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NANO MEDICINE FOR OCULAR DRUG DELIVERY

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Abstract
Nano emulsions are considered as the most promising solution to improve the delivery of ophthalmic drugs. The design of ophthalmic nano emulsions requires an extensive understanding of pharmaceutical as well as technological aspects related to the selection of excipients and formulation processes. Nano emulsions are liquid-in-liquid dispersion with a droplet size of about 100 nm. They have a transparent appearance, high rate of bioavailability, and increased shelf life. Nano emulsions mainly consist of oil, water, surfactant, and cosurfactant and can be prepared by high- and low-energy methods. These nano emulsions are subjected to certain tests, such as safety, stability, pH profile, rheological studies, and so on. . This review focuses on nano technology-based eye disease treatment systems and highlights the obstacles affecting the drug management of eyes and nano-systems for the treatment of eye diseases. This paper summarizes the development prospect of nanotechnology and the challenges it faces in the treatment and diagnosis of ophthalmic diseases, to provide information and new ideas for the implementation of treatment and the development of a refractory eye disease management system. Ocular drug delivery has constantly challenged ophthalmologists and drug delivery scientists due to various ana tomical and physiological barriers. . State-of-the-art nano-formulations are currently being examined for their possible beneficial effects in diagnosing and treating various nervous-related ocular conditions. This review article summarizes the main characteristics of nano emulsions, ophthalmic nano emulsions, and cationic nano emulsions and their components, methods of preparation, and the evaluation parameters for ophthalmic nano emulsions

Keywords: Nano Emulsion, Ophthalmic Nano Emulsion, Ophthalmic Formulations.

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Introduction
Ophthalmic therapy is largely based on topical administration of aqueous active pharmaceutical ingredients (API) solutions which are eliminated shortly after instillation by the nasolacrimal drainage system. Apart from the formulation of conventional topical drug dosage forms for ophthalmic diseases. Most ophthalmic diseases are treated by topical eye drop instillation; however, several problems, such as poor bioavailability, are associated with these formulations. Various metals, metal oxides, and semiconductor nanostructures can be used as nano-catalysts for multiple applications like energy-saving processes to fulfil human needs. For example, poly (vinyl alcohol) (PVOH) based films are widely used in the food industry due to their easy film-forming ability [1]. Ophthalmic preparations that can overcome such problems. Although the incorporation of drugs in different pharmaceutical vehicles, such as ointments, suspensions, and emulsions, can improve the bioavailability and provide sustained drug release, they cannot be regarded as the formulation of choice given their ocular adverse effects, including irritation, redness of the eye, interference with vision, and low product stability. In addition, chronic administration may increase systemic availability and cause severe systemic complications.

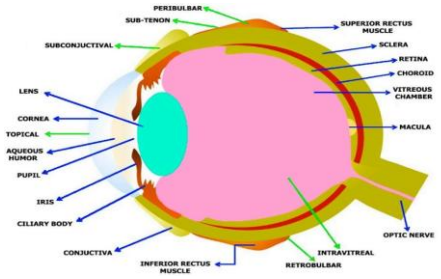


Fig 01: Graphical representation of the human eye and administration routes for both nano-based and traditional medicines.

Ocular Anatomy and Barriers

The anatomical structure of the eyeball can be divided into the anterior and posterior segments based on the lens. Figure 1 illustrates the anatomy of the human eye. Various absorption barriers exist in the human eye. The anterior segment includes the cornea,

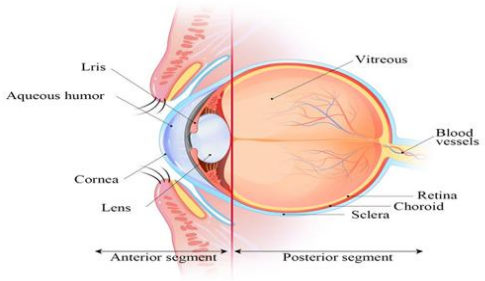


Fig 02: The anatomy of the eye

conjunctiva, iris, ciliary body, aqueous humor and lens, while the pos terior segment includes the sclera, choroid, retina and vitreous body barriers to prevent foreign substances, including therapeutic agents, from targeting various eye tissues.

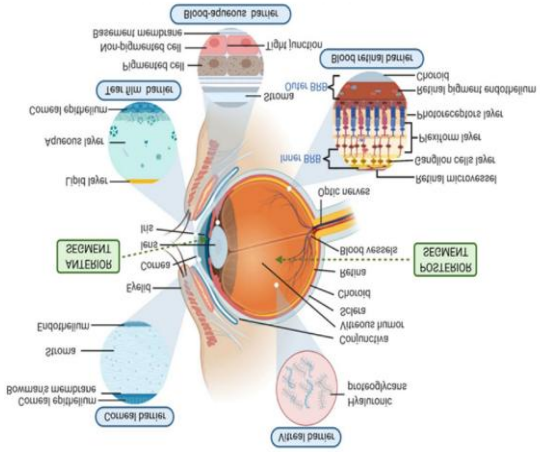


Fig 03: Drug delivery barriers in ocular routes. The absorption barriers of the eye mainly include tear film barrier, corneal barrier, conjunctival and scleral barriers, vitreal barrier,blood-aqueous barrier, blood-retinal barrier. Copyright 2022, Drug Delivery and Translational Research.

Conjunctival and Scleral Barriers

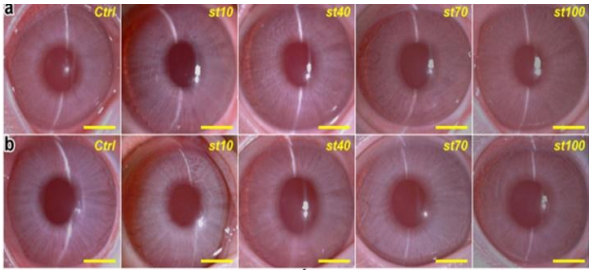
The alternative route of drug entry into the eye after topical instillation is the non-corneal route comprised of the conjunctiva and sclera. The conjunctiva, a mucous membrane formed by a vascularized epithelial group.

Nano-Formulations in Neuro-Ophthalmology

Nano-formulations have been extensively studied for their possible utilization in diagnosing and treating neuro-ophthalmological diseases due to their unique physicochemical characteristics and their variability in structure and composition. Natural biopolymers and inorganic nanomaterials include metal-based nanoparticles, Quantum Dots (QDs), carbon nanotubes, and mesoporous silica nanoparticles [2].

Nano suspensions

Nano suspensions are colloidal dispersions in which the hydrophobic phase is uniformly dispersed in the aqueous medium with the help of surfactant. For example, prednisone, dexamethasone, hydro cortisone, and other corticosteroids have been ad ministered through nanosuspensions to treat anterior inflammation without the expected side effects of high-dose application, such as cataract and glaucomatous optic neuropathy. The nanosuspension consists only of submicron colloidal dispersions of drug nanocrystals.



The representative images of rabbit eyes taken with a slit-lamp biomicroscope after intracameral administration of pilocarpine-loaded HPLA NP (st10, st40, st70, and st100) dispersions or BSS buffer (Ctrl group) at 0 (a) and 56 (b) days. c The scores of slit-lamp examinations at 56 days d Central corneal thickness at 56 days.

Nano Fibers

Nanofibers are 1–100 nm diameter fibers. Various natural polymers (such as chitosan, fibronectin, gelatin, collagen, silk, and ethyl cellulose) or synthetic polymers (such as PLA, PLGA and PCL) Nanofibers have the advantages of a high-surface to-volume ratio, high porosity, adjustable mechanical properties, strong drug-loading capacity, high encapsulation efficiency, and simultaneous delivery of multiple therapeutic agents [3].

Polymer Nanoparticles

Nanofibers are made of solid fiber materials with a diameter of less than microns. They have a porous structure and a very high surface area. They are composed of highly organized polymer fibers and aqueous compounds comprised of protein polysaccharides to support tissue formation. Therefore, tissue engineering is one of its main applications. In addition, because the diameter of nanofibers is very small and the surface area is very large, higher drug content can be loaded in a very small part packages [4]. In this system, the drug is bound or dissolved in the structure, encapsulated or captured in the structure by binding to the matrix, and a general drug delivery system is generated, including microemulsion, liposome, niosomes, dendrimer, and cyclodextrin [5].

Characterisation of nano technology-based drug delivery systems

Nanotechnology refers to treating structures at the nanoscale level, which ranges in size from 1 to 100 nm

and is proportionally comparable to peptide drugs. Teir basic physicochemical properties, such as visual appearance, size, zeta potential, refractive index, pH, retention, viscosity, osmolality, biodegradability, surface charge, hydrophobicity and biodegradability are closely related to their therapeutic efficacy in the ocular pathological environment [6].

1 Morphology

Microscopic techniques were used to study the morphology of nanocarriers. Electron microscopy approaches, including transmission electron microscopy (TEM), freeze-fracture transmission electron microscopy (FFTEM), and negative staining transmission electron microscopy (NS-TEM), are preferred for liquid samples, while scanning electron microscopy is used for solid samples . In addition, TEM and atomic force microscopy (AFM) techniques can be used to reconfirm the results obtained from photon correlation spectroscopy or dynamic light scattering measurements [7].

2 Refractive index (RI)

Refractive index is measured by Abbe's refractometer to determine soft contact lenses' water content, salinity and sugar concentration The tear RI was generally between 1.340 and 1.360. Therefore, the recommended RI value for ocular formulations must For instance, the RI values of intraocular NEs prepared by Ismail et al. ranged from 1.334 to 1.338, which was satisfactory to meet the demands [8].

3 Drug loading and release

Drug loading and release are essential to the ocular drug delivery system. Nanocarriers require a high drug payload, which can improve biocompatibility and achieve better therapeutic effects. The primary determinant of drug load is drug solubility. The drug is released continuously in nano capsules with high encapsulation efficiency, and the release rate is critical to achieve an effective therapeutic effect and avoid drug toxicity. Pharmacokinetics can be studied via a series of in vivo and in vitro experiments. Besides, the results can be analyzed by some pharmacokinetic parameters, such as the maximum drug concentration (Cmax), the time required to reach Cmax (Tmax), and the area under the concentration–time curve (AUC0t)[9].

Evaluation of ophthalmic nano emulsion

1 Zeta potential

Zeta potential is the measurement of charge repulsion among oil nanodroplets. This variable is one of the most important parameters affecting the dispersed system stability. A high zeta potential results in a stable nano emulsion.

2 pH

The pH can be measured by using a pH meter, and the pH of nano emulsions should be about 7.2±0.2 for maximum comfort. it results in discomfort and irritant effect, which depends on the contact period with the eye surface, volume instilled, and buffering capacity.

3 Cytotoxicity Test

This test examines the effects of a preparation on a certain culture of mammalian cells. N Thus, diverse studies cover the use of nano emulsions as ophthalmic drug delivery vehicles, as summarized in Table 4. such as Restasis® (Allergan company) which is used as a nano emulsion formulation for dry eye disease, or in clinical trials (brimonidine tartrate eye drops for dry eye disease under phase III).

Table 4. Studies of several ophthalmic nanoemulsion formulations with types of surfactants and cosurfactants and oil used[68]

S. no.	Drug	Surfactants and co-surfactants	Oil	Comment
1	Timolol	Lecithin	Isopropyl myristate	Nanoemulsion bioavailability in aqueous humour was 3.5 times more than Timolol alone.
2	Dexamethasone	Cremophor EL, ropyleneglycol,	Isopropyl myristate	Enhanced ocular bioavailability (about three times compared with the conventional dosage form) and sustained effect of drug without ocular irritation.
3	Indomethacin	Phospholipids miranol-MHT	MCT	Significant increase in corneal permeability compared with the marketed formulation (Indocollyre®) and showed almost 4 times corneal permeability coefficient without toxicity in *ex vivo* studies.
4	Levobunolol	Lecithin, glycerol	Soybean oil	Improved *in vitro* permeability with a reservoir effect.
5	Pilocarpine	Macrogol 1500-glyceroltriricinoleate, 6PEG 200, propylene glycol,	Isopropyl myristate	Enhanced ocular bioavailability of up to 1.68 times with sustained effect and no ocular toxicity in comparison with aqueous solutions.
6	Chloramphenicol	Span20, Span80, Tween20, Tween80	Isopropyl palmitate and isopropyl myristate	Improved stability in nanoemulsion formulation in comparison to conventional system as chloramphenicol is relatively prone to degradation in conventional dosage form.

6. Safety and Toxicity Issues

Despite the beneficial effects of nanomedicine in managing various conditions, ROS production, cytotoxicity, genotoxicity, neurotoxicity, and immune activation are some of the major limiting factors that need to be considered for the development of nanocarriers. Multiple mechanisms are responsible for neuronal toxicity, such as the production of ROS. For example, titanium dioxide (TiO2) NPs boost the production of intracellular ROS in neurons and microglia. Cationic Au NPs exhibit dramatic changes in cell viability, haemolysis, and bacterial viability compared to anionic Au NPs [10].

Fututre perspectives

In this review, we first introduced the anatomy and barriers of the eye, where effective treatments and drug delivery are significant challenges due to the diversity of the diseases and the presence of ocular barriers, especially in the posterior segment of the eye. Although traditional drug administration has achieved certain efficacy in treating ocular diseases, some limitations remain, such as poor permeability, ineffective distribution, and insufficient bioavailability. Many new drug delivery techniques are primarily tested in animal experiments or in vitro studies, lacking comprehensive in vivo evaluations in human eyes [11].

Conclusion

The ophthalmic drug market has significantly grown in recent years globally. Between 2015 and 2018 there was an 800% increase in approvals of new ophthalmic drugs including topical treatments. Guarantee the desired properties, stability, and tolerance of the formulation during shelf life and after its application.

Author Contributions

All authors are contributed equally

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Declaration of Competing Interest

The Authors have no Conflicts of Interest to Declare.

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