



ISSN: 2347-6567

International Journal of Allied Medical Sciences and Clinical Research (IJAMSCR)

IJAMSCR | Vol.14 | Issue 3 | Jul - Sep 2026

www.ijamscr.com

DOI : <https://doi.org/10.61096/ijamscr.v14.iss3.2026.1227-1238>

Recent Advances in Nanoparticulate Ocular Drug Delivery Systems: Strategies to Overcome Ocular Barriers and Enhance Therapeutic Efficacy

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Published on:

15.07.2026

Published by:

Futuristic

Publications

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Abstract: Ocular drug delivery is a significant challenge because of the eye's unique structure and function. These characteristics limit how well drugs can penetrate and lead to low effectiveness of standard eye treatments. Common methods like eye drops, ointments, injections, and implants often need to be applied frequently. They can also lead to systemic side effects and issues with patient compliance. Recent progress in nanotechnology offers promising ways to address these challenges with nanoparticulate drug delivery systems. Nanocarriers can improve corneal penetration, extend the time drugs stay on the eye's surface, protect drugs from breaking down, allow for controlled and consistent drug release, and enhance their effectiveness while reducing how often patients need to dose and minimising systemic toxicity. Different nanoscale delivery systems, such as nanoparticles, nanocapsules, nanospheres, liposomes, solid lipid nanoparticles, nanostructured lipid carriers, polymeric nanoparticles, and nanomicelles, have shown great potential in boosting eye drug effectiveness and enabling targeted delivery. Additionally, these systems come with benefits like high drug retention rates, better stability, easier sterilisation, and improved patient compliance. This review looks at the latest developments in nanoparticulate ocular drug delivery systems. It highlights their benefits, how they work, and their possible uses in treating eye diseases. The advancements in ocular nanomedicine aim to lead to safer, more effective, and more user-friendly eye treatments for future medical use.

Keywords: Ocular drug delivery; Nanoparticles; Nanocarriers; Controlled drug release; Enhanced bioavailability; Site-specific drug delivery; Improved therapeutic efficacy; Nanomedicine.

Introduction

The eye is a complex organ that has many protections. These protections make it hard to deliver medications effectively. Conventional eye medications, especially eye drops, make up most of the products available for eye treatment¹. However, their effectiveness is limited by several factors. These include the quick turnover of tears, the drainage system around the nose, low permeability of the cornea, and short drug residence time². As a result, the bioavailability of the drugs in the eye is low, which means patients need to use them often. These issues can lead to poor patient compliance and lower treatment effectiveness. Recent advances in nanotechnology have opened new opportunities for improving ocular drug delivery. Nanoparticulate systems have unique physical and chemical properties that allow better corneal penetration, longer precorneal residence time, controlled and

sustained drug release, protection against chemical and enzymatic breakdown, and targeting specific sites³. Several nanocarrier systems, including polymeric nanoparticles, liposomes, nanomicelles, solid lipid nanoparticles, nanostructured lipid carriers, cubosomes, nanoemulsions, and spanlastic vesicles, have shown significant potential in overcoming ocular barriers and enhancing drug bioavailability⁴. Nanoparticulate systems used in ocular drug delivery help achieve better efficacy with less frequency, improve patient compliance, offer higher drug loading, improve formulation stability and reduce systemic side effects. The use of nanotechnology-based ocular drug delivery is a promising strategy for anterior and posterior segment diseases⁵. This review highlights the benefits and recent advances of nanoparticulate ocular drug delivery systems in enhancing drug delivery efficiency and improving ophthalmic therapy.

Ideal Characteristics of Ocular Drug Delivery Systems

An ideal ocular drug delivery setup needs to handle drug delivery safely while getting decent penetration through the cornea. Prolonged contact time on the surface helps with absorption overall and that leads to better results in the end⁷. It also makes sense for the prep to keep releasing the drug slowly so you do not have to use it as often and patients stick with it more. Local action stays important for treating actual eye issues and that means cutting down on how much gets absorbed elsewhere to limit any unwanted effects. The whole thing has to stay compatible with the eye in a basic way. That covers being close to tear fluid in terms of salt balance around the usual range⁸. pH works best near the natural level of tears since big swings cause discomfort fast. I think staying away from extremes helps protect the tissue proteins and keeps function normal but it is not always simple to balance everything perfectly in one go. Physiological fit seems to support better uptake and acceptance, which matters for these kinds of preps.

1. Ocular anatomy and constraints to ocular drug delivery

The human eye is a globular structure organ with size of about 24 mm and consists of two main parts: the anterior and posterior segments¹¹ (Fig.1). The both parts have various biological barriers to protect the eye from foreign substances. The anterior portion includes the cornea, iris, lens and aqueous humor. The posterior portion consist of the vitreous body, retina, choroid and back of the sclera⁽⁸⁾. The cornea is transparent and contains five layers: epithelium, Bowman's membrane, stroma, Descemet's membrane and endothelium^{12, 13}. The human corneal epithelium is the most important part of corneal barrier since it has multi layers of corneal epithelial cells which inter connected by tight junctions. These tight junctions can severely limit ocular penetration of drugs, especially many types of hydrophilic molecules. The corneal stroma is mostly composed of charged and very organized hydrophilic collagen which in derspassage of hydrophobic molecules^{14, 15}. Inrecent studies, various efflux transporters on epithelial cells were proved to be of importance in preventing permeation of anti-viral and anti-glaucoma drugs¹⁶⁻¹⁹.

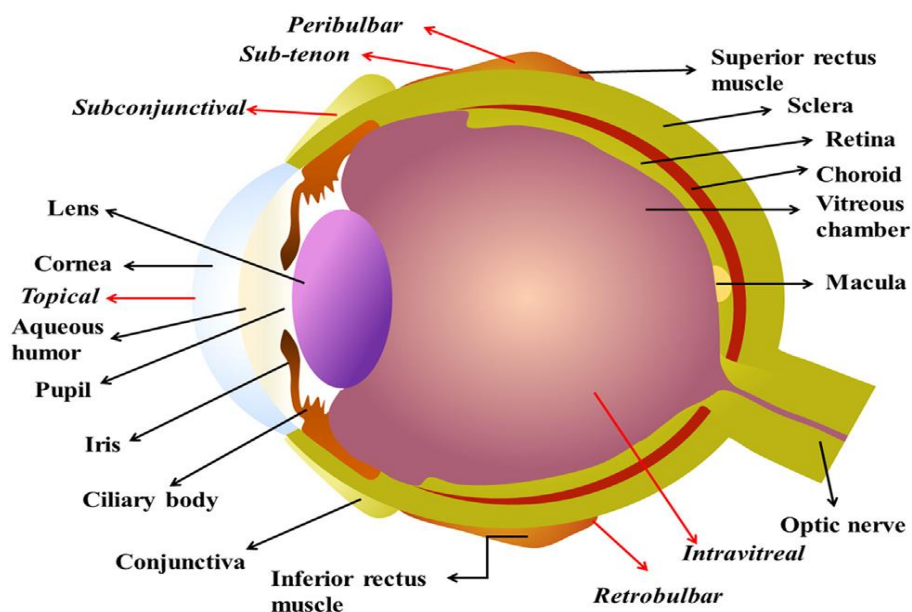


Fig 1: Ocular anatomy and administration routes of both traditional drugs and nanosystems: the black arrows show different eye structures and there arrows show various administration routes.

The intraocular space has a couple barriers that keep most molecules out. There is the blood aqueous barrier and then the blood retinal one too. It seems the first one comes from non pigmented epithelium around the ciliary body including iris parts and vessel walls with tight junctions. Those junctions control both active and paracellular transport.

The retinal barrier splits into inner and outer sections. Inner comes from retinal vessel endothelium while the outer part is a monolayer of pigment epithelium. Both restrict penetration into the chamber. This makes therapy on intraocular tissues pretty inefficient overall. Maybe the tight junctions are the main reason but I am not totally sure how the two barriers compare in strength. Drugs for the eye when used on top often do not work well. Clearance from the cornea surface limits it a lot. Precorneal factors add to this problem too. Blinking happens and tears turn over fast. The restoration time for tear film is only two to three minutes. Most of the drug gets washed away within seconds. Volumes larger than thirty microliters cause waste from drainage. It seems the total efficacy stays under five percent because of all that suggests poor bioavailability.⁴⁵

2. Nanoparticulate ocular drug delivery technologies³⁷:

People have tried different ways to fix problems with regular eye drops and such by getting more drug to stay before it gets lost. Nanotechnology has been one method looked at for getting drugs to both the front and back parts of the eye. It seems like making particles the right size helps avoid irritation while getting better absorption. There are several kinds of these carriers being used now. Nanoparticles and nanoemulsions are examples along with nanosuspensions and liposomes too. Some of them work pretty well for making the drug stay longer in the eye area. Maybe dendrimers are another option that shows promise but I am not totally sure how they compare yet. This part gets a bit messy when you think about all the options together.

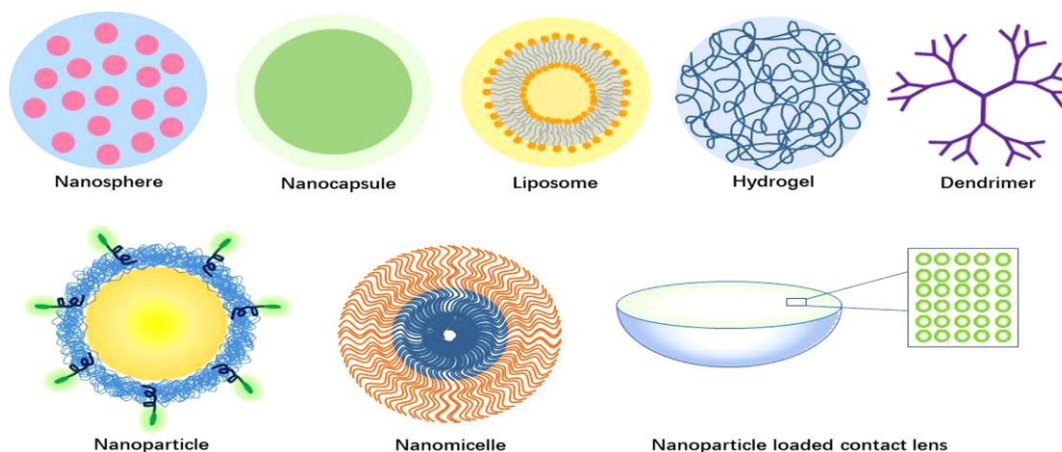


Fig 2: Schematic illustration of different nanotechnology-based ocular delivery systems.

2.1 Nanomicelles

Nanomicelles form in an O/W solution and can transport medicines inside. When the concentration of polymers is above the CMC, these particles form with sizes ranging from 10 to 200 nanometers. Since the inside of the micelles is hydrophobic, it enables for hydrophobic drugs to better overcome eye barriers since the outside of the micelle is hydrophilic which will allow for a better penetration. This makes them optimal to be used in eye drops. Significant benefits nanomicelles showed over the years are related with a reduced drug degradation rate and toxicity and higher bioavailability of lipophilic drugs³¹.

This category can be further divided in two: surfactant nanomicelles and polymeric nanomicelles (while surfactant nanomicelles are surfactant self-assembled molecules, polymeric nanomicelles have their origin in polymers³⁰). Some drugs already being used as therapies are for example nanomicelles made of hydrogenated castor oil-40 and octoxynol-40 encapsulating Cyclosporine-A to treat dry eye disease in the anterior ocular segment. It has shown increased bioavailability than conventional formulations with the absence of adverse effects. In more recent years, scientists have created fixed combination of substances that lead to lower CMC (critical micelle concentration). With this, we can achieve nanomicelles with higher stability and this can lead to higher bioavailability of the drug. If these nanomicelles are created from polymers like PEG (polyethyleneglycol) or PLA (Polylactic acid), they are called polymeric

nanomicelles and have also showed great potential to deliver antibiotics, immunosuppressants or even DNA for gene therapy to both the anterior and posterior part of the eye³¹. Another study took this technology a step further by designing a multi-layered nanomicelle, made with HCO-40 and OC40, with a hydrophilic interior that carried octreotide, aimed to treat proliferative diabetic retinopathy, inside a hydrophobic layer, being the outer layer hydrophilic. This was possible by assembling the different layers sequentially. These nanomicelles have increased loading characteristics, biocompatibility and stability, than can enable medicine to treat diseases specific from the posterior segment of the eye³². A study that investigated a polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer as a nanocarrier for curcumin administration in the eye, concluded that these nanomicelles enable an easier solubilization of drugs and has a higher storage capacity but also to have a better cell uptake and superior in vivo corneal permeation³².

2.2 Nanoparticles

Nanoparticles are essentially an extension of nanocarriers conceptively, and their size typically varies between 50 and 500 nm. They can either be deposited in the cul-de-sac or applied to the cornea. Due to their very small size, nanoparticles can easily enter the eye either by active transport mechanisms or by passive diffusion, or they can become trapped in the membranes that make up the ocular globe. In turn, this results in higher bioavailability, controlled drug release, and does not cause any discomfort to the patient. Besides, by changing the charge of such nanoparticles, we can tailor them for a specific part of the eye, because the cornea and conjunctiva are negatively charged, and cationic molecules are better retained in these areas. Nanoparticles in this category can be produced from polymers such as PLGA (poly lactic glycolic acid), PEG, PLA, PGA (polyglycolic acid), PCL (polycaprolactone), chitosan, albumin, hyaluronic acid, sodium alginate and gelatine, as well as from lipids like SLNs (Solid Lipid Nanoparticles). Intravitreal injection administration of fluocinolone acetonide encapsulated in PLGA nanoparticles for posterior ocular inflammation, a study was conducted to see if these particles could bypass the problems of the body's clearance and short half-life of fluocinolone acetonide. After the investigation, it was demonstrated that not only did the PLGA particles enhance the stability of the drug tested but also that the controlled release of the substance was maintained over 30 days, reducing the necessity for repeated injections and the use of higher doses of fluocinolone acetonide.³³

An experiment with a poly-(3-hydroxybutyrate-co-3-hydroxyvalerate) nanoparticle encapsulating hydrocortisone was tested as a topical administration route that would avoid the adverse effects of hydrocortisone while, at the same time, would penetrate to deeper layers of the cornea. After this investigation, it was concluded that this polymer could enable the administration of molecules that had more difficulty to pass through ocular barriers since results showed this drug delivery system lead to high bioavailability³⁴. In a study with another polymer, it was tested an etoposide loaded solid lipid nanoparticle to evaluate drug effective delivery to the posterior segment of the eye. In the end, after just 1 intravitreal injection, results showed that these particles continued to release etoposide over a period of 7 days without presenting adverse effects³⁵.

2.3 Liposomes

Liposomes are another strategy to encapsulate drugs, showing more biocompatibility than polymer-based molecules. These molecules that range from 0.025 and 10 (micrometers), and that sometimes might be confused by micelles, have a lipid bilayer whereas micelles have a lipid monolayer with a fatty and a polar side³⁶. The big limitation of this technology is their poor stability, which can lead to poor bioavailability and storage stability. However, it can be combined with other techniques to improve its characteristics. One example of that is a study done in China with a liposome coated with PAMAM G3.0, (a third generation polyamidoamine dendritic polymers) that, among other characteristics, make it easy to target to a specific site. This is especially important in this essay because the aim is the posterior part of the eye, which makes crucial to have a formulation stable and with enough capacity of penetration to overcome all the ocular barriers. The drugs administered through this route of administration were berberine hydrochloride and chrysophanol and it was concluded that with this formulation it was possible to reduce inflammation, better penetration and controlled release of both drugs³⁷. In another experiment, this one applying just the technology of liposomes with a HCl phosphatidylcholine liposome loaded with dorzolamide, aimed to make a comparison between this new formulation and the conventional one. In the end, the results lead them to conclude that the efficacy of the medicine and overall results were better due to the positive charged lipid bilayer of the liposome that makes it adhere better to the corneal layers, leading to a higher bioavailability³⁸.

2.4 Dendrimers

Dendrimers are branch-shaped structures. They are synthesised from a variety of polymers and due to their characteristic shape, they can encapsulate drugs, characteristic that is potentialized with the surface functionalized groups, and form structures that easily dissolve in a homogeneous way, being highly soluble in water³⁹. In ocular therapy, dendrimers can be either conjugated with other molecules or encapsulate these molecules. Dendrimers are usually used with other techniques to achieve better results and a recent innovation is the use of electrospinning to create PAMAM dendritic nanofibers loaded with brimonidine tartrate, a drug used to treat glaucoma. Despite short term results showing no difference in efficacy comparing to conventional formulations, long term results showed a significant difference when this formulation was applied daily due to accumulation of dendrimer nanofibers in the anterior segment of the eye, which indicates an alternative to current therapeutic strategies⁴⁰.

2.5 Microneedles

Steel microneedles are sharp shaped nanoparticles coated with drugs that penetrate in the eye in a very non-invasive way and can deliver medicines both to the anterior and the posterior part of the eye. This is a strategy to overcome the highly invasive route of ocular injections, especially intravitreal injections⁴¹. In two recent studies, it was tested the possibility of injecting microneedles at different sites and depths to have a controlled release of drugs in specific parts of the eye. In one study, microneedles coated with Rhodamine B were injected in the sclera with the use of a microneedle pen and the result showed that this route of administration allows us to administered drugs near injections sites, making it easy to overcome ocular barriers. In this case, the injection site was in the sclera and being released there, drug molecules were able to cross the sclera and reach the choroid within 6h⁴². In another study, a different approach was taken by designing a microneedle pen with a detachable tip that would penetrate the eye and be left there to be biodegraded over time. The drugs used were FITC-dextran to examine the drug release and polyhexamethylenebiguanide to examine the therapeutic applicability and results showed that this hybrid model, way less invasive than other injection strategies, had faster results than conventional therapies, while decreasing patient's discomfort⁴³.

2.6 Nanowafters

Nanowafters are rectangular or disc like structures made of polymers that are nanoreservoirs loaded with drugs and that are applied on the eye, releasing the substance over time while creating a membrane that can help heal corneal damage. Since these polymers are biodegradable, nanowafters end up being eliminated overtime⁴⁴. In one trial, a nanowafer made of sodium methylcellulose and PDMS (polydimethylsiloxane) and filled with dexamethasone was administered to see what the result of this formulation in a therapy for ocular burn and desiccating stress could be. This ended up leading to a controlled release overtime of the drug and that could increase the efficacy of similar treatments due to the controlled release and increase of patients' compliance, since 1 administration of this modified drops would replace 4 administrations of the previous ones⁴⁵.

2.7 Niosomes

Niosomes are also a colloidal system similar to liposomes and they are composed by a bilayer of self-assemble amphiphiles in an aqueous environment. They can take a shape of unilamellar or multilamellar vesicles. Despite being used in other therapies, it shows particular importance in ocular diseases due to its low toxicity and high adhesive properties. It has as a great characteristic the capacity of encapsulating both hydrophilic and lipophilic drugs with high biocompatibility and controlled release properties and, compared with liposomes, they have higher stability⁴⁶. A niosome prepared with Tween 60 and cholesterol and loaded with doxycycline hyclate was submitted to in vitro tests and also a Draize test that showed that these particles enabled a controlled release of the drug, could maintain its characteristics for 2 months when properly stored and did not cause any adverse effect when in contact with the eye⁴⁷. In other study, niosomes were coated with hyaluronic acid, a substance that is also present in the eye, more specifically in the aqueous body and vitreous body, could improve the bioavailability of tacrolimus, a drug used in prevent corneal allograft rejection. Since hyaluronic acid has mucoadhesive properties, it was concluded that niosomes with this coating had better precorneal retention, increasing the bioavailability of the drug⁴⁸.

3. Benefits of nanoparticulate ocular drug delivery

3.1 Self-administration by patients.

Patients with vision problems often struggle to put in eye drops the right way. It is hard to keep the hand steady and aim the bottle when you cannot see the tip well. This can make treatment less effective overall. Many eye conditions get treated with drops though. Most products on the market are still eye drops. Simplicity matters a lot for patients using them. Reduced dosing helps people stick to the schedule better it seems like that part gets overlooked some times. The formula needs the right thickness and amount so the drug does not wash away too fast before it reaches the eye. That is the part that stands out to me.

3.2 Avoid vision obstruction due to the small size.

Ocular drug transport barriers pose a challenge for drug delivery comprising the ocular surface epithelium, the tear film and internal barriers of the blood-aqueous and blood-retina barriers. Ocular drug delivery efficiency depends on the barriers and the clearance from the choroidal, conjunctival vessels and lymphatic. Traditional drug administration reduces the clinical efficacy especially for poor water-soluble molecules and for the posterior segment of the eye. Nanoparticles (NPs) have been designed to overcome the barriers, increase the drug penetration at the target site and prolong the drug levels by few internals of drug administrations in lower doses without any toxicity compared to the conventional eye drops. Nanoparticles (NPs) with size range from 10nm to 1000nm improved topical passage of large, poorly water-soluble molecules through the barriers of ocular system. Superficial barriers impede direct and systemic drug access to the specific site of action. Drug loaded nanoparticles favorable biological properties include prolonging the residence time of eye drops and decreasing toxicity and high ability of drug penetration into the deeper layers of the ocular structure and the aqueous humor minimizing precorneal drug loss by the rapid tear fluid turnover.²⁰ One possibility for such systems is the employment of small particles. These colloidal particles have the advantage that they may be applied in liquid form just like eye drop solutions. Thus they avoid the discomfort that is combined with the application of viscous or sticky preparations such as ointments. The latter preparations lead to a total blurring of vision if they are properly utilised. Large inserts, on the other hand, are difficult to administer or if they are designed as non-dissolving inserts they are even more difficult to remove, especially by elderly patients. Another alternative to small particle systems are liposomes. Liposomes, however, may have the disadvantage of lower stability. Suitable small particle systems include microspheres and microcapsules as well as nanoparticles and nanocapsules. Microparticles and microcapsules have a particle size above 1, μm . Microspheres are monolithic particles possessing a porous or solid polymer matrix, whereas microcapsules consist of a polymeric membrane surrounding a solid or liquid drug reservoir. Nanoparticles have a particle size in the nanometer size range below 1 μm .²²

3.3 Establish safety profile from enzymatic action like (peptidases and nucleases).

Nanoparticles can improve drug solubility and permeability, and help protect the drug from enzymatic degradation by peptidases and nucleases in the ocular region. This can enhance the bioavailability and therapeutic potential of protein and peptide drugs. However, the long-term toxicity of some polymeric nanoparticles, such as chitosan nanoparticles, remains unclear. These nanoparticles can be rapidly taken up by the conjunctival and corneal epithelium, potentially causing inflammation of the ocular surface with long-term exposure. The toxicity of other nanoparticle materials like PCL, PLGA, and PEGylated PLGA has also been studied in the context of ocular drug delivery. Overall, the safety profile appears to be mixed - nanoparticles can improve delivery but also raise potential long-term toxicity concerns that require further investigation.²³

3.4 Easy uptake into corneal cells

The corneal cell have characteristics that allow for easy uptake of substances. The corneal cell have a higher affinity for lipidic particles, which supports the penetration enhancement properties of the solid lipid nanoparticles (SLNs) loaded with cyclosporine A (CsA). The cellular uptake of the CsA- loaded SLNs was confirmed via confocal Le sab scanning microscopy (CLSM) studies. The CLSM microphotographs showed that the RCE cell substrate had RhB- loaded SLNs internalized and entrapped within the cells, demonstrating the easy uptake of the corneal cells to these nanoparticles.²⁵

3.5 Small and relatively narrow size distribution which provide biological opportunities for site-specific drug delivery by nano particles.

Nanoparticles offer several biological opportunities for site-specific drug delivery. They can be designed to target specific tissues, cells, or even subcellular compartments, allowing for more precise and efficient delivery of therapeutic agents. Nanoparticles can be functionalized with targeting ligands that bind to

receptors or antigens expressed in the target cells or tissues, enabling selective accumulation at the desired site. This can improve the therapeutic efficacy and reduce off- target effect.²⁶

3.6 Controlled drug release, improved drug bioavailability and reduction in the frequency of administration.

Controlled drug release:

Ocular drug delivery remains a major challenge due to anatomical and physiological barriers such as tear turnover, corneal epithelium, and limited drug residence time. Conventional eye drops show poor bioavailability, necessitating frequent dosing. This study explores the use of nanoparticle, and polymeric carriers, for controlled and sustained drug release in ocular tissues. The formulations were evaluated for drug encapsulation efficiency, release kinetics, and tissue retention. Results demonstrated that nanoparticles significantly improved drug bioavailability and prolonged drug release compared to conventional formulations. Additionally, these systems showed enhanced penetration into both anterior and posterior segments of eye. The findings suggest that nano particle based controlled release systems offer a promising approach for improving therapeutic efficacy and patient compliance in ocular diseases.²⁷

3.7 Improved drug bioavailability:

PLGA nanoparticles were developed to enhance the ocular bioavailability.²⁸ This research described cell penetrating peptide (CPP) modified PLGA and nanoparticles that increased ocular retention, permeation, and duration of drug action. In Vivo studies in rabbit eyes showed improved corneal transport, enhanced retention, and sustained drug levels in the aqueous humour.²⁹

4. Reduction in the frequency of administration:

4.1 The entrapped drug is protected against chemical degradation.

Nano carriers (liposomes, polymeric nanoparticles, solid lipid nanoparticles) enhance ocular drug delivery. Drugs entrapped within nanocarriers are protected from enzymatic and chemical degradation, while also improving penetration and retention. These systems overcome ocular barriers and allow controlled release and increased stability of drugs in Ocular tissues.³⁰

4.2 Possible sterilization by gamma radiation/autoclaving.

Gamma irradiation and autoclaving for sterilizing methazolamide-loaded lipid Nanoparticles. Results showed that autoclaving damaged Nanoparticle properties (size, charge), whereas gamma irradiation preserved entrapped drug and formulation stability. The system improved ocular Bioavailability and intraocular Pressure reduction, demonstrating that gamma sterilization is superior for sensitive ocular nanocarriers.³¹

4.3 They can be spray-dried as well as lyophilised.

Nanoparticulate ocular drug delivery systems can be converted into dry powder formulations using spray-drying and lyophilization techniques. These methods significantly improve the physical and chemical stability of nanoparticles during storage. Spray-drying is a rapid and cost-effective process that produces dry particles suitable for large-scale industrial manufacturing. Lyophilization, also known as freeze-drying, is particularly useful for thermosensitive drugs and biological molecules. The removal of water minimizes hydrolytic degradation and extends the shelf life of the formulation. Lyophilized nanoparticles can be easily reconstituted before administration without significant changes in particle size or drug entrapment efficiency. Cryoprotectants such as trehalose and mannitol are commonly used to prevent particle aggregation during freeze-drying. Both techniques facilitate easier transportation, handling, and storage of nanoparticulate formulations. Furthermore, they enhance formulation stability and maintain drug efficacy over prolonged periods. Therefore, spray-drying and lyophilization are valuable approaches for the successful commercialization of ocular nanoparticle-based drug delivery systems³⁷.

4.4 Relatively cheaper & stable dosage form.

Nanoparticulate ocular drug delivery systems are considered relatively economical and stable compared to many advanced ophthalmic delivery approaches. The small quantity of drug required and improved bioavailability help reduce overall treatment costs by minimizing drug wastage and dosing frequency. These systems can be manufactured using scalable and cost-effective techniques such as nanoprecipitation, spray-drying, and emulsification. Nanoparticles also protect the encapsulated drug from chemical,

enzymatic, and environmental degradation, thereby enhancing formulation stability. Their ability to maintain drug integrity during storage contributes to a longer shelf life and reduced product loss. In addition, the incorporation of stabilizing agents further improves physical stability by preventing aggregation and sedimentation. Many nanoparticulate formulations can withstand transportation and storage conditions more effectively than conventional formulations. The reduced need for preservatives and repeated administration also contributes to cost savings. Furthermore, improved therapeutic outcomes decrease the overall healthcare burden associated with ocular diseases. Therefore, nanoparticulate systems represent a cost-effective and stable platform for ocular drug delivery⁴⁷.

4.5 Tissue targeting reduction in drug dose and evasion of adverse effects.

Nanoparticulate ocular drug delivery systems offer the advantage of site-specific tissue targeting, enabling drugs to be delivered directly to the desired ocular tissues. This targeted delivery enhances drug accumulation at the site of action while minimizing exposure to non-target tissues. As a result, therapeutic efficacy can be achieved with lower drug doses compared to conventional formulations. The reduction in drug dosage decreases the risk of systemic absorption and associated side effects. Nanocarriers such as liposomes, polymeric nanoparticles, and solid lipid nanoparticles can be engineered to selectively interact with specific ocular cells and tissues. Their prolonged residence time and controlled drug release further improve treatment outcomes. Targeted delivery also reduces the frequency of administration, thereby enhancing patient compliance. By limiting off-target drug distribution, these systems help prevent local irritation and toxicity. Furthermore, improved bioavailability ensures maximum therapeutic benefit from a smaller amount of drug. Therefore, tissue-targeted nanoparticulate systems represent an effective strategy for reducing drug dose requirements and minimizing adverse effects in ocular therapy⁴⁶.

4.6 Surface alteration can be done easily & hence can be used for site-specific drug delivery system.

One of the major advantages of nanoparticulate drug delivery systems is the ease with which their surface properties can be modified. The surface of nanoparticles can be functionalized with various ligands, antibodies, peptides, polymers, or mucoadhesive agents to enhance their interaction with specific ocular tissues. Such surface modifications improve drug targeting efficiency and facilitate selective delivery to the desired site of action. This approach helps overcome ocular barriers and enhances drug penetration into target tissues. Surface-engineered nanoparticles can also prolong precorneal residence time and improve cellular uptake. Furthermore, targeted delivery minimizes drug distribution to non-target tissues, thereby reducing unwanted side effects. The attachment of specific targeting molecules allows nanoparticles to recognize and bind to particular cells or receptors within the eye. These modifications also contribute to improved bioavailability and therapeutic efficacy. As a result, lower drug doses are often sufficient to achieve the desired therapeutic effect. Therefore, surface alteration makes nanoparticulate systems highly suitable for site-specific ocular drug delivery applications⁵⁴.

4.7 They provide improved therapeutic effectiveness and overall pharmacological response/unit dose⁵⁹.

Nanoparticulate drug delivery systems significantly enhance the therapeutic effectiveness of ophthalmic drugs by improving their bioavailability, ocular retention, and penetration into target tissues. Owing to their nanoscale size and large surface area, nanoparticles can efficiently overcome ocular barriers and facilitate greater drug accumulation at the site of action compared with conventional formulations. This targeted delivery results in enhanced pharmacological activity and improved therapeutic outcomes. Furthermore, the controlled and sustained release characteristics of nanoparticles help maintain therapeutic drug concentrations for prolonged periods, minimizing fluctuations in drug levels. As a result, the desired therapeutic effect can be achieved with lower drug doses, thereby reducing dosing frequency and improving patient compliance. Enhanced corneal permeation and prolonged precorneal residence time further contribute to increased drug absorption and efficacy. In addition, nanoparticulate systems reduce drug loss caused by tear turnover and nasolacrimal drainage, leading to more efficient drug utilization. The localized delivery of drugs also minimizes systemic exposure and associated adverse effects. Therefore, nanoparticulate ocular drug delivery systems provide superior therapeutic efficacy and an enhanced pharmacological response per unit dose administered.

4.8 They also possess better stability and high drug entrapment efficiency⁵⁴.

Nanoparticulate drug delivery systems exhibit excellent physical and chemical stability, making them highly suitable for ophthalmic applications. The encapsulation of drugs within nanoparticles protects them from degradation caused by environmental factors such as light, oxidation, hydrolysis, and enzymatic activity. This protection helps maintain drug potency and extends the shelf life of the formulation. In addition, nanoparticles are capable of entrapping a large amount of drug within their matrix or core, resulting in high drug entrapment efficiency. High entrapment efficiency ensures maximum utilization of the incorporated drug and minimizes drug wastage during formulation development. The stable structure of nanoparticles also enables controlled and sustained drug release, which contributes to prolonged therapeutic action. Furthermore, the incorporation of stabilizing agents can prevent particle aggregation and maintain formulation integrity during storage. Enhanced stability improves the overall quality, safety, and effectiveness of the drug delivery system. These advantages ultimately lead to improved bioavailability and therapeutic performance. Therefore, nanoparticulate ocular drug delivery systems are recognized for their superior stability and high drug-loading capacity, making them promising carriers for ocular drug delivery⁵⁸.

5. Conclusion

Nanoparticulate ocular drug delivery systems can be used as an innovative means of overcoming some anatomical and physiological barriers of conventional ophthalmic drugs and hence ensuring better delivery and efficacy of such drugs. Several types of nanocarriers, which include nanoparticles, nanomicelles, liposomes, solid lipid nanoparticles, nanostructured lipid carriers, dendrimers, niosomes, microneedles, and nanowafers, have shown promising results in terms of enhancing ocular bioavailability and residence time, and providing controlled and targeted drug delivery. Nanoparticulate ophthalmic delivery systems improve the efficiency of therapeutic interventions due to increased penetration through the cornea, protection of drugs against degradation, reduced frequency of application, and decreased adverse effects on other body organs. Additionally, their potential in providing prolonged drug delivery, increased encapsulation efficiency, enhanced stability, and targeted drug delivery make them good choices for the treatment of both anterior and posterior segments of ocular disorders. However, there are several obstacles that still need to be overcome before the full realization of the benefits of using nanoparticles in ophthalmic medications. Such problems include manufacturing issues, safety concerns, regulation, and clinical translation.

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