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REVIEW ON A PROMISING STRATEGY FOR ENHANCED OCULAR DRUG DELIVERY SYSTEM

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ABSTRACT

Nano emulsions are dispersions formed by mixing two immiscible liquids, typically featuring droplet sizes around 100 nanometers. They are known for their clear appearance, enhanced bioavailability, and extended shelf life. These formulations usually include oil, water, surfactants, and co-surfactants, and can be developed using either high-energy or low-energy techniques. In ophthalmology, diluted Nano emulsions are employed to deliver drugs effectively, as they can penetrate deeper into ocular tissues, offer sustained drug release, and minimize both dosing frequency and potential side effects. Various tests such as safety evaluations, stability assessments, pH analysis, and rheological studies are performed to ensure their suitability. Cationic Nano emulsions, which contain positively charged agents, are particularly useful for topical ocular drug delivery, as they enhance drug retention on the eye surface by slowing down clearance, thereby improving absorption. This review highlights the key features of Nano emulsions, especially those used in ophthalmic applications, including their composition, preparation methods, and evaluation criteria.

KEYWORD: Nano emulsion, ophthalmic formulations /preparation, ocular delivery: barriers.

INTRODUCTION

The ophthalmic route remains a key method for drug administration in eye treatments, yet it presents significant difficulties for pharmaceutical developers. Topical eye drops are

commonly used to manage ocular disorders, but they often suffer from low drug bioavailability. This is primarily because the medication is quickly cleared from the eye's surface by tear flow and drainage through the nasolacrimal system. Furthermore, despite the promising features of Nano emulsions in enhancing ocular drug delivery, their commercialization is limited by issues such as poor formulation stability, high production expenses, and labor-intensive preparation techniques. Pharmaceutical scientists are working to develop ophthalmic formulations that address the challenges associated with traditional drug delivery methods. While using vehicles like ointments, suspensions, and emulsions can enhance bioavailability and offer sustained drug release, they are not ideal choices due to side effects such as eye irritation, redness, vision interference, and poor product stability. Moreover, prolonged use may increase the systemic absorption of the drug, leading to severe systemic complications. Formulations containing preservatives can also trigger adverse reactions when absorbed into the Blood stream.[21] Nano technology has emerged as a promising solution for ophthalmic drug delivery.

This technology is being utilized to target both the anterior and posterior parts of the eye. Nanotechnology-based systems with optimal particle sizes can be formulated to reduce eye irritation, improve bioavailability, and ensure compatibility with ocular tissues. These systems are particularly effective for delivering lipophilic drugs through the use of cationic Nano emulsions, which interact with the negatively charged corneal and conjunctival cells. This interaction prolongs the drug's residence time on the ocular surface,

Barriers for intraocular drug transport

1) Tear

Tears can influence the administration of ophthalmic drugs through binding with the administered drug. Tear Eye Drop is an eye lubricant or artificial tears used to relieve dry eyes. This can happen because not enough tears are made to keep the eye lubricated. It helps to soothe the irritation and burning seen in dry eyes by maintaining proper lubrication of the eye.

Common side effects of eye Tear

Bloor vision

Eye iritation

Eye redness

Foreign body sensation in eyes

2) Cornea

The cornea is the transparent, dome-shaped front part of the eye that acts as its "window," protecting deeper structures and allowing light to enter for vision. It's the primary structure responsible for focusing light and plays a crucial role in vision clarity, with approximately 60-75% of the eye's focusing power attributed to it. More permeable than cornea to hydrophilic drugs and macromolecules; has greater surface area.

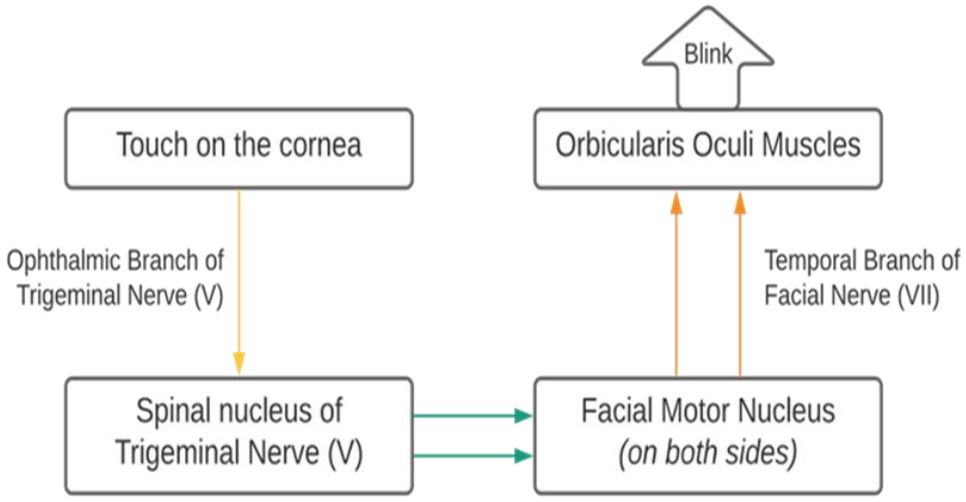


Fig. Epithelium-tight intercellular junctions……

3) Conjuctiva

The conjunctiva is a transparent mucous membrane that covers the eye's surface around the cornea, consisting of the upper epithelium and lower stromal layer that contains vascularized tissues with extensive blood and lymphatic flow. The conjunctiva is 25 times more absorbent than the cornea due to its time wider surface area, fewer layers of epithelial cells, and 250-time larger paracellular spaces, which makes it more permeable, particularly for large hydrophilic molecules However, due to its high blood vessel density, drugs that penetrate the conjunctiva may enter the general blood circulation via the conjunctival sac or the nasal cavity rather than into the ocular segments.

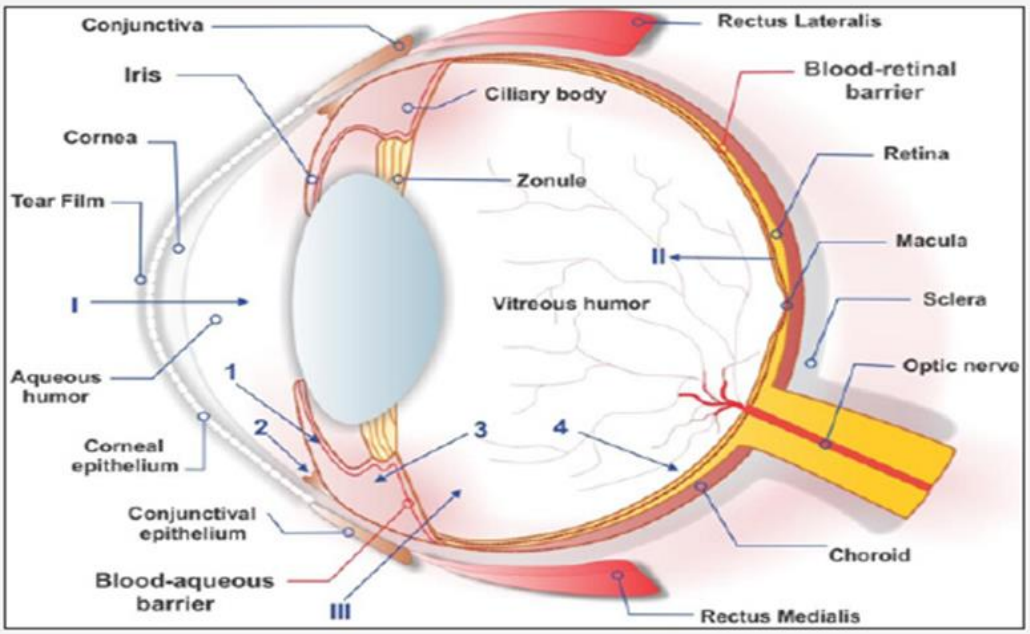


Figure 1: Schematic illustration of the main structure of the eye and the ocular barriers.

Vitreous. CD44, a surface molecule found in high levels on the retina, plays a crucial role in delivering drugs and gene-based therapies to this area.

4) Choroid

Reduced blood flow to certain ocular tissues limits the systemic delivery of drugs to these areas. Additionally, the choroid-Bruch's membrane complex serves as a barrier that impedes the diffusion of lipophilic compounds**.**

Table No. 1: Anatomical barrier for intra ocular drug transport. (Anatomical barrier+ Characteristics).

Anatomical barrier	Characteristics
Tear	Drugs bind with mucin, dilution of topical drugs. Induce lacrimation and tear film turnover increase drug clearance**.**
Cornea	Epithelium is a major barrier to passage of hydro-phallic drugs; tight intercellular junctions restrict paracellular diffusion. Stroma is a barrier to passage of highly lipophilic drugs.
Conjunctiva	More permeable than cornea to hydrophilic drugs and macromolecules; has greater surface area. Epithelium -tight intercellular junctions.
Sclera	Hydrated stroma better absorption of hydrophilic drugs. More permeability to macro molecules. Molecular radius is an important parameter to determine permeation.
Choroid	Receives less blood flow, resulting in less drug permeation from the systemic circulation. Choroid Bruch's membrane limits permeation of

	lipophilic drugs.
Retina	Permeable to small, lipophilic, or hydrophilic molecules. Inner limiting membrane limits entry of drugs from vitreous into retina.
Retina	Permeable to small, lipophilic, or hydrophilic molecules. Inner limiting membrane limits entry of drugs from vitreous into retina.
Vitreous humor	Hyaluronan- is more permeable to anionic drugs (due to negatively charge). Large lipophilic/hydrophilic drugs retained more in vitreous humor.

5) Sclera

The sclera, also referred to as the white part of the eye, forms the outermost layer of the eyeball and plays a key role in preserving its shape due to its fibrous composition. The ability of drugs to pass through the sclera is influenced by their hydrophobic properties; drugs with higher lipophilicity tend to have lower permeability, while more hydrophilic drugs pass through more easily. Additionally, the movement of therapeutic substances across the sclera is affected by how hydrated the tissue is and the level of intraocular pressure. Although normal eye pressure (15–20 mmHg) has little impact on this process, significantly elevated pressure levels (above 20–60 mmHg) can alter the permeability of substances through the sclera.

6) Retina: The retina, located at the back of the eye, is where light entering through the cornea and traveling through the front portion of the eye forms an image. This image is then processed by the brain. The retina is vulnerable to various diseases affecting the back part of the eye, such as diabetic retinopathy and age-related macular degeneration. Drugs present in the vitreous can be cleared from the eye through both anterior and posterior pathways, including elimination through the retina after crossing the internal limiting membrane, which separates the retina from the vitreous. CD44, a surface molecule found in high levels on the retina, plays a crucial role in delivering drugs and gene-based therapies to this area.

Challenges

Ocular drug delivery faces numerous challenges due to the complex anatomy and physiology of the eye. One major issue is absorption, as the bioavailability of traditional eye drops is low, typically around 3%-4%, due to the eye's impermeable structure and small surface area. Another challenge is poor drug solubility, particularly for lipophilic drugs, which cannot be incorporated into conventional aqueous drops and must instead be formulated as suspensions. Additionally, patient compliance is a concern because achieving the desired therapeutic effect often requires frequent instillations, which can be inconvenient. The limited range of excipients approved for ophthalmic use further complicates drug formulation. Finally,

delivering drugs to the posterior segment of the eye remains difficult with conventional eye drops due to barriers like the corneal epithelium and the blood-retina barrier.8 To overcome these hurdles, new delivery systems, such as nanoparticles or implantable devices, are being explored to improve bioavailability, solubility, and targeted delivery to the posterior segment.[19]

Blood ocular barriers

Blood aqueous barrier- tight junctions limit entry of solutes into aqueous humor and entry of hydrophilic drugs from plasma into aqueous humorous blood retinal barrier- major barrier to hydrophilic drugs. Inner blood retinal barrier- major barrier which limits entry of systemic drugs into retina. Blood ocular barrier.[1]

Definition of Nano emulsion

Nano emulsions are transparent and stable mixtures of oil and water, made up of a dispersed internal phase and a surrounding external phase. Surfactants and cosurfactants play a crucial role in their formation by lowering the surface tension between phases, which helps in producing small-sized droplets. These molecules, due to their dual hydrophilic and hydrophobic nature, also contribute to the stability of the nano emulsion through electrostatic repulsion and steric effects Typical nano emulsions have droplet sizes ranging from 100 to 500 nanometers, though they can extend up to 1000 nanometers. They are widely used as drug delivery systems because they can improve the effectiveness of drugs while reducing side effects and toxicity.[14]

Nano emulsions differ from microemulsions primarily in droplet size and stability. Microemulsions are isotropic, transparent systems with much smaller droplet sizes (10 –100 nm) and are thermodynamically stable. In contrast, nano emulsions require external energy such as heating or mixing to form and are prone to phase separation over time, making them less stable. This need for energy input and eventual instability marks a key difference between the two types of emulsions.[2]

COMPONENT OF NANOEMULSION

Main three components of Nano emulsions are as follows

1) Oil

2) Surfactant

3) Co-surfactant

4) Aqueous phase**.**

Preparation method of Nano emulsion

Nano emulsions can be prepared by using high and low energy methods. In high energy methods, mechanical devices deliver required large disruptive forces. On the other hand, in low energy methods, there is no need for an external force. Production of nano emulsions is achieved by using the intrinsic physiological properties of the system. In this nano emulsion preparation method, stored energy of the system is utilized by alteration of parameters such as temperature, composition of the system studies of nano emulsions, the high energy methods were only choice for researches and thus high energy stirring and ultrasonic emulsification were the most widely used methods. Nowadays, low-energy methods have drawn considerable attention since they are 'soft', nondestructive and cause no damage to encapsulated molecules. Several methods have been suggested for the preparation of nano emulsion.[15] The basic objectives of the nano emulsion preparation to achieve the droplet size range of 100-600 nm and another is to provide the stability condition. Formation of nano emulsion system required a high amount of energy. This energy can be provided either by mechanical equipment or the chemical potential inherent within the component[7] Here some methods are discussed which are freely used for the nano emulsion preparation.

High energy method

In high-energy methods, large disruptive forces are pro-vided by the use of mechanical devices such as ultrasonicates, microfluidizers and high-pressure homogenizers which produce droplets of small size. The droplet size depends on the equipment, production conditions, such as temperature and time, as well as the properties and com-position of sample. High-energy methods require sophisticated equipment and consume large amount of energytherefore, they are very expensive. Their positive side is that they allow good control of droplet size and large selection of integral components. These methods are not applicable for thermolabile active ingredients such as retinoids and macromolecules including proteins, enzymes and nucleic acid. High pressure homogenisation This method is widely used for the production of nanoemulsions it utilizes several forces such as hydraulic shear, intense turbulence and cavitation. In this method, two liquids including surfactants and cosurfactants are passed through a small orifice of piston homogeniser under high pressure (500-5000psi) to produce nano emulsion.[3] At first, emulsion is formed with large volume fraction of dispersed phase, which may be diluted later on. The problem of coalescence can be reduced

by adding surfactants in excess amount. High pressure homogenisation is a highly efficient method, available at both laboratory and large scale, but consumes a large which might deteriorate the components. This technique used high-pressure homogenizer/piston homogenizer to produce nanoemulsions of extremely low particle size (up to 1 nm). The droplet size depends on the number of homogenization cycles. More homogenization cycles lead to smaller droplet size.[3]

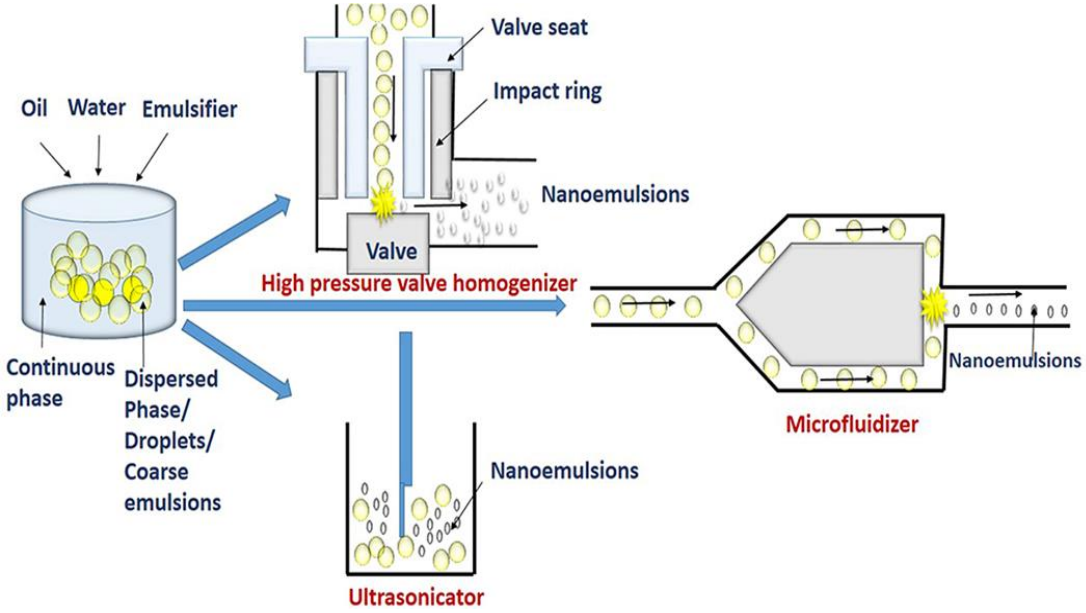


Fig. 2: High Energy Method.

The droplet size of the nano emulsion produced by this method decreases with decreasing the ratio of dispersed and continuous phase viscosities to certain extent (0,05 < < 5c Dann), where ND is the viscosity of the dispersed phase, and Nc is the viscosity of the continuous phase. With this method only O/W (oil in water) liquid nanoemulsions of less than 20% oil phase can be prepared. Some problems associated with homogenizer are poor productivity[18], component deterioration due to generation of substantial amount of heat.

Nevertheless, this is the most used frequently method for preparation of nanoemulsions.

Low-Energy Methods

Low-energy techniques create nanoemulsions by utilizing the system's internal physical properties, such as temperature or composition.[11]

Phase Inversion Techniques

The phase inversion (or condensation) approach involves shifting phases during the emulsification process. These shifts occur due to changes in the surfactant's spontaneous curvature, and can be triggered in two ways:

By altering temperature at a constant composition

This method, known as the Phase Inversion Temperature (PIT) technique,[16][15] adjusts the no ion surfactant through temperature changes and is widely applied in industrial processes.

By modifying composition at a fixed temperature

This is referred to as the Emulsion Inversion Point (EIP) method.

Advantages

Carrier of hydrophobic drugs.

Improves bioavailability drugs

Good shelf stability.

Toxicologically safe**.**

Disadvantages

Require large amount of surfactant and cosurfactant.

Low capability to solubilization high melting point drugs.

Low stability in especially in acidic condition.

Toxicity of surfactant and cosurfactant is possible

Properties of emulsions

Emulsion Droplet Size Thermodynamic Appearance Macro emulsion 0.1-100 μm Unstable Turbid Microemulsion 5-100 nm Stable Transparent Nano Emulsion 5-200 nm Unstable Transparent.

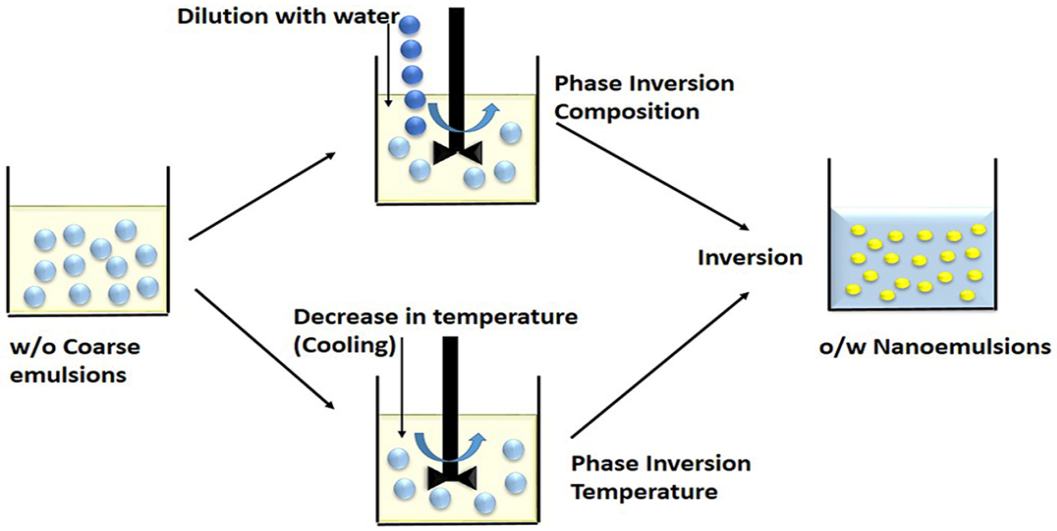


Fig. 3: Low Energy Method.

Evaluation of ophthalmic Nano emulsion

1) Zero potential

Zero potential measures the electrostatic repulsion between oil nanodroplets and is a key factor influencing the stability of dispersed systems.[12] A higher zeta potential generally indicates a more stable nanoemulsions, as it helps prevent droplet aggregation. The value of the zeta potential is determined by the difference between the electrical potential of the surrounding medium and that of the stationary fluid layer near the oil nanodroplets. For optimal stability, the zeta potential should typically fall within the range of +20 mV to +40 mV.[9]

2) Refractive index

An Abbe refractometer is commonly used to measure the refractive index, which is important for evaluating potential vision disturbances or discomfort after using eye drops. The refractive index of natural tear fluid typically falls between 1.340 and 1.360. To prevent visual impairment, the refractive index of eye drops should not exceed 1.476.

3) Percentage transmittance

The percentage transmittance can be measured by spectrophotometer 50,54 at a specific wavelength with distilled water as a blank. The formulated nano emulsion is considered transparent if the percentage transmittance is more than 99%.57.

4) PH

Developed formulations were evaluated for pH by preparing 1% aqueous solution of prepared gel using calibrated Equip-Tronic's digital pH meter model EQ- 610. The pH of the formulations was found in the range of 6-7 indicating safe in chronic treatment of eye infection.

5) Surface Tension

Damage to the tear film can occur when the surface tension of eye drops is significantly lower than that of natural tear fluid, which typically ranges between 40 and 50 mN/m.

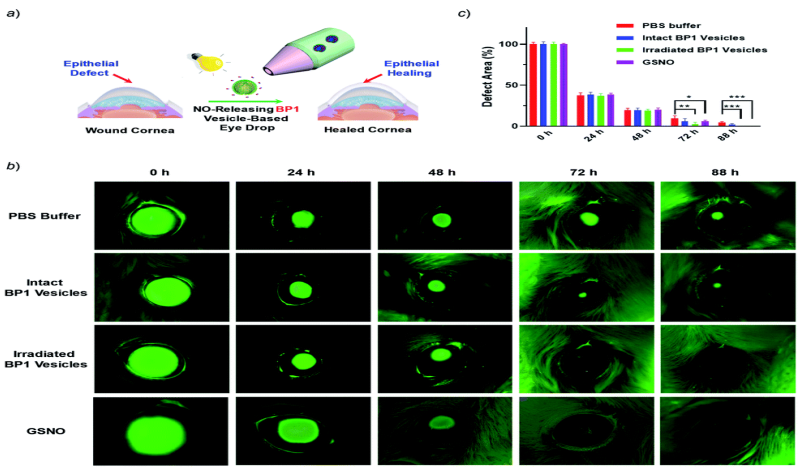
Ophthalmic formulations should have minimal impact on the natural behavior of tears. Preparations with lower viscosity tend to cause less blinking discomfort and are generally better tolerated, while those with higher viscosity can enhance drug retention time and improve ocular bioavailability.[17] Ideally, the viscosity of eye drops should not exceed 20 maps.

6) Osmolality

The lacrimal (tear) fluid osmolality normally ranges between 280–293 mOsm/kg. However, when the eye is open, evaporation causes the osmolality to vary more widely, between 231–446 mOsm/kg. If the osmolality of an instilled solution is less than 100 mOsm/kg or greater than 640 mOsm/kg, it can cause irritation to the eye. Nevertheless, after the administration of a non-isotonic solution, the eye's natural mechanisms typically reestablish normal osmolality within 1–2 minutes.

Ophthalmic products include

- **Eye Drops**



- **Eye Lotion**

- **Eye ointment**

- **Contact lens Solution**

CONCLUSION

Ophthalmic nano emulsion drug delivery systems represent a promising advancement in ocular therapeutics. By enhancing the solubility, stability, and bioavailability of both hydrophilic and lipophilic drugs, nanoemulsions offer improved drug penetration and prolonged residence time on the ocular surface. Their small droplet size allows for better absorption and less irritation, increasing patient compliance.[8][13] Despite some formulation and scalability challenges, ongoing research and development continue to optimize their safety, efficacy, and commercial viability. Overall, nano emulsion-based eye drops hold significant potential for more e treatment of various ocular diseases. Ophthalmic nanoemulsions represent a promising advancement in ocular drug delivery, offering enhanced bioavailability, sustained drug release, and improved patient compliance compared to conventional eye drops. Due to their small droplet size and high surface area, nanoemulsions can efficiently penetrate ocular barriers, allowing for targeted delivery and reduced dosing frequency. Their ability to solubilize both hydrophilic and lipophilic drugs further broadens their therapeutic applications. Overall, nano emulsion-based formulations hold significant potential to overcome the challenges of ocular drug delivery and improve the treatment of various eye diseases.[20][5]

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