CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Online at: http://www.iajps.com *Review Article*

NEW TECHNOLOGY RELATED TO DRUG DELIVERY OF MICROEMULSION FOR OCULAR DRUG DELIVERY

Pawan Bhandari*, Ashutosh Badola
M.Pharm, Pharmaceutics, Shri Guru Ram Rai University Dehradun,
School of Pharmaceutical Sciences.

Article Received: May 2021 **Accepted:** May 2021 **Published:** June 2021

Abstract:
Delivery of drugs into eyes using conventional dosage form or conventional drugs eg.solutions is a complicated and considerable challenges to the scientist for the treatment of ocular diseases. In Ocular drug delivery system the scientist faced many challenges due to unique structure, anatomy and physiology of eye. The aim of the present study was to develop Erythromycin Microemulsion for Ocular drug delivery. Micro emulsions (ME) are thermodynamically stable and clear mixtures of oil, surfactants, and water sometimes also available in combination with co surfactants. Erythromycin belongs to the class of Macrolide antibiotics & drug delivery through microemulsion via ocular enhaned bioavailability. 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. The microemulsion was prepared by using different ingredients are as follows: oleic acid as an oil phase, tween 80 as surfactant, ethanol as co surfactant and 0.5 N NAOH as aqueous phase. The optimization and formulation chart was carried out using 2^3 factorial design. The prepared microemulsion was evaluated by using various evaluation parameters such as PH, Particle Size and Zeta potential etc.

Keywords: *Microemulsion, Conventional dosage form, Thermodynamically, Surfactant, Co-surfactant, Isotropic, Bioavailability, Amphiphile, Patent, Evaluation of Microemulsion.*

Corresponding author:
Pawan Bhandari,
M.Pharm, Pharmaceutics,
Shri Guru Ram Rai University Dehradun,
School of Pharmaceutical Sciences.
E-Mail: pbhandari52538@gmail.com

QR code

Please cite this article in press Pawan Bhandari et al., ***New Technology Related To Drug Delivery Of Microemulsion For Ocular Drug Delivery****., Indo Am. J. P. Sci, 2021; 08(06).*

INTRODUCTION:

Micro emulsions (ME) are thermodynamically stable and clear mixtures of oil, water and surfactants, and sometimes also available in combination with co surfactants & it is formed by surfactant, co-surfactant, oil phase, aqueous phase. 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 [1]. The human eye is a Senstive and complex structure designed in a way that its physiology, anatomy, biochemistry, pre-physiology parameters render or requital it almost imperviable to foreign agents, pathogens, impurities along with drugs.The human eye is divided into two segments one is anterior segment & second one is posterior segment, in anterior segment (conjunctiva, cornea etc.) and in posterior segment (retina, vitreous humor etc.) in details it's shown in the figure1. 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. 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 7.5g. In human eye the corneal epithelium serves or represent one of the most rate limiting barrier which inhibit or hinders permeation of macromolecules and hydrophilic drugs. In human eye another common rate limiting barrier is stroma which prevents the diffusion of highly lipophilic drugs. The diffusion of highly liophilic drugs due to high amount of hydrated collagen contents [2].

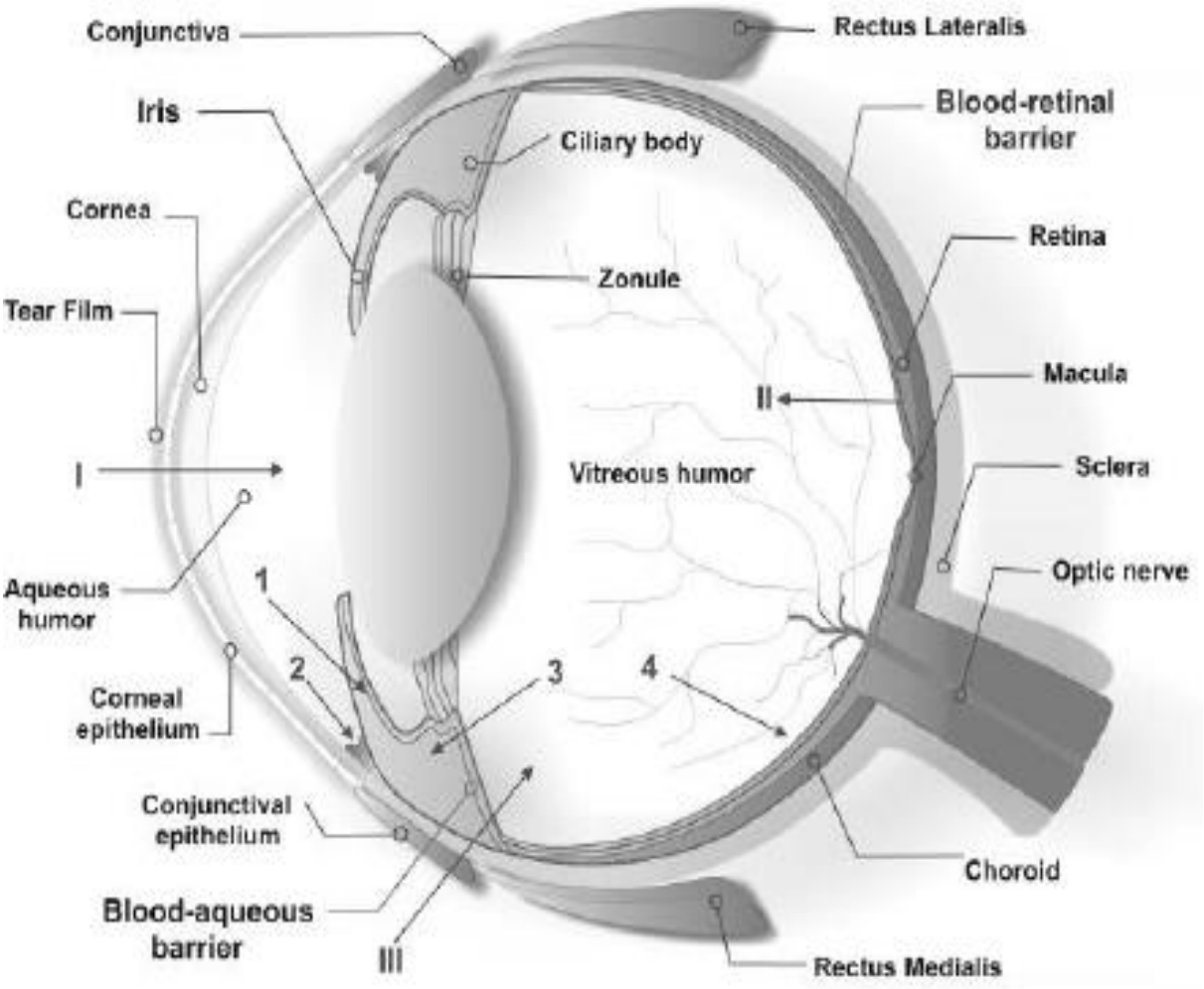

Figure1: Schematic illustration of ocular structures and barriers. Figure 1 is taken from Barriers et,al, 2009 [3,4].

A.Ocular drug delivery:

Ocular administration of drug is primarily associated or linked with the need to treat ophthalmic Diseases & ocular dosage form prevent from infection and minimizes the chance of bacterial infection in the eye. These are specialized dosage forms designed in a manner to treat the infections or to be instilled onto the different surface of eye such as external surface of eye topical, administered inside intraocular surface or used in conjunction with an ophthalmic controlling device [5]. In human eye the topical application or administration of drugs is the most significant route for the treatment of diseases & minimizes the chances of infection in the various diseases like eye flu, dryness, redness in the eye , conjunctiva etc. Human eye have a protective criteria or mechanism such as baseline, reflex lachrymation, blinking and drainage decrease the bioavailability of drugs administered and these mechanism can aslo help to remove dust particle, pathogens, bacteria, including drugs from the surface of human eye [6].

The following characteristics are required to optimize ocular drug delivery systems they are as follows [7] :

- A prolonged contact time of drug with the corneal tissue.
- Good corneal penetration.
- Appropriate properties such as rheological properties and concentration of viscolyzer.
- Concentration of surfactant & co-surfactant.
- Patient awareness & know about the ocular diseases.
- Easiness of installation or administration and removal for the patient.
- Easy to administered.

The challenging task for pharmaceutical formulator or pharmaceutical researcher is to build up a formulation with enhanced visual maintenance, increased corneal absorption and lessened side effects therefore to beat and control this issue numerous plans and strategies have been produced, for example, various pharmaceutical formulation such as in situgels, nanoparticles,bio adhesive gels, liposomes, small scale emulsions [8].

B. ANATOMY & PHYSIOLOGY OF EYE

Human eye, is the most sensitive & complicated organ of human body, human eye is located/ contained inside the cavity where it is protected from impurities, dust particle, injuries and external damages. Human eye is also known as organ of sight. In Ocular drug delivery system the scientist faced many challenges due to unique structure, anatomy and physiology of eye. Human eye with a diameter of 24nm & a volume of 6.5cm3, human eye weigh is about 7.5g. the human eye is composed of different layers & classified it in two segments: one is anterior and second one is posterior.

There are many factors which effects the administration of drug they are as follows [9,11]:

1. Anantomical & physiological features
   - Secretion of tears
   - Blinking of human eye
   - Reflex lachrymation
   - Nasolachrimal drainage

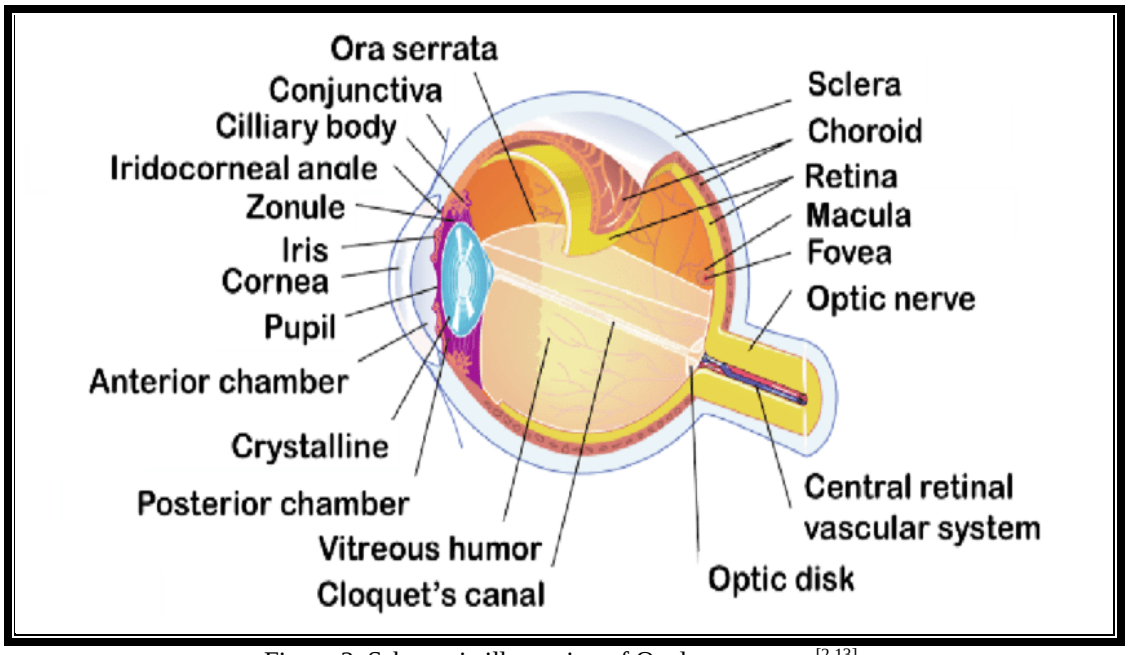

Figure 2. Schematic illustration of Ocular structure [2,13].

Different Layers of Human Eye:

Human eye is surrounded by three different layers they are as follows:

- ❑ Outer layer
- ❑ Medium layer
- ❑ 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 [14].
- **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. It supplies nutrients and oxygen to the iris and retinal photoreceptors [15].
- **The innermost layer:** 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 [16].

Eye related Diseases:

Some eye problems are minor and go away.The disease, symptoms and treatment related to the eyes is given as well as following in table:

TABLE 1: Eyes, Disease, Symptoms and Treatments; [17]

DISEASE	SYMPTOMS	TREATMENTS
Glaucoma	Vision loss, Redness to the eye, Pain in the eyes	Eye drops, Laser surger
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
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: [18]

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

TABLE 3: Marketed Product of Ocular Drug Delivery System [19]

Various list of dosage form used in ocular drug delivery are mentioned below in table 3:

Brand Name	Dosage form	Uses
Acuvail	8.5mg/ml ketorolac tromethamine solution (0.45%) in a single-use vial.	Cataract surgery
Alocril	2% is a clear, yellow, sterile solution	Allergic conjuctivis
Elestat	0.05% epinastine HCl ophthalmic solution	Allergic conjuctivis
Ozurdex	0.7 mg dexamethasone intravitreal ocular implant.	Retinal vein occlusion
Pred Forte	1% prednisolone acetate ophthalmic suspension, USP.	Bulbar conjunctiva
Zymar	0.3% gatifloxacin ophthalmic solution.	Bacterial conjunctiva
Zymaxid	0.5% gatifloxacin ophthalmic solution.	Bacterial conjunctiva
Trivaris	80mg/mltriamicinolone acetonide injectable suspension	Sympathetic ophthalmia

C. MICROEMULSION SCIENCE;

- Microemulsion can be defined in many ways, one of the best definitions of microemulsions is from Danielsson and Lindman "a microemulsion is a system of water, oil and an amphiphile which means having a tendancy of both hydrophilic and lipohilic componds or drug, which is a single optically isotropic and thermodynamically stable liquid solution". 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. Microemulsion formed by using Surfactant, co surfactant, oil phase, & aqueous phase [1].

- Microemulsion & emulsion can be defined or classified in many ways such as appearance, optical isotropy, droplet size, viscosity, surfactant concentration, size rang, miscelle diameter, microstructure, cost etc. Microemulsion have low surface pressure & little bead size in range (5-20nm), which may result about penetration and high medication retention[20]. Difference between emulsion and microemulsion are shown in table 4.

Table 4: Difference between emulsion and microemulsion[21,22].

Property	Emulsion (Macro emulsion)	Microemulsion
Appearance	Cloudy	Transparent
Optical isotropy	Anisotropic	Isotropic
Microstructure	Static	Dynamic
Droplet size	>500 nm	20-200nm
Stability	Thermodynamically unstable	Thermodynamically stable and long shelf life
Size Range	0.5- 5 µ	<0.1 µ
Cost	Higher Cost	Lower Cost

TYPES OF MICROEMULSION:

Three type of microemulsion are most likely to be formed depending on the composition:

- Oil in water micro-emulsions wherein oil droplets are dispersed in the continous aqueous phase.
- Water in oil micro-emulsions wherein water droplets are dispersed in the continous oil phase.
- Bi-continous micro emulsion where in micro domains of oil and water are inter dispersed within the system.

In all three types of microemulsions, the interface is stabilized by an appropriate combination of surfactants and/or co-surfactants.

D. METHODS OF PREPRATION OF MICROEMULSION

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

1. Phase Titration Method

2. Phase Inversion Method

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[23].

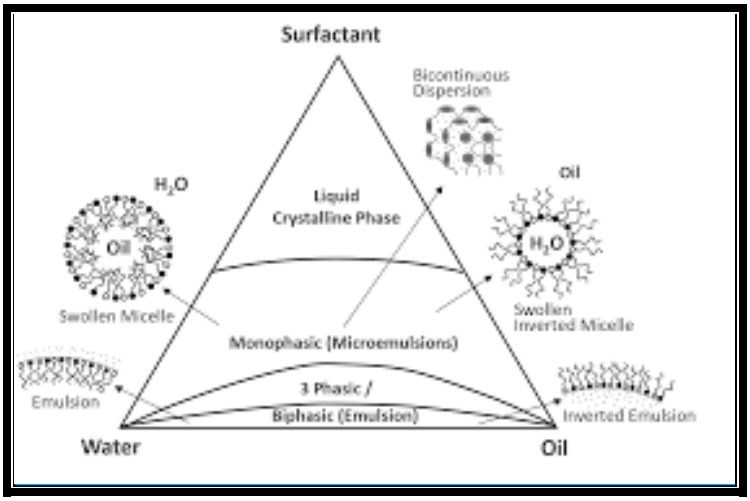

Figure 3: Pseudo ternary Phase Diagram of Oil, Water, and Surfactant of Microemulsion

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 [24].

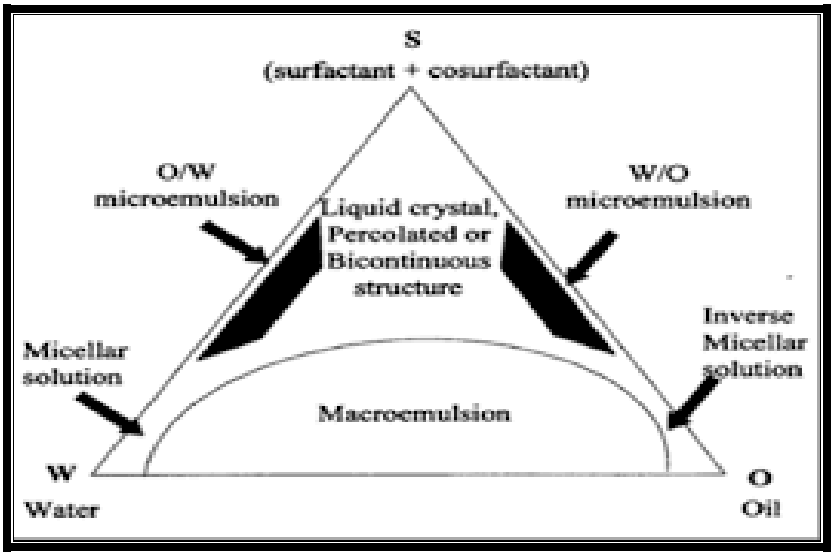

Figure 4: Hypothetical Phase region of Microemulsion system

E. CHARACTERIZATION OF MICROEMULSION:

Characterization of microemulsion can be divide into 3 major parameters they are as follows physical evaluation, electrochemical evaluation, and microscopic evaluation. Physical nature of microemulsion can be determine by appearance, viscosity, and optical clarity etc. Conductivity measurements can be used to determine whether a microemulsion is oil-continuous or water continuous and may also be used to monitor or evaluate percolation or phase inversion phenomena. To investigate both the structural and dynamic features of microemulsion dilectric measurement have been used. Small droplet size of microemulsion give an indication that the microemulsion are formed slightly & shows optical clarity which is evaluated by microscopic methods & also with light scattering method[25].

The basic components for the physiochemical characterization of microemulsion are as follows:

- Shape.
- Size.
- Surfactant & co surfactant ratio.
- Interfacial tension.
- Interaction and dynamics.
- The local molecular rearrangement.
- Phase behaviour and phase stability properties.

- The dimensions of the micro emulsion.
- Microstructure.
- Centrifugation; The micro emulsion systems can be centrifuged at 5000 R.P.M. for 30 minutes and then checked for phase separation [26].

ADVANTAGES OF MICROEMULSION IN OPTHALMIC DD:

- Ability to carry both hydrophilic & lipophilic drug.
- It is used as bioavilability enhancer for poorly water soluble drug.
- Good corneal penetration.
- High capacity of drug holding.
- Maximise ocular drug absorption through prolong contact time with corneal tissue.
- Reduces the frequency of drug adminstartion.
- It can improve the efficacy of a drug, minimizing side effects with reduced total dose[27].

F. Recent patents on microemulsion for ocular therapeutics

Many inventors or Researcher or formulator patent on ocular drug delivery utilizing microemulsion as a delivery system; in this review article only the patent mentioned in the past five years are listed below in table 5.

Table 5: Recent patents filed dealing with ocular MEs

Recent patent	Drugs used	surfactants	Co-surfactant	Other ingredients
Sergioetal., WO154985A1, 2011[49	Steroids (difluprednate), prostaglandin (latanoprost) NSAID(diclofenac), antioxidant,and pegaptanib	d-α-tocopherylPEG 1000succinate	Glycerol	VitaminE, MCT,and disodium phosphate
Gobel, European patent EP2485714A1, 2012[50]	Tacrolimus	Lecithin,decylglucoside, span80(sorbitan monooleate),andbrij30 (polyoxyethylene(4)laurylether	Pentylene glycol, propylene glycol,and PEG-20	Dibutyl adipate, isopropyl myristate,and tartaricacid
Carlietal., USPatentUS 8414904B2, 2013[51]	Prostaglandin analogue (latanoprost, travoprost,and bimatoprost	Tween80, brij52,56,58	Tween20	Ethyloleate, miglyol812, ricinusoil sorbitol, glycerol, chlorobutanol, and buffer(pH7.4

Description and outcome of the study

The inventors developed o/w ME for encapsulation of water insoluble drugs for topical ophthalmic application.The developed ME carrierre mainedstable for aperiod of 6months displaying a particle size of 15nm without any signs of instability or separation

G. EVALUATION OF THE MICROEMULSIONS:

1) Measurement of PH: The pH values of Micro emulsions were determined using digital pH meter standardized using PH 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.

3) Measurement of Electrical Conductivity: The electrical conductivity of micro emulsions was measured with a conductivity meter equipped with inbuilt magnetic stirrer.

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

9) 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.

10) 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[29].

11. **Assessment of the Rheological Properties**: The rheological properties play an important role in stability. It can be determined by Brookfield digital viscometer [30].

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. MEs may constitute an effective system for the delivery of both water soluble and insoluble drugs to the ocular tissues without compromising the convenience to the patients as well as ophthalmologists for adjustment of dose and dosing frequency.

Future Prospects:

The ME systems for ocular delivery have been reported to possess excellent physicochemical properties and stability. Apart from this, they are easy to fabricate and characterize. MEs are expected to deliver any drug to both the anterior and posterior segments of the eye, at the right time in a safe and reproducible manner at required level. MEs is the effective treatment of ocular diseases.

ACKNOWLEDGEMENT:

Dr. Ashutosh Badola would like to acknowledge the support during this review article from, SGRRU,

Dehradun (U.K.), for its esteemed support and encouragement.

REFERENCES:

1. Sushama Talegaonkar, Adnan Azeem, Farhan Ahmad J, Roop Khar K, Shadab Pathan A, Zeenat Khan I; Micro emulsions: A Novel approach to enhanced drug delivery; Recent Patents on drug delivery and formulation, 2008; 2: 238-257.
2 A.Urtti,"Challenges and obstacles of ocular pharmacokinetics and drug delivery," Advanced Drug Delivery Reviews, vol.58,no. 11,pp.1131–1135,2006
3. https://www.researchgate.net/figure/Schematic-illustration-of-ocular-structures-and-barriers-The-primary-physiologic_fig1_233806768.
4. J. Barar, M. Asadi, S. A. Mortazavi-Tabatabaei, and Y. Omidi, "Ocular drug delivery, impact of in vitro cell culture models," Journal of Ophthalmic and Vision Research, vol.4,no.4,pp.238– 252,2009.
5. Gan, L,.Wang, J.; Jiang, M.; Bartlett, H.; Ouyang, D.; Eperjesi, F.; Liu, J.; Gan, Y. Recent advances in topical ophthalmic drug delivery with lipid-based Nano carriers. Drug Discover. Today 2013, 18, 290– 297
6. Lee VHL, Robinson JR: Topical ocular drug delivery: recent developments and future challenges. Journal of Ocular Pharmacology 1986; 2: 67–108.
7. Keister JC, Cooper ER, Missel PJ, Lang JC and Hager DF: Limits on optimizing ocular drug delivery Journal of Pharmaceutical Science 1991; 80:50-53.
8. Sahoo KS, fahima SAD, kumar K: Nanotechnology in ocular drug delivery, Drug delivery today 2008; 13: 144-151.
9. Lee VHL: Precorneal, corneal and postcorneal factors. In AK Mitra, Ophthalmic Drug Delivery Systems. Marcel Dekker, New York, Edition 1, 1993:59:81.
10. Tang NEML, Zuure PL, Pardo RD, Keizer RJW and Van Best JA: Re.ex lacrimation in patients with glaucoma and healthy control subjects by uorophotometry. Invest Ophthalmologic Visual Science 2000; 41: 709–714.
11. White WL, Glover AT and Buckner AB: Effect of blinking on tear elimination as evaluated by dacryoscintigraphy Ophthalmology. 1991; 98: 367–369.
12. Henry grey; anatomy of the human body, the organ of sense and common integument, the organ of sight (1821- 1865)
13. Hugh Davson honorary research associate, department of physiology university of London, author of physiology of the human eye.
14. Alany RG, Rades T, Nicoll J, Tucker IG and Davies NM: W/O micro emulsions for ocular delivery: Evaluation of ocular irritation and precorneal retention. Journal of Controlled Release 2006; 111: 145152.
15. Robinson JC: Ocular anatomy and physiology relevant to ocular drug delivery, Ophthalmic Drug Delivery Systems, New York, A.K. Mitra Edition, 2006, 29– 57.
16. Lawrence MJ: Microemulsion-based media as novel drug delivery systems, Advanced Drug Delivery. Rev. 2000; 45: pp. 89–121.
17.Janoria KG, Gunda S, Boddu SH, Mitra AK. Novel approaches to retinal drug delivery. Expert Opin Drug Deliv 2007;4:371-88
18. Hasse A., Keipert S., Development and characterization of micro emulsions for ocular Application, Eur. J. Pharm. Bio pharm.,2012; 430: 179-183.
19. www.allergan.com.
20. Paul B.K. and Moulik S.P, Micro emulsions: Over view, J. Disp. Sci. Technol, 2007; 18: 301-36.
21. Fialho SL: New vehicle based on a microemulsion for topical ocular administration of Dexamethasone. Clinical Express Ophthalmology 2004; 32: 626–632.
22. Chien YW: Ocular drug delivery and delivery systems, special edition, 269-296.
23. Aboofazeli R., Lawrence MJ, Pseudo-ternary phase diagrams of systems containing Water-lecithin-alcoholisopropyl myristate, Int. J. Pharm, 2011; 93: 161-175
24. Eskandar Moghimipour., Anayatollah Salimi., Fatemeh Leis., Preparation and Evaluation of Tretinoin Microemulsion Based on Pseudo-Ternary Phase Diagram, Advanced Pharmaceutical Bulletin, 2012;2(2):141-147.
25. D. P. Acharya and P. G. Hartley, "Progress in microemulsion characterization," Current Opinion in Colloid and Interface Science,vol.17,no.5,pp.274–280,2012.
26. Parag Patel., Mansi A Monpara., S N Mandal., Nikita Patel., Rajesh KS., Formulation and Evaluation of Microemulsion Based Gel of Itraconazole, Pharma gene, 2009; 1, (2):32-36
27. K. P. Sampath Kumar1*, Debjit Bhowmik2, Shravan Paswan3, Shweta Srivastava4 Department of pharmaceutical sciences, Karpagam University, Coimbatore, Tamil Nadu, India, Recent Challenges and Advances in Ophthalmic Drug Delivery System, THE PHARMA INNOVATION,2012 1(4).

28. Shafiq un Nabi S, Shakeel F, Talegaonkar S; Formulation development and optimization using Nano emulsion technique: A technical note; AAPS Pharm Sci Tech., 2007; 8: 1-6.
29. Badawi, Nour, Sakran, El-Mancy; Preparation and Evaluation of Microemulsion Systems Containing Salicylic Acid; AAPS Pharm Sci Tech., 2009; 10: 1081-1082.
30. Sarkhejiya Naimish A, Nakum Mayur A, Patel Vipul P, Atara Samir A, Desai Thusarbindu R; Emerging Trend Of Microemulsion In Formulation And Reserach; International Bulletin of Drug Research.,2013 1(1): 54-83.