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REVIEW ARTICLE **OPEN ACCESS**

Advances in Ocular Drug Delivery System: Harnessing Synthetic Nanoparticles for Enhanced Therapeutic Efficacy

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ABSTRACT
Ocular drug delivery systems are intended to transport medicinal substances to different regions of the eye in order to treat disorders such as macular degeneration, uveitis, dry eye syndrome, glaucoma, and others. Eye drops and ointments are examples of traditional drug delivery techniques that frequently encounter difficulties such as low bioavailability, quick elimination by tears, restricted penetration, and systemic side effects. It increases targeted delivery, penetration, bioavailability, adverse effect reduction, and administration frequency. Biocompatibility and biodegradability are two important considerations for researchers when selecting a material for nanoparticles. Assessment of the safety and biocompatibility of nanoparticles is essential for the clinical application of these findings. By helping medications pass through ocular barriers such the blood-retinal barrier, cornea, and conjunctiva, nanoparticles can raise the bioavailability of pharmaceuticals in the eye. Increased stability: The stability that nanoparticles give to encapsulated medications keeps them from degrading and lengthens their shelf life.

Keywords
Ocular drug delivery; Synthetic nanoparticles; Polymeric nanoparticles; Lipid-based nanoparticles; Inorganic nanoparticles

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INTRODUCTION

The eye has an intricate physiology and is an extremely sensitive organ. It is made up of segments that are anterior and posterior. Generally speaking, visual impairment brought on by different diseases has a considerable impact on quality of life. Globally, cataracts are the leading cause of blindness. A cataract's side effects are responsible for between 40 and 60 percent of blindness worldwide [1]. One well-known optic neuropathy condition associated with increased intraocular pressure (IOP) is glaucoma. In the later stages, it results in lifelong blindness. Furthermore, aging, diabetes, and fungal infections are associated with visual impairment. Ocular illnesses include retinoblastoma, fungal keratitis, diabetic retinopathy (DR), and age-related macular degeneration (AMD). According to a recent study, there are roughly 196 million AMD sufferers, 92.6 million DR patients, and 76 million glaucoma sufferers [2]. Ocular formulations can be administered intraocularly (within the eye), periocularly (subtenon or juxtascleral), on the anterior surface of the eye (topical route), or in conjunction with ocular devices. There are four possible ocular dosage forms: liquid, semi-solid, solid, or mixed. Emulsions, suspensions, and drops are examples of liquid dosage. Over 95% of the marketed ocular products are eye drops. They have a brief residence period and are used to administer medication to the anterior portion of the eye. Although ocular suspensions and emulsions can transport hydrophobic medications, they may cause visual impairments. Semi-solid ointments and gels for the eyes may greatly extend residence length. Solid dose forms have the potential to be employed in the administration of water-sensitive pharmaceuticals (powder), zero order release models (insert), and therapeutic contact lenses (residence time) [3]. Various classes of occular dosage forms were given in Figure 1.

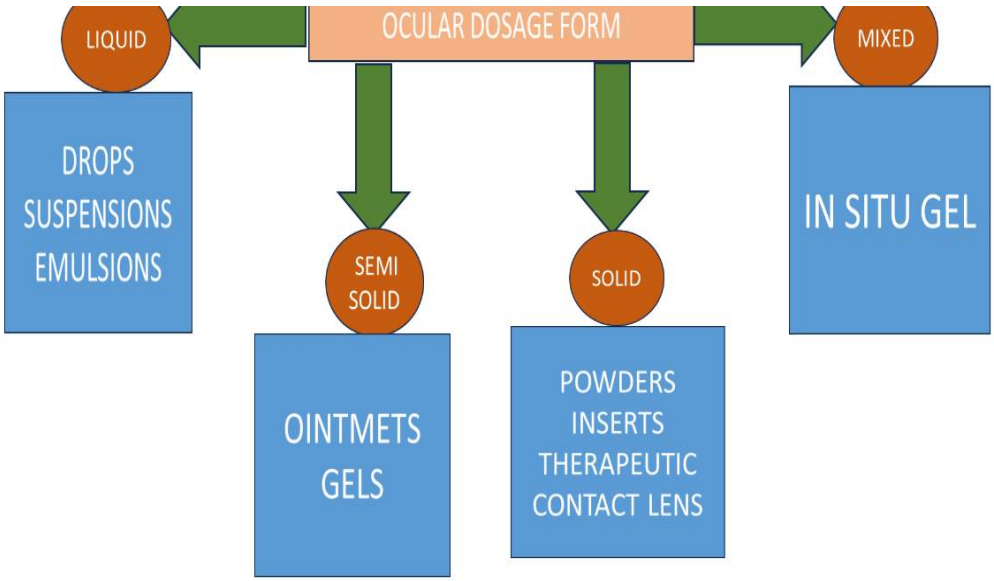

Figure 1: Classification of ocular dosage forms

Nanoparticles

Environmental, agricultural, food, biotechnology, medicinal, pharmaceutical, and other fields are only a few of the industries in which nanoparticles find extensive use. Examples include waste treatment, environmental monitoring [4], functional food additives, and antibacterial agents. The biotechnological and applied microbiological uses of nanoparticles (NPs) have grown as a result of their cutting-edge characteristics, which include nature, biocompatibility, anti-inflammatory and antibacterial activity, efficient drug administration, bioactivity, bioavailability, tumour targeting, and bio-absorption. A nanoparticle, or ultrafine particle, is a particle of matter with a dimension of one to one hundred nanometers (nm). Due to their minuscule size and massive surface area, nanoparticles often display unique size-dependent properties. When a particle gets close to or smaller than the de Broglie wavelength or the wavelength of light, its distinctive length scale is eliminated, destroying the periodic boundary conditions of the crystalline particle [5]. As a result, a great deal of the physical properties of nanoparticles are different from those of bulk materials, which opens up a variety of unique applications for them [6].

Benefits of utilizing nanoparticles in ocular drug delivery system

The benefits of employing nanoparticles as drug vehicles are because of two key characteristics: their tiny size and the use of biodegradable materials in the majority of cases. The effectiveness of most medication delivery methods is found to be largely reliant on particle size. Drug nanoparticles exhibit increased solubility and superior bioavailability which is a result of their small particle size and large surface area . Additionally, their ability to cross the blood brain barrier, entering pulmonary system, endothelium of tumors and absorption through tight junctions of skin endothelial cells, give them added value. The nano-range size of these particles, in general, allows for effective absorption by various cell types as well as selective drug accumulation in the target locations [7,8]. Nanoparticles also have the benefit of being more adequate for intravenous administration than conventional microparticles. The smallest body capillaries have a diameter of 5-6 m. To make sure that particles do not cause embolism, the size of particles dispersed in the circulation should be substantially less than 5 m [9]. Using both natural and synthetic biodegradable polymers for nanoparticle preparation give them the advantages of targeted drug delivery, improve bioavailability and achieve sustained release behaviour of medications from a single dose at the target site over a prolonged period of time; by adaptation of the system, endogenous enzymes can be prevented from destroying the drug. Furthermore, typical oral or injectable medicines now accessible for use are not necessarily provided in the most suitable formulation. As a result, goods containing proteins or nucleic acids will require more creative carrier systems (nanoparticles) to improve their efficacy and avoid any instability. Nanotechnology is the molecular-scale fabrication of various functioning systems. These systems have special physical, electrical, and optical characteristics that make them appealing in a variety of domains, ranging from materials science to biology. Nanomedicine is one of the most well-known nanotechnology research fields. It uses nanotechnology to develop highly targeted medicinal interventions for disease detection, prevention, and treatment. Over the last few decades, there has been a spike in nanomedicine research, which is currently being turned into commercialization activities around the world, culminating in the marketing of numerous products. Drug delivery systems now dominate nanomedicine, with revenues accounting for over 75% of total sales [10]. Nanoparticles have a diameter of

10–1000 nm. Entrapped, encapsulated, dissolved, or linked to the nanoparticle matrix is the active pharmaceutical ingredient (API) [11]. Nanoparticles can be made by altering the method of fabrication. Nanoparticles have been proven to be useful as drug delivery vehicles. Many uses for nanoparticulate drug delivery systems exist, including gene therapy, cancer therapy, AIDS therapy, and radiation. It can also be used to transport proteins, antibiotics, and vaccinations, as well as serve as vesicles to cross the blood–brain. The major aims of nanoparticle design as a delivery system are to control particle size, surface properties, and drug delivery and API release so as to ensure site-targeted drug activity at an appropriate therapeutic rate and dosing regimen. In this review, we will discuss the advantages of nanoparticles as drug delivery systems, different types of nano systems and their applications. We will also explain different methods used in the fabrication and characterization of nanoparticles. Examples of marketed nanoparticles products will be provided as well.

Nanoparticles (NPs)

Carbon – nanotubes

The discovery of carbon nanotubes occurred in 1991. These constructions are made of tubular carbon. These tubes, which range in length from 1 to 100 nm, are composed of cylinders formed of graphite sheets that are sealed at one or both ends by bucky balls. Two designs of nanotubes that have gained prominence recently are single-walled and multiwalled nanotubes. Common combinations also contain C60-fullerenes. They are characterized as hollow and cage-like structures and are available in a range of graphite cylinder forms (nanotubes and fullerenes). Their size, surface characteristics, and other important physical attributes make them appropriate for drug encapsulation. The diameter of the DNA helix is half that of SWNTs. However, depending on how many walls they have in their construction, MWNTs can have widths ranging from a few nanometers to tens of nanometers [12]. The most popular techniques for creating fullerenes and carbon nanotubes include chemical vapor deposition, combustion processes, and electric arc discharge. In order to make these structures reliable drug transporters, they are characterized by their strength and stability. Nanotubes enter cells by endocytosis or insertion across the cell membrane. Fullerene structures shown the ability to target specific tissues and mitochondria within cells. Furthermore, it was discovered that they exhibit antibacterial and antioxidant activities [13].

Quantum dots

The quantum dots (QDs) are tiny, semi-conducting structures that range in size from 2 to 10 nm. These nanocrystals, which contain an organic shell coated with zinc sulphide to enhance optical qualities, and an inorganic semi-conductor core are designed to glow when exposed to light. The inclusion of a cap improves QD solubility in aqueous buffers. The particle has a radius of two to ten nanometers. Numerous characteristics have been connected to long-term tracking of intracellular activity, bio-imaging in vitro, and real-time monitoring. Broad UV excitation, strong photo-stability, narrow emission, and amazing fluorescence are a few of these qualities [14]. the creation of non-viral carriers, DNA hybridization, cell labelling, gene therapy, immunoassays, biomolecule detection, and biological performance

Nanotubes

The bubble-shaped particles known as nanobubbles are created at the nanoscale at the liquid-lipophilic surface interface. They combine to create stable microbubbles at room temperature when heated to body temperature. They emerge in supersaturated liquids due to air gas trapping caused by gas nucleation at the hydrophobic surface. These nanoparticles come in four varieties: interfacial nanobubbles, plasmonic, bulk, and oscillating. These particles were successfully filled with cancer-fighting medications, which allowed them to target tumor tissues and boost the uptake of tumor cells under the effect of ultrasonic exposure. [15]

Paramagnetic nanoparticles

A magnetic field can influence tiny particles known as magnetic nanoparticles, which have a diameter of less than 100 nm. These particle materials are made of magnetic elements. These nanoparticles are categorized based on their sensitivity to magnetic fields. Paramagnetic nanoparticles have a greater magnetic sensitivity than conventional contrast forms. These nanoparticles are employed in therapeutic and diagnostic approaches. Targeting particular organs using magnetic nanoparticles works well for this purpose. [16]

Liposomes

Artificial particles called liposomes are made of amphiphilic phospholipids that self-assemble. They are made up of spherical, double-layered vesicles that surround an aqueous core domain, which can range in size from several micrometers to 50 nm, depending on the kind. The biodegradability and general biocompatibility of liposomes are two fascinating biological properties. Liposomes are the most often employed nanosystem for drug administration in clinical research. They can be used to decrease a drug's toxicity, systemic effects, and clearance. The transfer of siRNA, proteins, DNA, and cancer treatments is made possible by the advantageous pharmacokinetic characteristics of nanoscale modified liposomes. The

absence of customizable drug release patterns, rapid drug release, and low loading capacity of liposomes are among their disadvantages. Drugs are also discharged into the extracellular fluid because liposomes cannot enter cells. After oral or parenteral administration, surface modification can be employed to achieve stability and structural integrity against a hostile bio-environment [17]. To slow down the drug's rapid release, medications can be introduced to the liposomes' aqueous phase using an ammonium sulfate gradient. from liposomes. Little drug loss will occur during circulation as a result, and drug trapping will remain consistent. Drugs have also been delivered to particular sites using liposomes and antibodies [18].

Niosomes

A particular kind of molecular cluster known as a niosome is created when non-ionic surfactants self-assemble in an aqueous phase. Because of their distinct design, noisome can be used as a novel delivery system for both lipophilic and lipophobic drug. Niosomes are seen to be a viable alternative to liposomes because of their great stability, lack of toxicity, and composition of non-ionic surfactants. Noisome function similarly to liposomes in vivo, extending the drug's circulation and altering organ distribution and metabolic stability. niosome characteristics depend on the bilayer in addition to the method of synthesis. It has been demonstrated that intercalation of cholesterol in the bilayers causes a decrease in the entrapment volume during formulation, which in turn causes a drop in the entrapment efficiency. Current findings about the use of noisome in drug delivery mostly concern the entrapment of powerful medicines [19], anticancer, and antiviral agents [20].

Polymeric nanoparticles

Researchers are lured to biodegradable polymeric nanoparticles (PNPs) as a drug-delivery system because PNPs are mostly biodegradable and biocompatible [21,22]. PNPs are separated into matrix systems (nanospheres) and vesicular systems (Nano capsules). Researchers have recently investigated advanced modification of natural polymers, including synthetic polyesters. Chitosan is among the most well-known naturally occurring polymers. With artificial polymers, several polymers lessen hazardous problems. Natural PNPs were more efficient and effective than traditional distribution methods, which is why they won over. They do, however, have certain shortcomings, including low repeatability, issues with degradation, and possible antigenicity. The manufacturing process regulates the release behaviour of the encapsulated medication. PNPs have the ability to target specific sites within cells.

Table 1: Marketed products in nanoparticles

Nanomaterials	Drug	Brand name	Application	Function	Reference
Liposomes	Acyclovir	Zovirax	Topical	Prolong drug penetration	[23]
	Edaravone	Radicava	Topical	Decrease progression of dry AMD	[22]
Niosomes	Tacrolimus	Prograf	Topical	Increase pre corneal drug retention	[24]
	Doxycycline hyclate	Vibramycin	Topical	Prolong drug release rate	[25]
Solid – lipid NPs	Cyclosporine A	Neoral	Topical	Prolong drug release	[26]
	Tobramycin	Tobrex	Topical	Increased drug retention	[27]
Polymeric NPs	Amikacin	Amikin	Topical	Improved ocular penetration controlled release	[28]
Dendrimers	Acetazolamide	Diamox	Topical	Enhanced drug residence time	[29]
Dendrimers	Anti - VEGF	Avastin		Reduced CNV progression	[30]
Nano suspension	IBU Sodium salt	Advil	Topical	Increased penetration prolonged drug release	[31]
Nano suspension	Glucocorticoid	Prednisone		Prolonged drug absorption	[32]
Nano emulsion	Terbinafine Hydrochloride	Lamisil		Improved drug residence time increased bioavailability	[33]
Nano emulsion	Acyclovir	Zovirax		Increased corneal permeation	[34]

Nanomedicine for eye disease

The use of materials to create nanoparticles having at least one dimension between 1 and 100 nm is known as nanomedicine, which is the medical application of nanotechnology. Lipids, proteins, cyclic oligosaccharides, synthetic polymers, and inorganic chemicals like cerium oxide nanoparticles are the materials most frequently employed in nanomedicine. NPs are interesting in the field of ophthalmology because of their capacity to make hydrophobic drugs more soluble, to deliver sustained drug release with

less toxicity and more effectiveness, to extend the duration of drug retention and improve drug penetration through ocular barriers, and to effectively target drugs to particular tissues and cells. NPs can be administered topically, orally/systemically, subconjunctivally, subtenon, retrobulbarly, intracamerally, and intravenously (IVT).

Table 2: Description of the principal materials in nanomedicine for eye drug delivery

Nanoparticle	Characteristics	References
Nanospheres	Easily fabricated using biodegradable polymers to ensure long-term medication release	[35]
Nano micelles	Produced by the dispersion of amphiphilic molecules, which are made up of both hydrophilic and hydrophobic elements in a solution. Micelles form via means of self-assembly. They are suitable for controlled and prolonged drug delivery, have low cytotoxicity, and are relatively stable. It is possible to add hydrophobic medications to the micelle cores. Because of the inner core's high drug loading capacity, polymeric micelles are advantageous for targeted therapy and long-term drug administration. Some drugs are stimulus-sensitive, meaning they release when they are exposed to external stimuli like light or temperature or internal stimuli like pH.	[36]
Nano capsules	Medications and nucleic acids, including as DNA, microRNA, siRNA, and shRNA, that can be encapsulated in relatively large volumes	[35]
Liposomes	Tiny, spherical phospholipid-based amphipathic vesicles. Among their benefits are low toxicity, biocompatibility, biodegradability, and site-specific administration of hydrophilic and hydrophobic medications. Able to encapsulate medicines that are hydrophilic or hydrophobic	[36]

Because of their special physicochemical characteristics, which allow for targeted distribution to certain ocular tissues, sustained drug release, and efficient penetration of ocular barriers, nanoparticles are essential to ocular drug delivery systems. This is a thorough explanation of how nanoparticles are used to deliver drugs to the eyes. In summary, the unique properties of nanoparticles allow for efficient drug penetration, sustained release, targeted delivery, and protection of drug molecules, making them valuable platforms for the development of novel ocular therapies. These properties also offer promising solutions for overcoming the challenges associated with ocular drug delivery and improving therapeutic outcomes in various ocular diseases. In order to meet unmet medical needs in ophthalmology, further research and innovation in nanoparticle-based ocular medication delivery have tremendous potential [37].

CONCLUSION

Visual impairment is a health problem around the world. Topical application of eye drops is still the most common therapeutic route for treatment of eye diseases. Important improvement has been achieved at the preclinical level using nanoparticles as carriers for eye drug delivery. Nevertheless, it is necessary to translate these findings to clinical scenarios by designing controlled clinical trials.

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