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A REVIEW ON TOPICAL MICROEMULSION FOR ANTIBACTERIAL ACTIVITY

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ABSTRACT

Microemulsions have emerged as novel vehicles for drug delivery that allow sustained or controlled release for percutaneous, peroral, topical, transdermal, ocular, and parenteral administration of medicaments. They offer the advantage of spontaneous formation, ease of manufacturing and scale-up, thermodynamic stability, improved drug solubilization of hydrophobic drugs, and bioavailability. Topical formulations are attractive alternatives to oral formulations and offer several advantages, such as avoiding first-pass hepatic metabolism and gastric degradation. The major obstacle to drug delivery across the skin (transdermal) is the barrier nature of the skin, which limits the permeation of molecules. Skin penetration enhancement techniques have been developed to improve bioavailability and increase the range of drugs for which topical and transdermal delivery is viable. Microemulsions are shown to be an effective dermal delivery mechanism for several active ingredients for pharmaceutical and cosmetic applications. Topical microemulsions allow rapid penetration of active molecules due to the large surface area of the internal phase, and their components reduce the barrier property of the stratum corneum. Microemulsions thereby enhance dermal absorption compared with conventional formulations and are therefore a promising vehicle due to their potential for transdermal drug delivery. This review paper gives information about microemulsions.

KEYWORDS: Microemulsion, Topical Drug Delivery, Drug Absorption from Topical Formulations, Applications.

INTRODUCTION

Topical preparations pertain to medicaments applied to the surface of a part of the body and are a term used to describe formulations that have effects only in a specific area of the body and are formulated in such a manner that the systemic absorption of the medicament is minimal. The methods involved in conventional topical drug delivery involve either assisting or manipulating the barrier function of the skin (topical antibiotics, antibacterial, emollients, sunscreen agents) or breaching the horny layer at the molecular scale to direct drugs to the viable epidermal and dermal tissues without using oral, systemic or other therapies.[1]

The skin and underlying soft tissues are frequent sites of bacterial infection, and they are one of the most common reasons for administering antibiotic therapy. Skin infections range from relatively benign, uncomplicated conditions (e.g., carbuncles, impetigo) to complicated ones (e.g., significant abscesses, traumatic wounds, and diabetic foot infections). The most common pathogens involved with skin infections are Gram-positive cocci, Staphylococcus aureus, and streptococci.[2] Microemulsions are homogeneous thermodynamically stable dispersions of oil, water, and a surfactant, usually combined with a co-surfactant. The term microemulsion was coined by Schulman and co-workers (1959). Oil and water are two immiscible liquids. Hence, the emulsion formed is unstable and separates into constituent phases. Emulsifier decreases the interfacial tension at the oil/water interface and stabilizes emulsion. Surfactants are a group of amphiphilic surface-active agents that act as emulsifiers and help make the emulsion stable. A potential advantage is that they are thermodynamically stable and require very little energy to formulate emulsion. Microemulsions are potent antimicrobial agents. Microemulsions have proven to be one of the powerful delivery agents of lipophilic drugs and their controlled release.[3] Microemulsion increases the transdermal permeation of drugs by interacting with the stratum corneum and changing the structural rearrangement of its lipid layers, thereby acting as a penetration enhancer. Microemulsions can deliver more significant amounts of water and topically applied agents into the skin than water alone or other traditional vehicles because they act as a better reservoir for a poorly soluble drug through their capacity for enhanced solubilization.[4]

Topical Drug Delivery Systems[5]

Topical drug administration involves localised drug delivery to the body, for example, ophthalmic tissue, the vaginal epithelium, and skin for local or systemic effects. The main

route of topical drug administration is the skin due to the fact that it is the largest human organ of the integumentary system.

Anatomy and Physiology of The Skin[6,7]

Skin is one of the most readily accessible organs on the human body for topical administration and is the main route of the topical drug delivery system. The total area of skin is about 20 square feet. The skin protects us from microbes, and the elements help regulate body temperature and permit the sensations of touch, heat, and cold. The pH of the leather varies from 4 to 5.6. Sweat and fatty acid secreted from sebum influence the pH of the skin surface. The skin is composed of three layers.

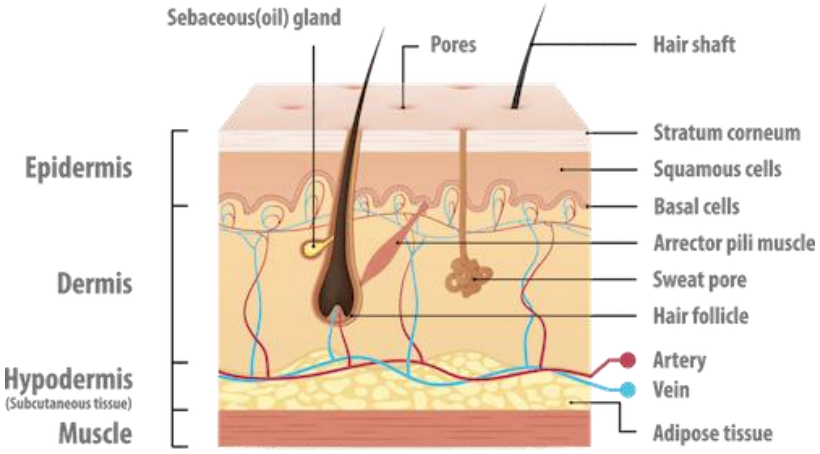

Fig No 1: Structure of Skin.

1. Epidermis

The multi layered epidermis varies in thickness, depending on cell size and number of cell layers of epidermis, ranging from 0.8 mm on palms and soles down to 0.06 mm on the eyelids. It consists outer stratum corneum and viable epidermis.

2. Dermis

The dermis is a 3 to 5mm thick layer composed of a matrix of connective tissue, which contains blood vessels, lymph vessels, and nerves. The cutaneous blood supply has an essential function in regulating body temperature. It also provides nutrients and oxygen to the skin while removing toxins and waste products.

3. Hypodermis

The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as a fat storage area. This layer helps to regulate temperature provides nutritional support and

mechanical protection. It carries principal blood vessels and nerves to the skin and may contain sensory pressure organs.

Drug Absorption From Topical Formulations[8]

The total amount of active ingredients absorbed in topical applications varies greatly depending on many factors, including the region of application, the frequency with which it is applied, and the viscosity or thickness of the involved vehicle. Other factors influencing drug absorption include the application location, age, and skin condition. An active ingredient can reach the dermis more quickly if not keratinized. The drug diffusion through the skin is managed in the best topical formulations by ensuring that the drug is only soluble enough in the vehicle to allow drug release at the desired rate. This is accomplished by assuring that the whole drug is dissolved in water.

Basic Principle of Permeation[9]

It is well known that substances usually penetrate the skin by three different routes: through the stratum corneum between the corneocytes (intercellular route); through these cells and the intervening lipids (intracellular route); or through the skin appendages, such as hair follicles and sweat glands. Molecules with adequate solubility in water and oil, with a log of oil/water partition co-efficient between 1 and 3 and a molecular weight lower than 0.6kDa, may penetrate the skin.

Factors Affecting Topical Absorption Of Drug[10]

- **Physiological factors**

1. Skin thickness.
2. Lipid content.
3. The density of hair follicles.
4. The density of sweat glands.
5. Skin pH.
6. Blood flow.
7. Hydration of skin.
8. Inflammation of skin.

- **Physicochemical factors**

1. Partition coefficient.
2. The molecular weight (<400 Dalton).

3. The degree of ionisation (only unionised drugs gets absorbed well).
4. Effect of vehicles.

Advantages Topical Drug Delivery[11]

- Avoidance of first pass metabolism.
- Convenient and easy to apply.
- Avoidance of the risks and inconveniences of intravenous therapy and of the varied conditions of absorption, like pH changes, presence of enzymes, gastric emptying time etc.
- Achievement of efficacy with lower total daily dosage of drug by continuous drug input.
- Avoids fluctuation in drug levels, inter- and intrapatient variations.
- Ability to easily terminate the medications, when needed.
- A relatively large area of application in comparison with buccal or nasal cavity.
- Ability to deliver drug more selectively to a specific site.
- Avoidance of gastro-intestinal incompatibility.
- Providing utilization of drugs with short biological half-life, narrow therapeutic window.

Disadvantages Topical Drug Delivery[12]

- Excessive irritability of the skin.
- The risk of an allergic response.
- Some drugs have a low permeability through the skin.
- Large-particle drugs are difficult to absorb via the skin.
- Contact dermatitis causes skin inflammation.
- The occurrence of a bubble during emulgel formulation.

Microemulsions[13]

Microemulsions, often in conjunction with a co-surfactant, are transparent, inert, isotropic liquid mixtures of oil, water, and surfactant. Microemulsions are bicontinuous systems consisting of significant phases of separated water and oil by a surfactant/co-surfactant rich interfacial region. Such systems have advantages over traditional emulsions in that they are thermodynamically stable and spontaneously generated liquid systems.

Structure of Microemulsion[14]

Microemulsions or Micellar emulsions are dynamic systems in which the interface is continuously and spontaneously fluctuating. Structurally, they are divided into oil in water (o/w), water in oil (w/o), and bi-continuous microemulsions. In w/o microemulsions, water droplets are dispersed in the continuous oil phase, while o/w microemulsions are formed when oil droplets are distributed in the ongoing aqueous phase. In a system where water and oil are similar, the bi-continuous microemulsions may result. The mixture of oil, water, and surfactants can form a wide variety of structures and phases depending upon the proportions of the component.

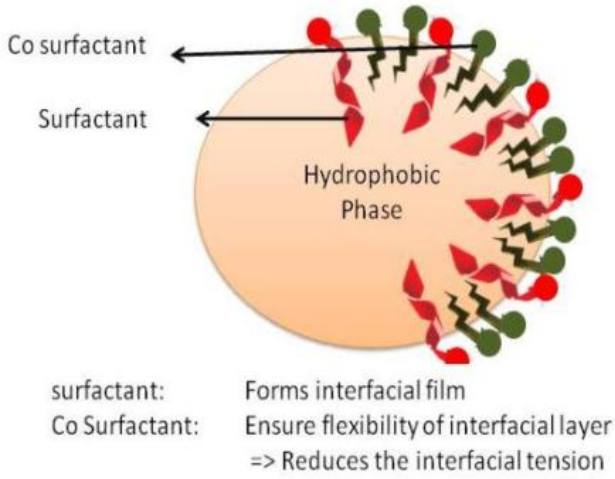

Fig No 2: Structure of Microemulsion.

Theories of Microemulsion Formation and Stabilization[15]

There are three main theories of microemulsion formation and stabilization.

1. In mixed film theory, the interfacial film is considered a duplex film, having different properties on the water and oil sides of the interface. According to this theory, the micro-emulsion can form instantaneously and spontaneously generate a negative interfacial tension in the surfactant and co-surfactant in working together. The film, which may consist of surfactant and co-surfactant molecules, is considered a liquid „two dimensional" third phase in equilibrium with oil and water. Such a monolayer could be a duplex film, i.e., giving different properties on the waterside and oil sides.
2. Solubilization theory considers microemulsions as swollen micellar systems, i.e., solutions with solubilized water or solubilized hydrocarbon; in effect, one-phase systems. The microemulsion formation involves soluble oil and water phases by micelles or

reverses micelles. It gradually becomes more prominent in micellar, and swelling to a specific size range result.

3. The thermodynamic theory proposes that the free energy of formation of the microemulsion, ΔGm, consists of different terms, such as interfacial free energy, the energy of interaction between the droplets, and an entropy term. Irrespective of the mechanism of microemulsion stabilization, the reduction of the interfacial free energy to a very low value is critical in facilitating microemulsion formation.

Construction of Phase Diagram[16]

Pseudo-ternary phase diagrams of oil, water, and co-surfactant/surfactants mixtures are constructed at fixed co-surfactant/ surfactant weight ratios. Phase diagrams are obtained by mixing the ingredients, pre-weighed into glass vials, titrated with water, and stirring well at room temperature. The formation of the Monophasic/Biphasic system is confirmed by visual inspection. If turbidity appears followed by phase separation, the samples are considered a biphasic system. Monophasic, clear, and transparent mixtures are visualized after stirring, and the samples are marked as points in the phase diagram. The area covered by these points is considered the microemulsion region of existence.

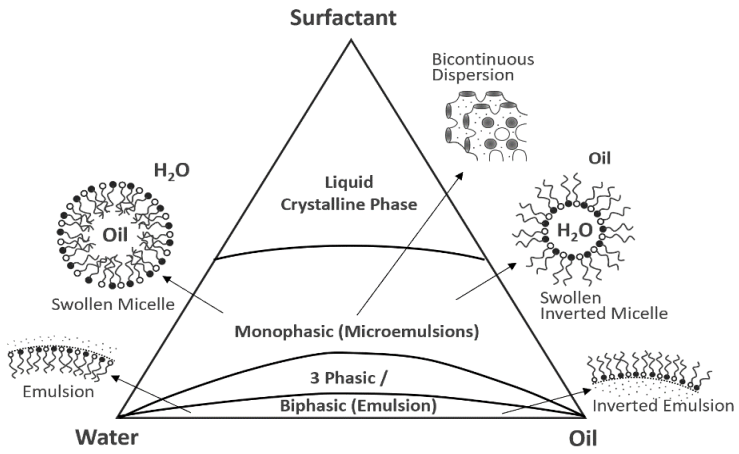

Fig No 3: Construction of Phase Diagram.

Method of Formulation[17]

Microemulsions are prepared when interfacial tension at the oil/water is kept very low. The interfacial layer is kept very flexible, and the fluid concentration of surfactants should be high enough to give surfactant molecules to stabilize the microemulsion at an extremely low interfacial tension. Two main methods are reported for the formulation of the microemulsion; these are

1. Phase Inversion Method
2. Phase Titration Method

1. Phase titration method

Microemulsions are prepared by the spontaneous emulsification method, illustrated with the help of phase diagrams. Phase diagram construction is a practical approach to studying complex series of interaction that occurs when different components are mixed. The aspect of the phase diagram is phase equilibrium and demarcation of phase boundaries. Most often, pseudo-ternary phase diagrams are constructed to figure out microemulsion zone, as quaternary phase diagram is time-consuming and challenging to interpret.

2. Phase inversion method

Phase inversion of microemulsion happens upon adding an excess of the dispersed phase. Phase inversion leads to radical physical changes as particle size changes that alter drug release. During cooling, this system crosses the point of zero spontaneous curvature and minimal surface tension, prompting the formation of finely dispersed oil droplets. Microemulsions can be prepared by controlled addition of lower alkanols (butanol, pentanol, and hexanol) to milky emulsions to produce transparent solutions comprising dispersions of either o/w or w/o or colloidal dispersions. The lower alkanols are called co-surfactants. They lower the interfacial tension between oil and water.

Ingredients of Microemulsion[18,19]

Various ingredients are used in the formulation and development of microemulsions. Mainly oil and surfactants are used in microemulsion they should be biocompatible, non-toxic and clinically acceptable. Main components of microemulsion are

1. Oil phase
2. Aqueous phase
3. Surfactant
4. Co-surfactant

1. Oil Phase

Oil is one of the most important microemulsion components because it can solubilize the required dose of the lipophilic drug. It increases the fraction of lipophilic drugs transported via the intestinal lymphatic system. Oil is defined as any liquid having low polarity and low

miscibility with water. The examples of such phases are cyclohexane, mineral oil, toluene, & vegetable oil etc.

2. Aqueous Phase

Generally, the aqueous phase contains hydrophilic active ingredients and preservatives. Sometimes Buffer solutions are used as aqueous phase.

3. Surfactants

The surfactant chosen must be able to lower the interfacial tension to a minimal value which facilitates the dispersion process during the preparation of the micro-emulsion and provide a flexible film that can readily deform around the droplets and be of the appropriate lipophilic character to give the correct curvature at the interfacial region. It is generally accepted that low HLB surfactants are favored for the formulation of w/o micro-emulsion, whereas surfactants with high HLB (>12) are preferred for the formation of o/w micro-emulsion. Surfactants having HLB more significant than 20 often require the presence of co-surfactants to reduce their effective HLB to a value within the range necessary for micro-emulsion formation.

4. Co-surfactants

In most cases, single-chain surfactants alone cannot sufficiently reduce the o/w interfacial tension to enable a micro-emulsion to form. The presence of co-surfactants allows the interfacial film sufficient flexibility to take up different curvatures required to develop microemulsion over a wide range of compositions. If a single surfactant film is desired, the lipophilic chains of the surfactant should be sufficiently short or contain fluidizing groups (e.g., unsaturated bonds). Short to medium chain length alcohols (C3-C8) are commonly added as co-surfactants which further reduce the interfacial tension and increase the fluidity of the interface.

EVALUATION[20,21,22]

1. Appearance

The microemulsions were checked for optical transparency and homogeneity by visually observing against the light. The monophasic systems were also checked for the presence of any undissolved drug or solid particulates.

2. Zeta potential

The assessment of the physical stability of colloidal dispersions is characterized by measuring zeta potential of microemulsions. This was measured using Malvern Zetasizer.

3. Viscosity

The viscosity of microemulsion was measured using a Brookfield viscometer with spindle LV-S63.

4. pH

pH was determined using pH meter.

5. Percent Transmittance Test (Limpidity Test)

The Percent Transmittance Test of the micro emulsion can be measured spectrophotometrically using spectrophotometer.

6. Measurements of Droplet Size

Size examination of micro-emulsion can be obtained by Dynamic-Light-Scattering experiments or electron microscopy. The polydispersity can be done by the similar Instrument.

7. In-Vitro Drug Release

The diffusion study is often disbursed on a changed Franz-Diffusion cell, among capacity of 20mL. The Receptor section was occupied with of Buffer. The donor section was secure with plastic wrap membrane, holding the micro-emulsion preparation and also the basic drug solution, distinctly. At prearranged time intermission trials were reserved from the receptor section and examined for drug content, employing a Ultra Violet spectrophotometer at definite wavelength.

8. Determination of Residual Drug Remaining in The Skin On Tropical Administration

The skin in the above permeation studies can be used to determine the amount of drug in the skin. The skin cleaned with gauze soaked in 0.05% solution of sodium lauryl sulfate and shall bathed with distilled water. The permeation area shall be cut and weighed and drug content can be determined in the clear solution obtained after extracting with a suitable solvent and centrifuging.

9. Estimation of Skin Irritancy

As the formulation is intended for dermal application, skin irritancy should be tested. The dorsal area of the trunk is shaved with clippers 24 hours before the experiment. The skin shall be scarred with a lancet. 0.5 ml of product is applied and then covered with gauze and a polyethylene film and fixed with a hypoallergenic adhesive bandage. The test should be removed after 24 hours, and the exposed skin is graded for the formation of edema and erythema. Scoring is repeated 72 hours later. Based on the scoring, the formulation shall be graded as 'non-irritant,' 'irritant,' and 'highly irritant.'

Applicatios of Microemulsions[23,24,14]

During the last two decades, microemulsions are used as drug delivery system, they are offer the advantages like thermodynamic stability, optical clarity, easy of penetration.

1. Parenteral application

Parenteral administration (especially via the intravenous route) of drugs with limited solubility is a significant problem in the pharmaceutical industry because of the meager amount of drugs delivered to a targeted site. Microemulsion formulations have distinct advantages over macro emulsion systems when returned parenterally because of the fine particle. The microemulsion is cleared more slowly than the coarse particle emulsion and, therefore, has a longer residence time in the body. Both O/W and W/O microemulsion can be used for parenteral delivery. Rhee et al. formulated Iitraconazole containing parenteral microemulsion, using an o/w microemulsion system. The average droplet size of the microemulsions was < 150 nm, and the haemolysis test showed this formulation to be nontoxic to red blood cells. The pharmacokinetic profiles of the ITZ-micro emulsion for Itraconazole and its major metabolite, hydroxyitraconazole, were compared with those of a PEG 400 solution and cyclodextrin formulations in rats. Overall, these results highlight the potential of an ITZ-micro emulsion formulation for the parenteral route.

2. Oral Delivery

The development of effective oral delivery systems has always been challenging to researchers because drug efficacy can be restricted by instability or poor solubility in the gastrointestinal fluid. Microemulsions can enhance the solubilization of poorly soluble drugs (particularly BCS class II or class IV) and overcome dissolution-related bioavailability problems. Due to the presence of polar, nonpolar, and interfacial domains, hydrophilic drugs, including macromolecules, can be encapsulated with varying solubility. These systems

protect the incorporated drugs against oxidation enzymatic degradation and enhance membrane permeability. Presently, Sand immune Neoral(R) (Cyclosporine A), Fortovase(R) (Saquinavir), Norvir(R) (Ritonavir), etc., are the commercially available microemulsion formulations. Microemulsion formulation can potentially improve the oral bioavailability of poorly water-soluble drugs by enhancing their solubility in the gastrointestinal fluid.

3. Topical delivery

Topical administration of drugs can have advantages over other methods for several reasons: the avoidance of hepatic first-pass metabolism, salivary and degradation of the drug in the stomach, and related toxicity effects. Another is the direct delivery and target ability of the drug to affected areas of the skin or eyes. Nowadays, there have been several studies on drug penetration into the skin. They can incorporate hydrophilic (5-fluorouracil, apomorphine hydrochloride, diphenhydramine hydrochloride, tetracaine hydrochloride, methotrexate) and lipophilic drugs (estradiol, finasteride, ketoprofen, meloxicam, felodipine, triptolide) and enhance their permeation. Since microemulsion formation requires high surfactant concentration, the skin irritation aspect must be considered, primarily when intended to be applied for a more extended period.

4. Nasal Delivery

Recently, microemulsions are being studied as a delivery system to enhance uptake of drug through nasal mucosa. In addition, with mucoadhesive polymer helps in prolonging residence time on the mucosa. Lianly et al. investigated the effect of diazepam on the emergency treatment of status epilepticus. They found that the nasal absorption of diazepam fairly rapid at 2 mg kg-1 dose with maximum drug plasma concentration reached within 2-3 min.

5. Drug Targeting

Drug targeting to the different tissues has evolved as the most desirable goal of drug delivery. By altering pharmacokinetics and biodistribution of drugs and restricting their action to the targeted tissue, increased drug efficacy with concomitant reduction of their toxic effects can be achieved. Shiokawa et al. reported a novel microemulsion formulation for tumor targeting of lipophilic antitumor antibiotic actinomycin A (ACM). They said that a folate-linked microemulsion is feasible for tumor-targeted ACM delivery. They also reported that folate modification with a sufficiently long PEG chain on emulsions effectively targets emulsion to tumor cells.

6. Brain Targeting

Intranasal administration confers a simple, practical, cost-effective, convenient and non-invasive route of administration for rapid drug delivery to the brain. It allows a direct transport of drugs to the brain circumventing the brain barriers. Vyas *et al*. prepared mucoadhesive microemulsion for an antiepileptic drug clonazepam. The aim was to provide immediate delivery to the rat brain. Brain/blood ratio at all sampling points up to 8h following intranasal administration of clonazepam mucoadhesive microemulsion compared to i.v. was found to be 2-fold higher indicating a more significant extent of distribution of the drug in the brain.

Table no 01: List of Recent Research Work Reported On Topical Microemulsions.

Sl. No	Author Name	Drug	Method of Preparation	Components	Inference
1	Chandrasekaran et. al., (2018)[25]	Azithromycin	Water Titration Method	Surfactant- Tween80 Cosurfactant-Span20 Oil- Lemongrass Oil	The LG oil ME possesses potent anti-bacterial activity, which makes it a safer system for solubilizing hydrophobic antimicrobial drugs to enhance its antibacterial activity.
2	Alkhatib et. al., (2016)[26]	cephalosporin	Water Titration Method	Surfactant-Chromophore EL Co-surfactant-Transcutol Oil- Ethyldecanoate	They enhanced the cellular permeability, their study suggests that ME formula has a good potential as an antibacterial agent
3	Sadan P. Gowda et. al., (2020)[27]	Salicylic Acid	Water Titration Method	Surfactant-Tween20 Co-Surfactant-Propylene glycol Oil- Clove Oil	They are concluded that the ME system studied is a promising tool for the topical delivery and Salicylic acid be formulated as ME with good release and consistency.
4	Bregni et. al.,(2015)[28]	Amphotericin B	Water Titration Method	Surfactant-Tween80 Co-Surfactant-Ethanol Oil- Isopropyl myristate	Drug penetration into skin was significant so this AmB loaded gel-like ME is promising for the treatment of skin infections
5	Raghu Kumar H M et. al., (2021)[29]	Levofloxacin	Water Titration Method	Surfactant-Tween20 Co-Surfactant-Propylene glycol Oil- Eucalyptus Oil	They are concluded that the ME system studied is a promising tool for the topical delivery and levofloxacin be formulated as ME with good release and

					consistency.
6	Shweta et. al.,(2014)[30]	Caffeine	aqueous phase titration method.	Surfactant-Tween20 Co-surfactant-capryol 90 Oil- Almond Oil	ME formulations as compared to their aqueous forms indicated that MEs enhanced the antibacterial activity
7	Jantrawut et. al.,(2018)[31]	Orange Oil	Water Titration Method	Surfactant-Tween80 Co-surfactant-propylene glycol Oil- Orange Oil	This study indicated that microemulsion is an interesting technique of potentiating orange oil antibacterial activity in film formulation

CONCLUSION

Microemulsions are a commercially convenient and straightforward vehicle for delivering medicaments that enhance drug absorption with a reduced systemic side effect. Microemulsion can protect labile drugs, control drug release, increase drug solubility, increase bioavailability and reduce patient variability. Furthermore, it has proven possible to formulate preparations suitable for most routes of administration. They can be potential drug delivery systems for delivering more than one medicament simultaneously. Microemulsions have very crucial importance in the drug delivery system as well as in the industrial process. They can optimize drug targeting without a concomitant increase in systemic absorption.

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