



Original Research Article

Nanoparticulate based ocular drug delivery technology: “Nanoemulsion a novel approach”

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ABSTRACT

Many ocular diseases or disorders require frequent administration of the drug. But poor ocular bioavailability of drugs (< 1%) from conventional ophthalmic formulations is a serious concern. The epithelial layers protect the eye and consequently limit the penetration of ocular drugs. In order to overcome the shortcomings of the standard form of ophthalmic dosage, much has been done to improve the absorption of pre-corneal drugs and to reduce the loss of pre-corneal drugs. Ophthalmic formulation based on Nanotechnology is one of the approaches to internal and external drug delivery. Nanotechnology systems with the right particle size can be made to ensure minimal irritation, adequate bioavailability, and tissue compatibility. Many of them have shown promising results in improving ocular availability. Nanoemulsions are the colloidal oil in water (o/w) or water in oil (w/o) nano-dispersions and homogenous systems, stabilized by surfactants and co-surfactants to reduce the interfacial tension. Typically, the droplet size is <150 nm. Due to the presence of very narrow size range of droplets, they appear as transparent, homogeneous and thermodynamically stable systems. They offer a high penetration rate into the deeper layers of tissue due to the nano-droplet size range.

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1. Introduction

The human eye is a unique and sensitive organ, both anatomically and physiologically. It contains several extensively varied structures with self-regulating physiological functions that render the organ highly impervious to foreign materials. The inner and outer blood-retinal barriers are having no cellular components and separate the retina and the vitreous body from the systemic circulation consequently reduces the diffusion of molecules. Eye strain poses a challenge before a pharmacist to prevent barriers that protect the eye without causing permanent tissue damage.¹

1.1. Anatomy and physiology of the eye

The eye consists of specific physiological barriers of the aqueous mucosal barrier, corneal epithelium barrier, corneal layer, retinal barrier and ciliary body layer. Generally, the eye can be divided into two parts: the anterior and posterior.

1.1.1. Anterior segment

The anterior segment is directly visualized from the front segment and covers one-third portion of the entire eye and is composed of a cornea, conjunctiva, iris, ciliary body, aqueous humor and lens.²

1.1.1.1. Cornea. It is the outermost part of our eye, convex in shape and is responsible for refracting and bending of light rays to focus on the retina. As it is devoid of vasculature the corneal tissue receives nourishment from the tear film, aqueous humor and limbal vessels.³

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1.1.1.2. Conjunctiva. It is the thin, transparent vascularized mucous lining extending from the lateral margin of the cornea, across the sclera, covering the inner surface of the eyelids. It facilitates lubrication in the eye by generating mucus and offers less resistance to drug permeation relative to the cornea.³

1.1.1.3. Iris. It is a circular, muscular, lightly pigmented diaphragm with a pupil in the center. It separates the anterior and posterior segment of the eye which releases aqueous fluids by the ciliary body. It consists of two layers of smooth muscles and pigment cells. The contraction and expansion of the muscles of the iris adjust the size of the pupil in response to the light entering the eyeball.^{3,4}

1.1.1.4. Ciliary body. It consists of anterior continuation choroid of ciliary smooth muscle and secretory epithelial cells. It provides mechanical attachment of suspensory ligament which is attached to the lens. Any alteration in the ciliary muscles like contraction and relaxation causes alteration in the thickness of the lens which leads to refraction and bending of the light rays. Epithelial cell secretes aqueous fluid into the anterior segment.³

1.1.1.5. Aqueous humor. It is the protective and nutritive fluid between the cornea and lens. It is secreted from the ciliary body and circulates to the anterior chamber from the posterior chamber. If the outflow of aqueous humor is impaired then it causes permanent damage to optic nerve due to elevated intraocular pressure.⁵

1.1.1.6. Lens. It is circular, biconvex, highly elastic and present behind the pupil. The lens refracts light rays refracted by objects into the front portion of the eye. When the object is located near, the lens becomes thicker to allow focusing.³

1.1.2. Posterior segment

The posterior segment cannot be visualized directly and includes sclera, choroid, retina, optic nerves and vitreous humor.⁵

1.1.2.1. Sclera. It is the external layer over choroid. It is a vascular, tough and opaque white-yellow protective layer consisting of collagen, elastic fibers and proteoglycan. It helps protect the inner organ of the eye. Its importance is to maintain the shape of the eyeball and to provide resistance to an internal and external force.⁵

1.1.2.2. Choroid. The choroid along with the ciliary body and iris form the vascular middle layer of the eyeball. The choroid lies in between the sclera and retina and is dull reddish-brown. Within this vascular layer, large vessels are located near the sclera (vascular lamina) and extended smaller vessels are pressed against the light-sensitive layer of the retina. These capillaries provide nourishment and

oxygen to the outermost layers of the retina.⁵

1.1.2.3. Retina. It is the most sensitive organ of the eye located in the innermost layer of the wall in the posterior segment of the eye. These layers are sensitive to light rays due to the presence of sensory receptor cells called rods and cones. The blood supply to the innermost retina is from the retinal artery.

The retina is one of the most metabolically active tissues in the human body. Therefore, its functional integrity relies upon nutrients supply and the expulsion of waste. This is achieved through the inner retinal blood and choroidal circulations.³

1.1.2.4. Optic Nerves. Light rays converted into electrical impulses are transferred by the optic nerve to the brain where images are formed.³

1.1.2.5. Vitreous humor. It is a transparent substance confined between the retina and the lens (vitreous chamber). The constituents of the vitreous body are approximately water (the water percentage increases with age), collagen and natural macromolecules like hyaluronic acid (HA).³

1.2. Ideal characteristics for ocular delivery

1. It should have enhanced corneal penetration.
2. The contact time with the corneal tissue should be prolonged.
3. The number of dose administration should be less.
4. The local activity should be more than the systemic effect.
5. The tonicity should be equal to that of 0.9% NaCl solution or osmolality should be within the range of 100-640 mOsm/kg.
6. The pH of the formulation should be in the range of 7.4 ± 2 or else it may cause irritation to the eye.
7. The formulation of either being acidic or being basic will cause damage to the protein environment in the eye, so this should be avoided.^{6,7}

1.3. Drawbacks of conventional ocular drug delivery system

Many ocular diseases or disorders require frequent administration of the drug. But poor ocular bioavailability of drugs (< 1%) from conventional ophthalmic formulations is a serious concern. The epithelial layers protect the eye and consequently limit the entry of ocular drugs.⁸

The drawbacks are discussed in the following section:

1.3.1. Low ocular bioavailability

Conventional ophthalmic dosage forms are drained from conjunctival sac into the nasolacrimal duct or are cleared from the precorneal area resulting in poor bioavailability of the drugs.⁹

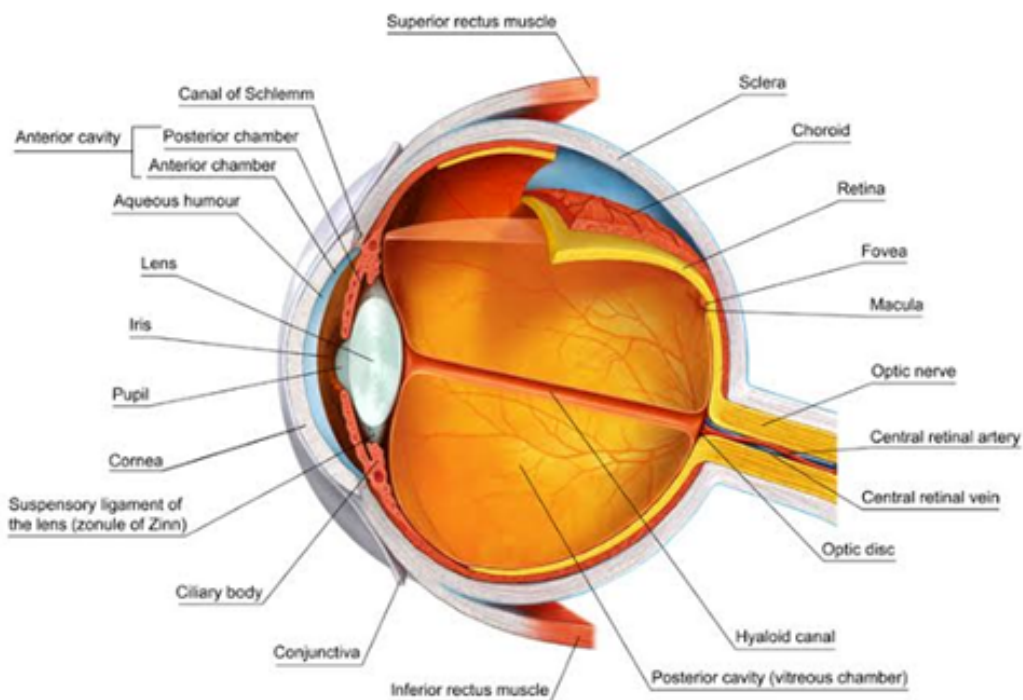


Fig. 1: Anatomy of the human eye



Fig. 2: Drawbacks of conventional ocular drug delivery

Low ocular bioavailability is the result of the following:

1.3.1.1. Rapid tearing. The rapid elimination of the drug by blinking of the eyes and tear flow results in a short duration of the therapeutic effect leading to the frequent dosing regimens.

1.3.1.2. Transient residence time. Transient residence time in the cul-de-sac involves poor bioavailability of drugs because of tear production, non-productive absorption and impermeability of corneal epithelium.

1.3.1.3. Non-productive absorption. Drugs applied topically are potentially available for absorption by the scleral and palpebral conjunctiva (the so-called 'non-productive' absorption). Although direct transscleral access to other intraocular tissues cannot be ruled out, it is well documented that drugs entering the conjunctiva are quickly removed from the eye by local circulation and take up systematic absorption.¹⁰

1.3.2. Precorneal drug loss

Drugs are mainly eliminated from the precorneal lacrimal fluid by solution drainage, lacrimation and non-productive absorption to the conjunctiva of the eye.

1.3.3. Impermeability of drug to the corneal epithelium

The physiological restriction is the inadequate permeability of cornea leading to low absorption of ophthalmic drugs.¹¹

1.3.4. Nasolacrimal drainage

The nasolacrimal drainage system consists of three parts:

1.3.4.1. Secretory system. The secretory system consists of basic secretaries that are stimulated by blinking and temperature changes due to evaporation of tear and a secret reflex with parasympathetic nerve supply that is secretive in response to physical or emotional stimulation.

1.3.4.2. Distributive system. The distributive system comprises of the eyelids and also the tear meniscus around the lid edges of an open eye, which spread tears over the ocular surface by blinking and thus preventing dry areas from emerging.

1.3.4.3. Excretory system. The excretory part of the nasolacrimal drainage system consists of the lachrymal puncta, the superior, inferior and common canaliculi; the lachrymal sac; and the nasolacrimal duct. In human beings, the two puncta are the openings of the lachrymal canaliculi and are positioned on an elevated part known as the lachrymal papilla. It is also believed that tears are basically absorbed by the mucous membrane that lines the ducts and the lachrymal sac; only a small quantity reaches the nasal passage. Tears dilute the drug remaining in the cul-de-sac of eyes, which in turn reduces the trans-corneal flux of the

drug.¹²

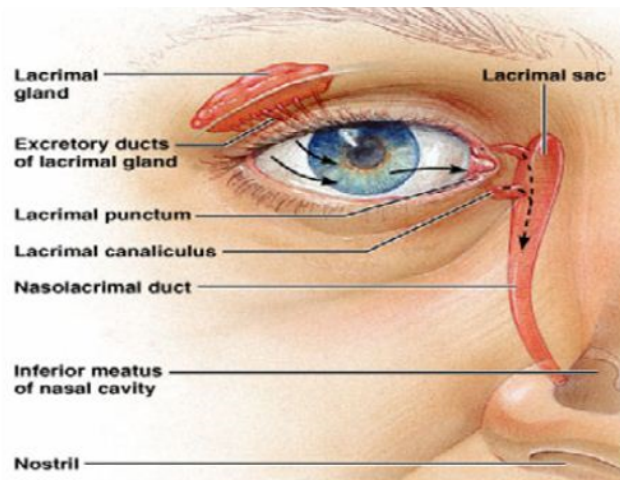


Fig. 3: Nasolacrimal drainage apparatus

1.3.5. Systemic toxicity of the drug

Systemic absorption of the drug and additives drained through nasolacrimal duct may result in undesirable side effects and toxicity.¹³

1.4. Nanoparticulate ocular drug delivery technologies

To overcome the drawbacks of conventional ophthalmic dosage forms, many developments have been done to improve the pre-corneal drug absorption and minimize pre-corneal drug loss.

Nanotechnology-based ophthalmic formulation is one of the approaches which is being pursued for both anterior, as well as posterior segment drug delivery.

Nanotechnology-based systems with an appropriate particle size can be fabricated to ensure minimal irritation, adequate bioavailability, and ocular tissue compatibility. Several nanocarriers, such as nanoparticles, nanoemulsions, nanosuspensions, liposomes, nano-micelles and dendrimers have been developed for ocular drug delivery. Many of them have shown promising results for improving ocular bioavailability.¹⁴

1.5. Benefits of nanoparticulate ocular drug delivery

1. Self-administration by patients.
2. Avoid vision obstruction due to the small size range.
3. Establish safety profile from enzymatic action like (peptidases and nucleases).
4. Easy uptake into corneal cells.
5. Small and relatively narrow size distribution which provide biological opportunities for site-specific drug delivery by nanoparticles.
6. Controlled drug release, improved drug bioavailability and reduction in the frequency of administration.

7. The entrapped drug is protected against chemical degradation.
8. Possible sterilization by gamma irradiation/autoclaving.
9. They can be spray-dried as well as lyophilized.
10. Relatively cheaper & stable dosage form.
11. Tissue targeting, reduction in drug dose and evasion of adverse effects.
12. Surface alteration can be done easily & hence can be used for site-specific drug delivery system.
13. They provide improved therapeutic effectiveness and overall pharmacological response/unit dose.
14. They also possess better stability and high drug entrapment efficiency.^{15–17}

1.6. Constraints of nanoparticulate ocular drug delivery

1. Because of their small size, the physical handling of nanoparticles is difficult in liquid and dry forms.
2. Present bio-acceptability restrictions.
3. Difficult to manufacture in a large scale.¹⁶

2. Nanoemulsions

Nanoemulsions are the colloidal oil in water (o/w) or water in oil (w/o) nano-dispersions and homogenous systems, stabilized by surfactants and co-surfactants to reduce the interfacial tension. Usually, the size of the droplets is < 150 nm. Due to the presence of very narrow size range of droplets, they appear as transparent, homogeneous and thermodynamically stable systems. They offer a high penetration rate into the deeper layers of tissue due to the nano-droplet size range.¹⁸

Due to the presence of surfactant and co-surfactant, they promote the solubilization of both hydrophilic and hydrophobic drug candidates. The nano-size of the droplets that are adsorbed in the cornea assists in the avoidance of nasolacrimal drainage. Additionally, nanoemulsions can achieve sustained drug release along with high permeation and thereby improved ocular bioavailability.¹⁹

They offer a threefold increase in in-vitro corneal permeation as compared to conventional ophthalmic drops. The improved drug bioavailability and pharmacological response by nanoemulsion were attributed to nano-droplet size. They have low surface tension and high spreading coefficient, allowing the drug to spread and mix well with the precorneal fluid. This improves the corneal contact time of drugs.

2.1. Advantages

1. Overcome the adverse effects of pulsed dosing produced by conventional ocular systems.
2. Provide sustained and controlled drug delivery.

3. Provide targeting within the ocular globes to prevent the loss of other ocular sites.
4. Circumvent the protective barriers like drainage, lacrimation and diversion of exogenous chemicals into systemic circulation by conjunctiva.
5. Provide comfort and adherence to the patient but improve the effectiveness of the drug treatment beyond normal routines.
6. Ease of sterilization.
7. Improved stability.

2.2. Disadvantages

1. Causes toxicity at higher concentrations.
2. The selection of surfactant/co-surfactant and aqueous/organic phase may affect stability.²⁰

3. Types of Nanoemulsions²¹

4. Components of Nanoemulsion

4.1. Water

In o/w nanoemulsions, water acts as the continuous phase while in w/o nanoemulsions water acts as the dispersed phase.²²

4.2. Oil phase

The selection of a proper oil phase is an essential parameter as it influences the selection of other ingredients of nanoemulsions, the preparation of nanoemulsion system and solubilization of the drug. Usually, the oil having a maximum solubilizing capacity for the drug are selected as an oily phase for the formulation of nanoemulsions to attain maximum drug loading. Most commonly used oils for nanoemulsion formulation include oleic acid, isopropyl myristate, olive oil, triacetin, castor oil, palm oil, peanut oil, etc.²³

4.3. Surfactants

The selection of an appropriate surfactant is one of the most important critical issues in preparation of nanoemulsion as it provides stability to the nanoemulsion by reducing the interfacial tension between oil and water interfaces. It provides thermodynamic stability (lowering of Gibbs free energy) to nanoemulsion by forming a layer around oil (o/w system) or water (w/o system) droplets and hence, their proper selection (based on hydrophilic-lipophilic balance, HLB) plays a significant role in the nanoemulsion development.²⁴

Generally, surfactants with a lower HLB value favor the formation of w/o nanoemulsions, whereas surfactants with a higher HLB (>10) favor o/w nanoemulsions. However, a blend of surfactants and co-surfactants are usually preferred for the formulation of nanoemulsions. The most commonly

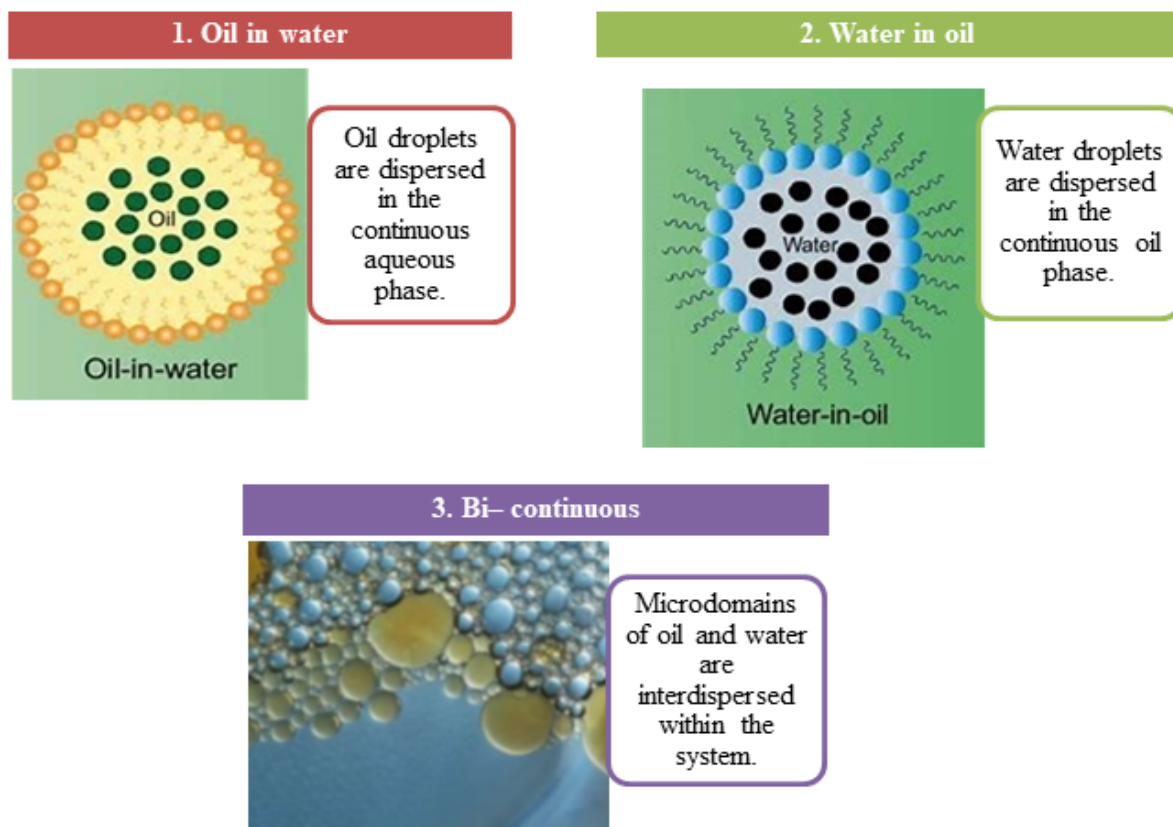


Fig. 4: Different types of Nanoemulsions

used surfactants in the preparation of nanoemulsions include Tween-20, Tween-80, Cremophore EL, Labrasol, Span 20, etc.²⁵

4.4. Co-surfactants

In many cases, surfactants alone cannot reduce the oil-water interfacial tension and offer the required stability to produce a nanoemulsion and hence, co-surfactants are added for the preparation of a stable formulation and bring the surface tension nearby to zero. The co-surfactants act by three ways: (i) improve thermodynamic stability of the nanoemulsion by lowering interfacial tensions, (ii) modify the curvature of the interface (iii) provide additional fluidity/flexibility to the interfacial film. The commonly used co-surfactants include Transcutol P, PEG 200, PEG 400, and propylene glycol, etc.²⁶

5. Method of Preparation of Nanoemulsion

The nanoemulsion can be prepared by both high and low energy methods.

5.1. High energy methods

5.1.1. High-pressure homogenization method

This method involves applying of high pressure with homogenizer over the system consisting of the oil phase, aqueous phase, surfactant and co-surfactant. Some problems associated with homogenizer are poor productivity, constituent deterioration due to the production of abundant heat. From this method, only oil in water (o/w) nanoemulsion of less than 20% oil phase can be prepared.²⁷

5.1.2. Micro-fluidization method

This technique makes use of a device known as microfluidizer. This device uses a high-pressure positive displacement pump (500-20000PSI) that allows the product through a communication chamber, consisting of small channels called microchannels.

Very fine particles of the sub-micron range are obtained when the product flows through the microchannels on to an impingement area. The two phases (aqueous phase and oily phase) are mixed and processed in an inline homogenizer to produce a coarse emulsion.

The coarse emulsion is further processed into a microfluidizer to yield a stable nanoemulsion of desired particle size.²⁸

5.1.3. Ultrasonication method

This technique is based on the principle that when the coarse emulsion is placed in an ultrasonic field and external pressure is increased, the cavitation threshold also increases to limit where fine nano-size particles are formed.²⁹

5.2. Low energy methods:

5.2.1. Phase inversion method

This technique requires excess addition of the dispersed phase or a change in temperature for the formation of a nanoemulsion. In this method, extreme changes in physical properties take place which includes changes in particle size. For non-ionic surfactants by a change in temperature of the system phase inversion can be achieved, a change in temperature from low to high converts o/w nanoemulsion to w/o nanoemulsion. Upon cooling, the system crosses a point of zero spontaneous curvature and minimal surface tension, which promotes the development of finely dispersed oil droplets.³⁰

5.2.2. Spontaneous emulsification method:

It comprises of three main steps:

1. Preparation of homogeneous organic solution which consists of oil and lipophilic surfactant in water-miscible solvent and hydrophilic surfactant.
2. i. The organic phase was introduced in the aqueous phase under magnetic stirring; the oil in water nanoemulsion was formed.
3. iii). The water-miscible solvent was finally, removed by evaporation under reduced pressure.³¹

6. Evaluation Parameters of Nanoemulsion

6.1. Thermodynamic stability screening

To assess the thermodynamic stability of nanoemulsions, clarity, phase separation, droplet size, and drug content were evaluated.

6.2. Centrifugation

Nanoemulsion formulations were centrifuged at 3500 rpm for about half an hour. Those nanoemulsions which failed to exhibit any phase separation were taken for the heating-cooling cycle.

6.3. Heating-cooling cycle

About six cycles were performed at two different temperatures i.e., refrigerated temperature (4°C) and the higher temperature (45 °C), with storage at each temperature for not less than 48 hours. Nanoemulsion formulations, which were stable at above-stated temperatures, were subjected to freeze-thaw testing.

6.4. Freeze-thaw cycle

Three freeze-thaw cycles between temperature -21 °C and +25 °C with storage for not less than 48 hours was done for the nanoemulsions formulations.³²

6.5. Dispersibility

This test assesses the stability of the prepared nanoemulsions. It helps in the determination of the formation of any precipitate or large oil globules upon the dispersion/dilution process. 1 mL of each nanoemulsion formulation was added to 500 mL of water at 37 ± 0.5 °C and the appearance of the nanoemulsions was graded as clear and turbid.³³

6.6. Rheological measurement

The rheological properties play a significant role in stability as viscosity is proximately affected by storage conditions. It can be determined with the help of Brookfield digital viscometer.³⁴

6.7. Droplet size measurement

Droplet size can be determined by photon correlation spectroscopy which analyzes fluctuations in light scattering due to the Brownian motion of the particles, using a Zeta seizer. The 0.1 ml nanoemulsion is dispersed in 50 ml of water, mixed thoroughly and light scattering was carried out at an angle of 90° at 25 °C.³⁵

6.8. PH measurement

pH not only affects the stability but also alters the solubility and bioavailability of the drug at the site of permeation. The apparent pH of the formulation was measured by a digital pH meter.³⁴

6.9. Refractive index measurement

The refractive index is defined as the ratio of the speed of a wave in a reference medium to the phase speed of the wave in the medium. It can be determined using an Abbes type refractometer at 25 ± 0.5 °C.³⁶

6.10. Surface tension measurements

Surface tension measurements were carried out at 20°C using a thermostatically controlled processor tensiometer provided with a Du Nouy ring (ring radius 9.545 mm, wire diameter 0.37 mm).³⁷

6.11. Poly-dispersity measurement

The poly-dispersity index of nanoemulsions was measured by Photon Correlation Spectroscopy, at temperature 25 °C.³⁸

6.12. Zeta potential measurement

It is one of the important parameters known to affect stability as well as bioavailability.

Samples are analyzed in the path of the laser. The light scattered was collected at 14.8° and detected using a photomultiplier tube finally, the zeta potential of the sample was determined.³⁹

6.13. Osmolarity determination

Osmolarity is an important parameter by which one can predict the irritability of the formulation caused to the eyes. It can be determined using Micro Osmometer.⁴⁰

6.14. Drug content determination

The drug content in nanoemulsion can be determined by spectrophotometer.⁴¹

6.15. Transmission electron microscopy

Morphology and structure of the nanoemulsions can be studied using transmission electron microscopy operating at 200 kV and capable of a 0.18 nm point to point resolution.⁴²

6.15.1. In vitro drug release studies

In vitro drug release studies can be performed in a USP dissolution tester apparatus type II at $34 \pm 0.5^\circ\text{C}$ using a dialysis membrane of 12,000 Da and drug concentration was determined spectro photometrically.

The drug release profiles can be fitted to various mathematical models like zero order, first order Higuchi and Korsemeyer-Peppas models to estimate the best fitting kinetic model having the highest correlation coefficient.⁴³

6.16. Stability studies

The principal objective of conducting stability testing is to determine the influence of environmental factors like temperature and humidity on the degradation of nanoemulsion. These studies help in establishing the storage conditions for prepared nanoemulsion.⁴⁴

7. Conclusion

Ocular nanoemulsions help in overcoming the limitations of many conventional ophthalmic therapies and are more stable than other systems. They offer several advantages by improving the contact time of the vehicle at the ocular surface, helps in lowering the elimination of the drug, improved patient compliance, and improved bioavailability and increase its penetration through cornea. Ophthalmic nanoemulsions also possess the ability to provide sustained release of a drug and higher penetration to the deeper layers of the ocular structure and aqueous humor and hence as compared to the conventional systems of the drug delivery

ocular nanoemulsion increases the therapeutic efficacy and pharmacokinetic parameters of the drug molecule. So, it is becoming an outstanding choice of formulation and has opened a new era in the arena of ocular drug therapy.

8. Source of Funding

None.

9. Conflicts of Interest

There is no conflict of interest between the authors.

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