by the use of the laser-heated method, but it is not suggested as it can damage the other regions of the eye like the retina [26,27]. At the time of experiments with human eye fluid samples, it was found that gold nanoparticles heated with a low-energy laser can assist in diminishing these problematic clumps of collagen bundles [26]. The technique might lead to a clinical therapy that is excellent for those currently in use.

Healthy eyeballs are filled with a transparent, gel-like substance known as the vitreous humor that is largely a bundle of collagen and the polysaccharide (glycosaminoglycans) called hyaluronic acid. The collagen has a tendency to form insoluble globules that float within the gel, scattering light and potentially disrupting the vision process. These floaters can be removed and cleared by vitrectomy, which is an essential and irreversible process and replaces the vitreous fluid with a saline solution [28]. In another way, we can flash a high-energy laser beam into the eye to break down the clumps into smaller fragments. It was found through various studies that less than half (38%) of patients informed that laser treatment helps to remove their symptoms, so gold nanoparticles provide a better solution [26]. These gold nanoparticles tend to remain stationary in the vitreous humor at the site of injection, as they are not capable of moving freely in the vitreous humor. This is because of the occurrence of hyaluronic acid a constituent in the vitreous humor. A film of hyaluronic acid can be applied to the nanoparticles to overcome this problem (the same molecule is present in the eyeball). It allows them to travel and cluster at the region of collagen bundles. This clustering of coated nanoparticles may be due to the repelling by likewise charged hyaluronic acid in the vitreous humour and permitting them to move towards the collagen bundles where hyaluronic acid is absent. But our problem is not solved only by targeting the nanoparticles in the vitreous humour, when laser light is given to the eyeball it can be easily absorbed by the coated nanoparticle which is surrounded by collagen fibre. So, the laser beam only selectively destroys the region where collagen clumping occurs, without hampering other parts of the eye like the retina and nerve fiber [29].

Nanoparticles in oxidative stress: Reactive oxygen species (ROS), which are created within cells or in the environment, cause Oxidative Stress (OS) in living organisms. The eye is the human body's most noticeable and delicate organ [30]. The anterior segment, lens, cornea, and trabecular network are all

part of this eye tissue. Reactive oxygen species may be generated due to the typical aerobic cellular metabolism (ETC of the mitochondrial inner membrane) or due to the occurrence of UV radiation. Our cells have a variety of antioxidant defense mechanisms that are critical for removing or neutralizing ROS. Due to the oxidative stress, there will be a mismatch in between the generation of ROS and the antioxidant defense mechanism of the cell. It causes injury to proteins and DNA, and that causes harmful effects, which causes the possibility of apoptosis (cell death). Neuronal cells may be harmed by oxidative stress. As a result, neurological disorders such as Alzheimer's disease, Parkinson's disease, glaucoma, and others arise. UV radiation, which causes ophthalmic tissue diseases such as glaucoma. As a result, the eye has a proclivity for producing good antioxidant defenses that may work on several levels [31,32]. The antioxidants are most probably used as therapeutic for various kinds of neurogenerative diseases as they could scavenge ROS. Our cell uses both enzymatic and non-enzymatic antioxidants in the antioxidant defense system. Non-enzymatic antioxidants work by decreasing Reactive Oxygen Species (ROS) and creating more stable molecules with lower toxicity. These compounds include various vitamins like vitamin A, vitamin E, and ascorbic acid. The main defect in most of these antioxidants is that they do not efficiently cross the membrane of the layers of the eye. So, at that time the role of nanoparticles takes an important place because this problem can be solved by coating the targeted material with gold nanoparticles [10,33].

Invitro experiment-Nanoparticles in oxidative stress: The distribution of different antioxidants to the eye's target structural area is a complicated procedure. Entrapment of the active chemical in a nanosystem is an effective treatment for a variety of eye illnesses in the previous decade. It aids superior ocular tolerance by increasing ophthalmic bioavailability. Nano systems, such as liposomes, micelle noisome, dendrimers, and nanoparticles, have a propensity to offer a good pool for drug delivery [15].

Hyaluronic acid's effect on gold nanoparticles: The chemical composition of hyaluronic acid includes an anionic, non-sulfated glycosaminoglycan that does not bind to a protein core. It was originally extracted and identified from a bull's eye vitreous body. It is mainly distributed broadly throughout the connective, epithelial, and eyeball. Because of its biological safety and water retention qualities, HAs have a variety of ophthalmic uses, including intravitreal injection, dry eye therapy, and contact lens information. As the HAs are made by both acidic sugar and amino sugar, the acidic sugar of the hyaluronic acid D-Glucuronic acid and the amino sugar N-acetyl D-glucosamine. It is found that the negative charge of the hyaluronic acid plays a crucial in the delivery of gold nanoparticles into the vitreous humor of the eye [29]. HA has a bioactive straight polysaccharide chain that has an antifouling function and inhibits the adsorption of various proteins on the surfaces of various biomaterials. Its hydrophilic and polyanionic properties give it this attribute. It is found that the gold nanoparticles tend to remain immobile in the vitreous humor when it is injected at a site but coating them with a layer of hyaluronic acid which is a similar molecule present in the eyeball allows the nanoparticles to move and cluster on collagen bundle (Figure 3) [34]. Solubility of the gold nanoparticles inside the vitreous humor of the eye can be increased by surface functionalization and this method also enriches the passing of AuNPs across the different walls of the eye. The hyaluronic acid augments the distribution of AuNPs via the retina [28].

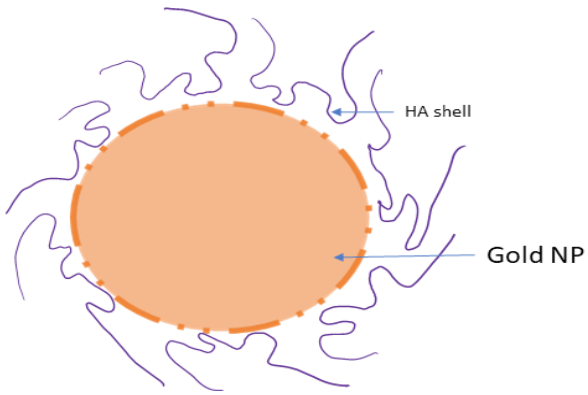

Figure 3: Au NPs coated with Hyaluronic acid.

In retinal models, gold nanoparticles have a variety of protective and anti-angiogenic properties. Hyaluronic acid also augments the strength of AuNPs in different mediums and pHs of the eye. This process can be done by using a small molecular weight of Hyaluronic Acid (HA) to enhance the flexibility of the NPs and target them to HA receptors. The HA receptors are articulated in distinct cells of the eye. This report found that a combination of Au and hyaluronic acid enhances the steadiness of the whole carrier. It also boosted their delivery through ophthalmic tissues and different hurdles to deliver to the retina. The experimental process through various studies showed the protective and antiangiogenic impact of AuNPs as inhibitors of AGEs-mediated-retinal pigment epithelium cell death and neovascularization. It was found that coupling with hyaluronic acid augments AuNP steadiness and its distribution due to the existence of a CD44 receptor interaction [35]. The ability of HA-AuNPs to disperse across the vitreous humor and their attraction for the deeper retinal layers ex vivo indicates that they are a potential delivery strategy for treating ophthalmic neovascularization and associated illnesses. In the assessment of the coated gold nanoparticles with HA in vitro, the first step is to heat a collagen solution, which causes the protein to clump and form fibers that mimic those that occur in the eye. Then the nanoparticles can be added to the solution and subjected the mixture to short pulses of low-intensity laser light [28]. The use of dark-field microscopy shows that the laser treatment tends to break the fibers into tiny pieces. If we compare it with larger nanoparticles, the 10 nm diameter gold nanoparticles scattered less light, which might less likely to affect vision. Due to this, less laser energy is required to heat up, so in this process, the surrounding of vitreous humor can be protected. Only 0.1 percent of the energy used in traditional laser treatment was used in this procedure. It is found that the nanoparticle-laser treatment had no impact on the sustainability of cultured human Muller cells, a type of cell found close to the retina of the eye. It will be necessary to conduct tests on living beings to see if the eye can clean up the nanoparticles after treatment or whether the particles cause any difficulties if they linger in the eye [36].

Nanoparticles in drug delivery: Nanoparticles are very crucial in drug delivery systems in ophthalmology than the ancient method due to its target-specific and less toxic method. Below are some of the advantages and disadvantages of ocular delivery channels [37]. Intravenous injection, which is utilized for ocular medication delivery, is an example of a systemic administration approach, as the choroid plexus of the eye has a vascular structure; medicines can readily pass via blood vessels and enter the choroid. The admission of different medications from the choroid into the retina is regulated by the external blood-retinal

barrier of Retinal Pigment Epithelium (RPE) cells [11]. The tight junctions present in the RPE cells obstruct most medicines. Only a very few percent (1 percent - 2 percent) of the medications that are administered can reach the retina and vitreous humor of the eye. Hence, a very strong challenge is to use the systemic administration procedure to transport different medications into the deep inner part of the eye [37]. There are different approaches for the delivery of drugs to the eye. However, these methods are not so effective, and they have side effects. The primary issue for these drawbacks is biopharmaceutical issues correlated to the new attribute of the eye that inhibits drug bioavailability. Several sorts of barriers (Figure 4) that block active absorption distinguish the eye from the remainder of the body. These obstacles include the following:

(1) Desmosomes and numerous tight connections around in the corneal epithelium,

(2) Blood vessels in the iris

(3) Mucous and aqueous layer of the tear film that protects the anterior aspect of the eye

(4) The blood-aqueous barrier is a non-pigmented layer of the ciliary epithelium that prevents molecules from passing from the blood to the inner region of the eye.

(5) The blood-retina barrier's inner and outer layers, as well as the endothelium of the retinal arteries, respectively, control the transit of molecules from the bloodstream to the retinal pigment epithelium and the transit of many medications via the vitreous humor [38].

Drug delivery by using the nanoparticle is one of the best ways for the eye. Among all these gold nanoparticles takes an important role. Among the several nanoparticulate-based drug delivery techniques, is nontoxic and extremely selective for the target [39]. Non-degradable polymers and biodegradable polymers, which are either water-soluble or water-insoluble, are used to create a variety of polymeric compositions [40]. The following are some examples of distinct nanosystems with various compositions: Liposomes, Niosomes (Table 2) (Figure 5), Nanosuspensions, Emulsions, Dendrimers, Contact lenses with nanoparticles, Carbon-based fullerenes and Nanotubes, Quantum dots and Nanogels (Table 3) [41].

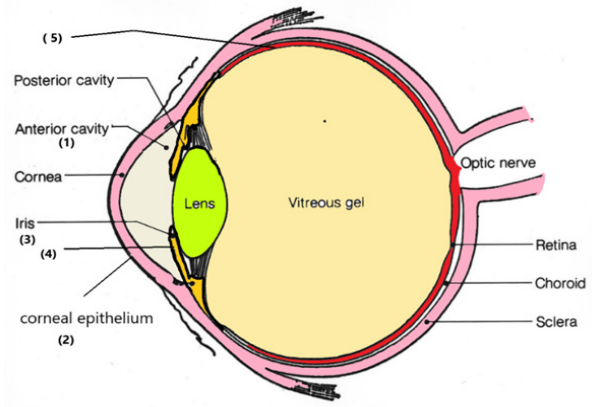

Figure 4: Different barriers to drugs in the human eye.

Conclusion

It has been found that Nanotechnology has a prevailing and efficient way of dealing with and verdicting ophthalmic diseases by making nanosystems. This review concentrated on advancements in various nanosystem models and expansion for a variety of ophthalmic diseases. Numerous nanosystems with various loads (cargos) have demonstrated enormous promise and efficacy in ocular medication delivery *in vitro* and in *vivo*. Both green synthesizers and synthetic nanoparticles are applicable in nanotechnology. Although nanoparticles produced by green synthesis are non-toxic, synthetic NPs cannot be excluded due to their specificity and wide range of applications. The main concept for green synthesis is the use of natural compounds. The human eye is a very sensitive organ of our body and complex in structure. It is a challenging process for the supply of medications to the eye. HAs-coated gold NPs are very effective in the removal of floaters from the vitreous humor of the eye, which are produced due to aging and affect vision. Nanoparticles are very effective in drug delivery due to some of their features like small size, specificity, and non-toxic. This study reports that the NPs efficiently reduce the oxidative stress that occurs in the eye.

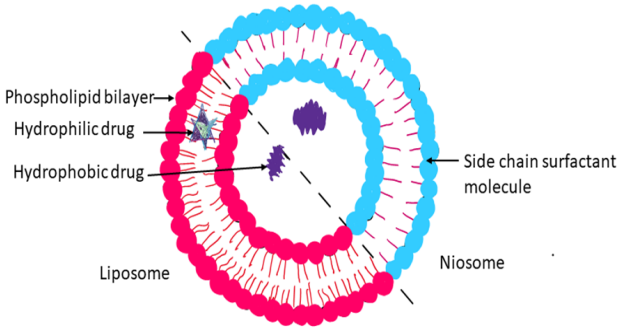

Figure 5: Structural representation of niosome and liposome.

Table 2: The difference between the liposome and niosome [42,43].

Niosomes	Liposomes
Vesicles are made up of single chain non-ionic surfactants	Vesicle are made up of phospholipid bilayer with hydrophilic head and lipophilic tail
Less toxic and more economical	As compared to niosomes more toxic and costly
Non-ionic surfactants are highly stable	Phospholipids are unstable
No special storage conditions are needed	Special storage conditions are needed
Size ranges from 10 to 100 nm	Size ranges from 10 to 3000 nm
No special methods needed for their formulation	Special methods are required for phospholipid handling and purification

Future prospective

A lot of research on ocular problem treatments employing nanoparticles has been done, several works have focused on in *vitro* analysis, and only a few work done on in vivo. More efforts in this sector should be made in the near future. Even though the rabbit is an often-utilized animal due to its size being approximately identical to that of a human eye, the difficulty is that rabbit eyes have a higher level of surface sensitivity and mucus production, as well as less flickering frequency and a lower number of tear production. Additional study is needed to increase the understanding of the intricacies of nanoparticles, which will make the construction of a good medication delivery system and its use easier.

Table 3: Various nanostructures used in ocular drug delivery.

Nanosystem	Composition	Potential application in the eye	Reference
Nanoparticles	Polymers, metals, lipids, and phospholipids, both natural and manufactured	Removal of floaters	Razavi et al. 2022 [44]
Liposomes	PLP	For drug delivery	Ashraf et al. 2018 [45]
Niosomes	Non-ionic surfactants; Curcumin in proniosomal gel	More potent due to non-ionic surfactant, sustained release over 24h	Aboali et al. 2020 [46]
Emulsions	Surfactant-containing oil-in-water and water-in-oil mixture	Increase natural ability to produce tears	Natesan et al. 2020 [47]
Nanosuspensions	Inert polymer resins	It shows enhanced solubility, corneal adhesion	Sahoo et al. 2008 [48]
Dendrimers	Synthetic polymers	Ocular delivery	Diebold & Calonge, 2010 [18]
Nanoparticle-loaded contact lenses	Various hydrogel lenses with nanoparticulate-based coatings	Preserve rate of drug delivery	Diebold & Calonge, 2010 [18]
Nanotubes and fullerenes	Nanomaterials made of carbon	Not tested yes	Diebold & Calonge, 2010 [18]
Quantum dot semiconductor	Semiconductor materials that have been encased in other materials	Potential effect	Diebold & Calonge, 2010 [18].
Nanogel	Polyvinylpyrrolidoine/polyacrylic acid	A sustained release profile for 24h, formulation increases the stability and bioavailability	Abd El-Rehim et al. 2013 [49]

Table 4: Nanoparticles formulated with different materials and their role in ophthalmology.

Formulation	Material type	Loaded with	Functions	References
Nanoparticles	Polymer	Polylactides; PLAS	Increase intra and transdermal penetration of drugs	Bourges et al. 2003 [50]
Nanoparticles	Polysaccharides	Chitosan	Better drug availability via enhancing pre-corneal residence time	Zhu et al. 2012 [51]
Nanoparticles	Mucoadhesive polymer	Thiolated chitosan	Increase mucoadhesive properties	Zhu et al. 2012 [51]
Nanoparticles	Polysaccharide	Sodium alginate	Utilized alone or in combination with various ocular delivery system	Zhu et al. 2012 [51]
Nanoparticles	Polymer	Amiated gelatin	Enhance transepithelial absorption of peptide drugs	Nagarwal et al. 2009 [52]
Nanoparticles	Polymer	Poly-l- arginine	Penetration enhancer for ocular drug delivery	Nagarwal et al. 2009 [52]
Nanoparticles	Polymer	Poly-ε-caprolectone	Better ocular penetration, as well as decrease in drugs systemic adverse effects	Nagarwal et al. 2009 [52]
Nanoparticles	Polymer	Polylactic acid	Potential ophthalmic drug delivery system for treating ocular viral infection.	Nagarwal et al. 2009 [52]
Nanoparticles	Solid lipid nanoparticles	Precirol ATO 5® Compritol® 888ATO, Stearic acid	Increased corneal penetration, no cytotoxicity effect on corneal tissues. Increased bioavailability & dissolution rate	Gorantla et al. 2020 [53]
Nanoparticles	Gel nanoparticles	PLGA RG 503H, Poloxamer 188 (P188) and P407	Increased bioavailability by enhancing precorneal residence time and reached deeper layers of the aqueous humour	Gorantla et al. 2020 [53]

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