MICROEMULSION IN OCULAR DRUG DELIVERY; A REVIEW

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ABSTRACT: Delivery of drugs into eyes using conventional drug delivery systems, such as solutions, is a considerable challenge to the treatment of ocular diseases. Medication misfortune from the visual surface by lachrymal liquid discharge, lachrymal liquid eye boundaries, and blood visual obstructions are fundamental deterrents. Various ophthalmic medication conveyance bearers have been made to enhance the bioavailability and to draw out the living arrangement time of medications connected topically onto the eye. The potential utilization of micro emulsions as a visual medication conveyance bearer offers a few ideal pharmaceutical and biopharmaceutical properties, for example, their astounding thermodynamic soundness, stage progress to fluid precious stone state, low surface pressure, and little bead size, which may bring about enhanced visual medication maintenance, broadened length of activity, high visual retention, Further, both lipophilic and hydrophilic attributes are available in micro emulsions.The main objective of the present investigation was to formulate and characterise microemulsion for ocular drug delivery.70% of the ophthalmic preparations are conventional dosage forms, extensive pre corneal loss caused by rapid drainage and high tear liquid are the main drawbacks associated with these systems, only 1 to 5% of the total drug penetrates into cornea and reaches to the intraocular tissue, to overcome these problems, microemulsion based systems are developed. In the first step solubility of drug in oil and surfactant was checked to identify components of microemulsion. The microemulsion was prepared by using oleic acid as an oil phase, tween 80 as surfactant, ethanol as co surfactant and 0.5 N NAOH as aqueous phase. The appropriate amount of drug was introduced into the oil phase with continues magnetic stirring, the mixture of surfactant and co surfactant was added into the oil phase with vigorous stirring, aqueous phase was added drop wise to form a transparent and stable microemulsion. The prepared microemulsion was evaluated for visual observation, PH, Particle Size and Zeta potential. The microemulsion prepared was appeared to be transparent, isotropic, monophasic and dynamic in nature, and have low viscosity with Newtonian behaviour, the PH value ranges from 6.8±7.1, particle size was found in micro range 213.2±100%, zeta potential -12.8.

KEYWORDS: microemulsion, ocular delivery, surfactants, isotropic

INTRODUCTION:

Ocular administration of drug is primarily associated with the need to treat ophthalmic Diseases. These are specialised dosage forms designed to be instilled onto the external surface of eye (topical) administered inside (intraocular) or adjacent (periocular) to the eye or used in conjunction with an ophthalmic device (1). Topical application of drugs to the eye is the well-established route of administration for the treatment of various diseases like dryness, conjunctiva, eye flu etc.The protective mechanisms of the eye such as Blinking, baseline, reflex lachrymation and drainage decrease the bioavailability of drug and also help to remove rapidly foreign substances like the dust particles bacteria, including drugs, from the surface of the eye (2). There are many eye related diseases which can effect and also eye vision, therefore marketed ophthalmic dosage forms are prepared which are classified as conventional and non-conventional (newer) drug delivery system.

- A large portion of the visual infections are deal with, by application or organization of medication arrangements as eye drops, 90% of the accessible ophthalmic preparations are conventional dosage forms because of the simplicity and convenience.(3)
- The most well-known issue related with ophthalmic medication is quick precorneal loss because of seepage and high tear liquid, Just 5% of the medication infiltrates into the cornea and reaches to the site of activity, and rest of the medication experiencing Tran's conjunctival drainage by means of nasolacrimal channel.(4)
- The challenging task for pharmaceutical formulator is to build up a formulation with enhanced visual maintenance, increased corneal absorption and lessened side effects therefore to beat this issue numerous plans have been produced, for example, in situgels, bio adhesive gels, nanoparticles, liposomes, small scale emulsions. (5) Microemulsion are the most encouraging Systems in light of their little size and lower surface strain, higher measure of dissolvability and corneal entrance. They are steady and clear arrangements and can give both hydrophilic and lipophilic medications to enhance visual maintenance.(6)

Major drawbacks in conventional dosage forms;

- The retention of the drug at the site of action is relatively poor.
- Administration of drug at frequent intervals which makes it inconvenient for the patient.
- Blurred vision, less bioavailability, lacrimation(7)

ANATOMY AND PHYSIOLOGY OF EYE:

Human eye, is the most complicated organ of human body, and also known as organ of sight and it is contained inside the cavity where it is completely protected from injuries and external damage, the eye ball is suspended in the bony socket by muscles and control its moments, and are cushioned by thick layer of fatty tissues which protect it during movement. Ocular drug delivery is the most difficult task for pharmaceutical scientists because of its unique structure, it restrict the entry of drug into the site of action, eye has a spherical shape included in the orbital cavity and protected by lids, With a diameter of 24 mm and a volume of 6.5 cm3, it weigh is about 7.5 several layers with specifics structures composes the eyeball and divide it in two segments: The anterior and posterior portion.

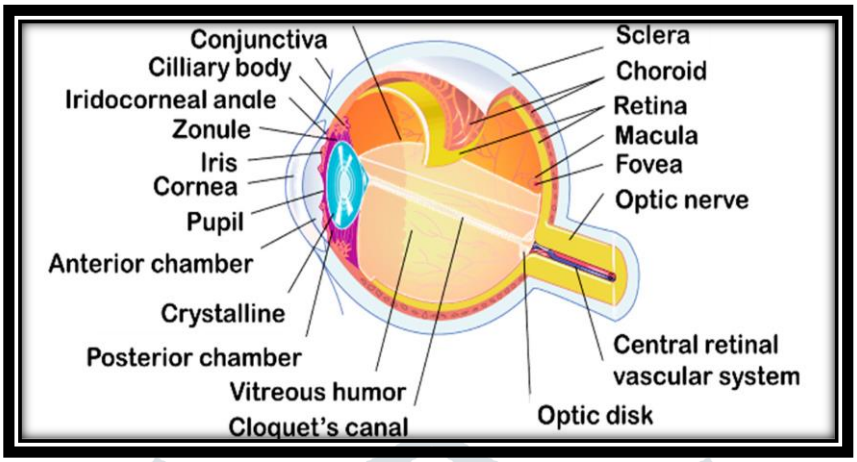


Figure 1. Schematic illustration of Ocular structures and Barriers (8, 9)

Three Different Layers of Eye:

The eye is surrounded by three different layers: the outer layer, the medium layer and the inner layer.

The outer layer; is composed by the cornea and the sclera. They are fibrous tissue and have a protective function for the eyeball. The sclera, continuous with the cornea, is an avascular, white, strong, and elastic tissue. It covers 80% of the eye's tunic. The cornea, joining the sclera at the limbus, is a thin (0.5 mm), avascular and transparent layer which allows the light penetration to the globe. The anterior and posterior segments of the eye are anatomically separated by the sclera and the cornea (Figure 1) (10)

The Middle layer; is a vascular envelope additionally called uvea, made up of iris, the choroid and the ciliary body. The iris is a contractile, roundabout film opened at its middle. At the back of the uvea, the choroid is an exceedingly vascularized layer. It supplies nutrients and oxygen to the iris and retinal photoreceptors. (11)

The innermost; tissue consist of retina and optic nerves, the neural tissue is composed of the photoreceptor (rods for the night and the peripheral vision and cones for the colour), the bipolar cells and the ganglion. (12)

VARIOUS PARTS AND ITS FUNCTIONS:

1)Cornea; Refracts light rays, the surface area of cornea is 1.3cm,in which anterior surface is 11.7mm (vertically) and 10.6mm (horizontally) , thickness is 0.52 from central and 0.67 from peripheral. It consist of different layers; basal layer (deepest layer), polyhedral cells (wing cells), squamous cells.

2) Sclera; protects and support eyeball Pupil; admits light

3) Choroid; Absorb stray light

4) Ciliary body; holds lens in place

5) Iris; regulates light entrance

6) Retina; contain sensory

7) Cones; Makes colour vision possible

8) Rods; Makes black and white vision possible

9) Optic nerve; Transmits impulse

10) Aqueous humour; clear and slightly alkaline liquid which is present in the anterior and posterior chambers of the eye, it resembles the blood plasma in composition but contains lesser amount of protein and glucose and more amount of ascorbic acid and lactic acid.(13)

EYE RELATED DISEASES:

Some eye problems are minor and go away. Others can cause vision loss. Learn about diseases of the eye, including symptoms, diagnosis, and treatment. The disease, symptoms and treatment related to the eyes is given as well as following in table. (14)

TABLE 1: Eyes, Disease, Symptoms and Treatments; (15)

DISEASE	SYMPTOMS	TREATMENTS
Cataract	blurred vision, Colours seems faded, Poor night vision	Cataract surgery
Glaucoma	Vision loss, Redness to the eye, Pain in the eyes	Eye drops, Laser surgery
Dry eye	Burning, itching, Redness of eye, Blurred vision	Cyclosporine eye drop eye drops (lotemax)
Low vision	Double vision, Headache, Blurred vision	Proper diet, and medicines
Eye infection	Pain/discomforting eyes, Itchy eyes, Burning in eyes, Eye won't stop tearing up	Broad-spectrum antibiotics, Macrolide antibiotics
Uveitis	Cloudy vision, Eye pain, Headache, Small pupil	Antibiotics and antiviral medications, Corticosteroid medications, Mydriatic eye drops(atropine)
Diabetic eye disease	Loss of vision, Discomfort in eyes	Healthy diet, Regular exercise
Conjunctivitis(pink eyes)	swollen conjunctiva, more tears than usual, itchy eyes, blurred vision	Antibiotics and Antiviral drugs

TABLE 2: Eyes Disease, marketed formulations and dosage forms: (16)

DISEASE	MARKETED FORMULATIONS	DOSAGE FORM
Cataract	Dexamethasone ophthalmic , Prednisolone acetate (1%)	Ophthalmic Eye drops, Ophthalmic Eye Suspension
Glaucoma	Latanoprost (XALATAN) , Travoprost (0.005%	Ophthalmic solution , Eye drops
Dry eye	Cyclosporine (0.05%), Lifitegrast (5%)	Ophthalmic emulsion, eye drops
Low vision	Dorzolamide, Brinzolamide	Ophthalmic Eye drops
e infection	Gatifloxacin(ZYMAR), Hydrocortisone	Ophthalmic eye drops , creams, lotions
Conjunctivitis (Pink Eyes)	Erythromycin, Azithromycin , Ciprofloxacin	Eye drops, ointments , suspensions

MICROEMULSION SCIENCE;

Micro emulsions (ME) are basically thermodynamically stable and clear mixtures of oil, water and surfactants, and sometimes also available in combination with co surfactants. In these types of preparations there are basically 2 phases, one is aqueous phase and another one is oil phase. The aqueous phase comprises of salt and different fixings while the oil phase comprises of various hydrocarbons, oils and waxes. Small scale emulsions are generally prepared by simple blending of components with no shear or weight, these are steady arrangements because of the presence of a large amount of surfactants, and they are either straightforward or translucent in appearance. High retention and absorption of smaller scale emulsion is because of their lower surface tension and little bead size (17).

The presence of micro emulsion has been distributed by Schulman and hoar in 1943. There works are the beginning stages of understanding micro emulsions. In the preparation of microemulsion the decision and determination of surfactant and co surfactant is critical (18).Generally the surfactants which are non-ionic are

chosen, because of their low irritation and poisonous quality. MEs are thermodynamically steady stage progress Systems, which have low surface pressure and little bead size (5– 200 nm), which may bring about high medication retention and penetration (19)

DIFFERENCE BETWEEN EMULSIONS AND MICROEMULSIONS:

The emulsions and micro emulsions are different in many ways, but some of the major differences between the emulsions and the micro emulsions are as follows: the most essential distinction between the emulsions and the micro emulsions is that their particles are of various sizes and diverse shapes. The micro emulsions persistently develop between the diverse structures which might be bead like or may even be swollen up misclles or the bi continuous structures which in some cases make the "water in oil" and the "oil in water" distinction superfluous.

Emulsions and Micro emulsions (In Fig.) are both stable dispersions of oil-in-water or water-in-oil. Surfactants are the principal agents that enable oil and water to mix. Emulsions are stable dispersions of immiscible liquids, but they are not thermodynamically stable. The following properties show the different between emulsion and Micro emulsions. (20).

Figure 2: Emulsion and Micro emulsions preparation

Table 3: Difference between Emulsion and Micro emulsions. (21, 22)

Property	**Emulsion (Macro emulsion)**	**Microemulsion**
Appearance	Cloudy	Transparent
Optical isotropy	Anisotropic	Isotropic
Optical isotropy	High	Ultra-Low

Microstructure	Static	Dynamic
Droplet size	>500 nm	20-200nm
Stability	Thermodynamically unstable	Thermodynamically stable and long shelf life
Phases	Biphasic	Monophasic
Preparation	Require a large input of energy	Facile preparation
Cost	Higher Cost	Lower Cost
Viscosity	High Viscosity	Low Viscosity with Newtonian Behaviour
Turbidity	Turbid	Transparent
Co surfactant Used	-No-	Yes
Surfactant Concentration	1-20 %	>10%
Size Range	0.5- 5 µ	<0.1 µ
Molecular Packing	Inefficient	Efficient
Micelle Diameter	20 nm +	3- 20 nm
Contact Position	Direct Oil / Water Contact at the Interface	No direct Oil and Water Contact at the Interface

TYPES OF MICROEMULSION:

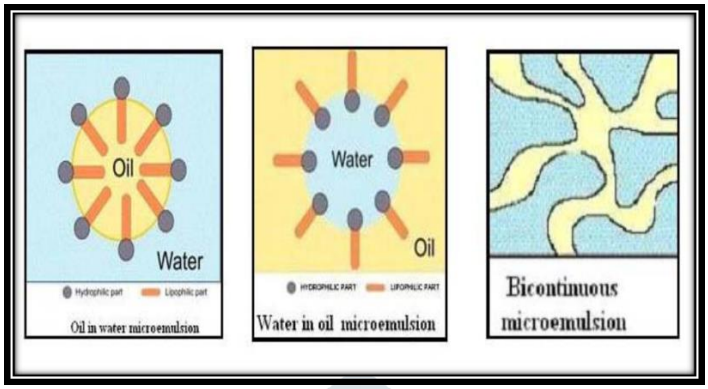
Winsor Classification:

Winsor I: With two phases, the lower (o/w) micro emulsion phases in equilibrium with the upper excess oil.

Winsor II: With two phases, the upper micro emulsion phase (w/o) micro emulsion phases in equilibrium with lower excess water.

Winsor III: With three phases, middle micro emulsion phase (o/w plus w/o, called bi-continuous) in equilibrium with upper excess oil and lower excess water.

Winsor IV: In single phase, with oil, water and surfactant homogenously mixture (23, 24)



METHODS OF PREPARATION OF MICROEMULSION:

Microemulsion prepared by following these methods; these are given as well as following;

I. **Phase Titration Method;** The micro emulsions can be set up by the stage titration strategy (unconstrained emulsification technique which can be portrayed with the assistance of stage graphs). Construction of the phase diagram is a functional approach to study the number of events undergoing when different components are mixed. These are formed with different shapes including micelles hexagonal, cubic, and lamellar depending on the composition. As quaternary phase diagram is a time consuming study and difficult to elucidate, pseudo ternary phase diagrams are prepared to find the zones including micro emulsion zone in which each side represents a particular component. The regions are separated into o/w or w/o micro emulsion by simply taking into account weather it is oil rich or water rich.(25)

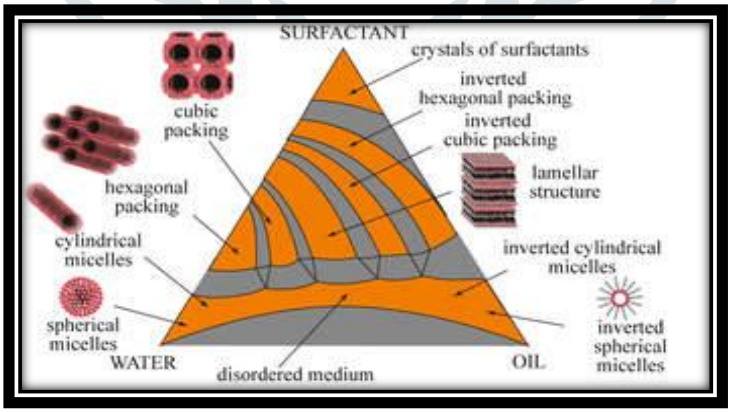


Figure 3: Pseudo ternary Phase Diagram of Oil, Water, and Surfactant of Microemulsion Region

II. **Phase Inversion Method;** Reversal of the micro emulsion happens because of the addition of excess of the dispersed phase or in response to temperature. At the season of stage reversal, extreme physical changes happen which incorporates the adjustments in the molecule estimate additionally which can additionally influence the medication discharge both in vitro and in vivo. This technique uses the changing in the unconstrained arch of the surfactant. This can be achieved by changing the temperature of the

System on account of Non-Ionic surfactants, which powers the progress from an O/w micro emulsion at low temperatures to a w/o micro emulsions at higher temperatures (transitional stage reversal.) at the season of cooling, the System crosses the purpose of zero unconstrained and flow insignificant surface strain, which advances the arrangement of the finely scattered oil beads. This strategy is additionally called the Phase Inversion Temperature Method (PIT). Be that as it may, rather than the temperature different parameters to be specific the pH esteem or the convergence of the salt can even be viewed as only rather than the temperature alone. Moreover, a progress in the unconstrained range of ebb and flow can be acquired by changing the water volume division. By progressively including water into oil, at first water beads are shaped in a continuous oil stage. By just simply expanding the water volume part changes the unconstrained ebb and flow of the surfactant from at first settling a w/o micro emulsion to an o/w micro emulsion at the reversal locus. The short-tied surfactants frame adaptable monolayers at the o/w interface bringing about a bi-consistent micro emulsion at the reversal point.(26)

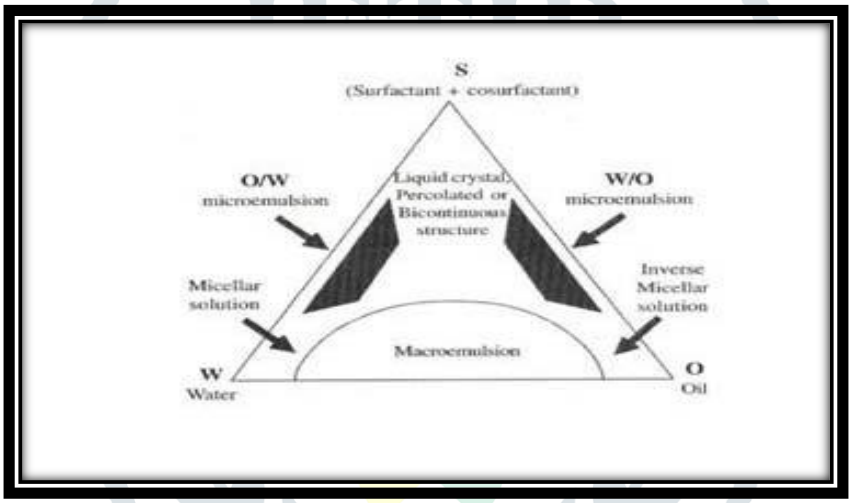


Figure 4: Hypothetical Phase region of Microemulsion system

CHARACTERIZATION OF MICROEMULSION:

There are various techniques by which micro emulsions are characterized. Because the micro emulsions are very complex, they have different parts engaged with their Systems, they have an expansive assortment of structures and furthermore there are different constraints appended to their strategies for portrayal, it is exceptionally hard to describe micro emulsions, yet their portrayal learning is especially imperative for their business misuse. Henceforth, correlative examinations utilizing the blend of different procedures are normally required to get a noteworthy perspective of the structure and the physicochemical properties of the micro emulsions.

For the physicochemical characterization of micro emulsion the basic components are:

- ✓ The dimensions and the microstructure of the micro emulsion.
- ✓ Phase behaviour and phase stability.
- ✓ The local molecular rearrangement.

- ✓ The surface features like charge distribution and the specific area.
- ✓ Shape
- ✓ Interaction and dynamics.

From these properties, the interactions and dynamics and the particle size are very much important as many general properties of the micro emulsions are governed by them.

There are various parameters on which the drug release from the micro emulsions depends such as droplet size, oil aqueous phase ratio, the distribution of drug in the phases of micro emulsion system and the rate of diffusion or the absorption in both phases (27)

Visual Observation; Microemulsion is usually observed to check their flow ability and clarity.

Interfacial Tension; by estimating the interfacial strain of the micro emulsion System, their properties and development can be considered. The specific low estimations of the interfacial pressure of the micro emulsion System are corresponded with stage conduct especially the presence of the surfactant stage or the centre stage micro emulsion in harmony with fluid and oil stages. For estimating the simple low interfacial strain turning drop mechanical assembly is utilized. The interfacial strains are taken out to quantify the state of the drop of low thickness stage and to pivot that into the round and hollow slim topped off with high thickness stage.

Centrifugation; The micro emulsion systems can be centrifuged at 5000 R.P.M. for 30 minutes and then checked for phase separation.

EVALUATION OF THE MICROEMULSIONS:

The micro emulsions are evaluated by the following techniques, they are

1) **Measurement of P^H:** The pH values of Micro emulsions were determined using digital pH meter standardized using P^H 4 and 7 buffers before use.
2) **Globule Size Analysis of the Micro emulsions:** The average globule size of the micro emulsions was determined by the photon correlation spectroscopy. Measurements were carried at an angle of 90°at 25°C. Micro emulsions were diluted with double distilled water to ensure that the light scattering intensity was within the instrument's sensitivity range. Double distilled water was filtered through 0.45µ membrane filters prior to globule size determination.
3) **Measurement of Electrical Conductivity:** The electrical conductivity of micro emulsions was measured with a conductivity meter equipped with inbuilt magnetic stirrer. This was done by using conductivity cell consisting of two platinum plates separated by desired distance and having liquid between the platinum plates acting as a conductor.
4) **Rheological Studies:** Changing the rheological characteristics help in determining the micro emulsions region and its separation from other related structure like liquid crystals bi continuous micro emulsions are dynamic structure with continuous fluctuation occurring between the bi continuous structure, swollen reverse micelle, and swollen micelle.

5) Viscosity Measurements: Micro emulsions are generally low viscosity systems. The viscosity measurements were performed using Brookfield viscometer at single mode (Spindle C-50). All the measurements were done in triplicate for 60 seconds at a temperature of 23°C.

6) Phase Behaviour Studies: Visual observation, phase contrast microscopy and freeze fracture transmission, electron microscopy can be used differentiate micro emulsions from liquid crystals and coarse emulsions. Clear isotropic one phase system are identified as micro emulsions whereas opaque system showing bifringence when viewed by cross polarized light microscopy may be taken as liquid crystalline system. (28)

7) Nuclear Magnetic Resonance Studies: The Fourier transform pulsed-gradient spin-echo (FTPGSE) technique uses the magnetic gradient on the samples and it allows simultaneous and rapid determination of the self-diffusion coefficients of many components.

8) Examination under Cross-polarizing Microscope: The micro emulsion systems are subjected to examination under cross polarizing microscope for the absence of birefringence to exclude liquid crystalline systems.

9) Limpidity Test (Percent Transmittance): The limpidity of the micro emulsion can be measured spectrophotometrically using spectrophotometer.

10) Assessment of the Rheological Properties: The rheological properties play an important role in stability. It can be determined by Brookfield digital viscometer. (29)

11) Long Term Stability: Stability can be examined according to ICH guidelines. The Microemulsion are stored under ambient conditions for 6 months, and the system was examined periodically after 1, 3, and 6 months by visual inspection and measurement of percent transmittance, pH, specific gravity, and rheological evaluation.

12) Determination of Thermal Stability: Twenty millilitres **(ml)** of drug-loaded micro emulsions are stored in a 25 ml transparent borosil volumetric container at three different temperatures, i.e. 4°, 25° and 40°C, 1°C in BOD for a period of 1 month. Samples are removed periodically for visual inspection to observe any physical changes like loss of clarity, coalescence and turbidity etc. Also, the samples can be observed for the determination of loss of aqueous phase that is an essential part of the micro emulsion stability.

13) Specific gravity testing at 28°C: To determine the specific gravity, a capillary gravity bottle method is used. Washed and dried, the precaution was necessary during the drying of the gravity bottle as a little amount of moisture could increase the errors in the data of the specific gravity of the samples. (30)

IDENTIFICATION TEST FOR TYPE OF MICROEMULSIONS:

a) **Dilution test:** If the continuous phase is added in micro emulsions, it will not crack or separate into phases. If water is added in o/w type of micro emulsions it will remain stable.

b) **Staining test:** Water soluble dye such as methylene blue or amaranth is added in water and micro emulsion is prepared with oil and surfactant. A drop of Micro emulsions is observed under microscope. Background is found to be blue / red and globule will appear colourless respectively.

c) **Dilatability test:** The Micro emulsions formed is diluted in 1:10, and 1:100, ratios with double distilled water to check if the system shows any signs of separation.

d) **Zeta Potential Measurement:** It must be negative or neutral, which indicate that droplets of micro emulsion having no charge and hence the system is stable. Zeta potential is determined by using Zetasizer. Zeta potential is essentially useful for assessing flocculation since electrical charges on particles influence the rate of flocculation. (31)

ADVANTAGES OF MICROEMULSION IN OPTHALMIC DRUG DELIVERY:

- High drug holding capacity, and good corneal penetration.
- It is used as bioavailability enhancers for poorly water soluble drug.
- Maximise ocular drug absorption through prolong contact time with corneal tissue.
- It reduces the frequency of administration.
- Minimal pre corneal drug loss.
- Doesn't cause blurred vision and non-greasy (32)

CHALLENGES IN MICROEMULSION BASED OCULAR DRUG DELIVERY:

- The concentration of surfactants and co-surfactants used must be kept low for toxicological reasons.
- Micro emulsion also suffers from limitations of phase separation.
- Sometimes causes blurring of vision.
- Dosage form cannot be terminate easily during emergency.
- Occasional drug loss during sleep or while rubbing eyes.(33)

CONCLUSION:

From the above study it was concluded that the microemulsion was prepared successfully and have good corneal penetration and prolong contact time with corneal tissues which may improve its therapeutic effectiveness, The main advantages of microemulsion is that it can be used to carry both the lipophilic drugs as well as the hydrophilic drugs, The absorption rate is tremendously increased in the case of micro emulsions, they are thermodynamically more stable than conventional dosage forms, The microemulsion systems are very much advantageous because of its many applications in the colloidal drug delivery systems for the purpose of controlled release of the drugs and for drug targeting.

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