Journal of Research in Pharmacy

Review Article

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Biomedical application of microemulsion delivery systems: A review

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Received: 28 January 2022 / Revised: 20 April 2022 / Accepted: 20 April 2022

ABSTRACT: Microemulsions are optically isotropic, thermodynamically mixture composed of two immiscible liquids (oil and water) stabilized by surfactant, sometimes along with cosurfactant with a diameter in the range 5-200 nm. They have emerged as novel drug delivery vehicle for controlled and sustained drug release for ocular, topical, parenteral, topical administrations. The ease of preparation and characteristics such as low viscosity, improved drug solubilization, long shelf-life make them as a unique candidate. Other than drug delivery, they possess a wide range of applications in the field of biotechnology, enhanced oil recovery and cosmetics. The core intent of this review article is to bring out details on types of microemulsions, structure, physiochemical characteristics, thermodynamic stability and applications in various fields.

KEYWORDS: Microemulsions; Thermodynamically stable; Bioavailability; Self-emulsification; Hydrophilic-lipophilic.

1. INTRODUCTION

Microemulsions are clear, optically transparent, thermodynamically stable dispersions of two immiscible liquid (oil and water), stabilized by an interfacial layer of surfactant often in addition to a co-surfactant [1]. The droplets or small particles are dispersed phase with a size ranging from 5- 200nm and possess very low interfacial tension. The droplet size being 25% smaller than that of the wavelength of visible light makes microemulsion appear transparent optically. The formation of the microemulsion is usually spontaneous and does not require any external high energy input [2]. The concept of microemulsion was presented by Hoar and Schulman in the 1940s. They formulated the first microemulsion by mixing the oil phase in an aqueous surfactant solution and addition of hexanol as a co-surfactant resulting in a stable transparent formulation. Later in 1959 the term "microemulsion" was coined by Schulman et al since then various alternative names such as swollen micelle, solubilized oil, micellar emulsion was used [3]. Microemulsions are presently the main theme of investigation because of the advantages it provides over conventional systems. The high solubility of drug solubilization, spontaneous formation, increased shelf life, enhanced clinical potency and reduced toxicity make it a suitable candidate for drug delivery [4].

2. ADVANTAGES OF ME

The ease of preparation and no external high energy requirement for the formulation makes it a suitable choice and its ability to solubilize both hydrophobic and lipophilic components make them "super solvents" [5].

Microemulsions allow self-emulsification of the system and are thermodynamically stable. The development of a microemulsion system is a reversible process i.e., it may turn unstable with drastic temperature change but it restores back when stable temperature range returns. They possess very low viscosity compared to emulsions.

The efficacy of the drug is improved by using microemulsion as a drug delivery vehicle, hence it can help in reducing the dose in the form of controlled and sustained release and the side effects associated with it [6]. It also helps in enhancing the drug solubility and improving the bioavailability.

How to cite this article: Tiwari N, Sivakumar A. Biomedical application of microemulsion delivery sytems: A review. J Res Pharm. 2022; 26(5): 1052-1064.

ISSN: 2630-6344

http://dx.doi.org/10.29228/jrp.203

Microemulsion offers protection against hydrolysis and oxidation as the drug is incorporated into the oil phase of O/W microemulsion and does not come in contact with water and air. It eliminates the variability in absorption as it bypasses first pass metabolism.

3. DISADVANTAGES OF ME

During storage and transportation creaming, cracking, flocculation is common issues observed. The requirement of a large amount of surfactant to stabilize the droplet contributes to major drawbacks [7]. The limited solubilizing ability for high melting components.

4. TYPES OF ME

In 1954, Winsor predicted four forms of microemulsion phases be present in equilibria which was later experimentally evinced and referred to as Winsor phases [8].

Oil-in-water (O/W) microemulsion or Winsor I: In O/W type of microemulsion the oil droplet is bounded by a surfactant (maybe along with co-surfactant) layer that makes the dispersed phase, dispersed in an aqueous continuous phase. This kind of microemulsion is prepared by solubilizing the surfactant preferably in the aqueous phase. The aqueous phase rich with surfactant are present with the oil phase and the surfactant subsists as a monomer unit at a relatively lower concentration.

Water-in-oil (W/O) microemulsion or Winsor II: In W/O type of microemulsion the droplets of water are distributed in a continuous oil phase. This type of microemulsion is prepared by dispersing the surfactant ideally in the oil phase. The oil phase rich in surfactant is mixed with an aqueous phase deprived of surfactant. These are also known as "reverse micelles", where the fatty acid tail group of surfactants is facing into the oil phase and the polar headgroup is facing droplet of water. These type of microemulsion, when administered orally or parenterally, could get disrupted by the water present in the biological system.

Bicontinuous microemulsion or Winsor III: It's a three-phase system constituting a bicontinuous surfactant loaded middle phase, which combines with both aqueous and oil phases in excess. In this type of microemulsion, both the phases i.e., aqueous and oil are surfactant deprived.

Single phase homogeneous microemulsion or Winsor IV: It's an expansion of Winsor type III where an inflated concentration of surfactant is used to attain isotropic (single micellar) microemulsion by extending the middle phase to become a single phase.

5. COMPONENTS OF ME

The main focus on the selection of the components for microemulsion formulation falls under the "Generally Regarded As Safe (GRAS)" category. There is a wide range of oils and surfactants available which can be chosen based on the purpose [9]. The ideal properties which are focused on are biocompatibility, clinically acceptable, and non-toxic [8]. The major components of the microemulsion system are:

5.1. Oil phase

Oil is the imperative component of the microemulsion as it has the ability to solubilize the desired amount of the hydrophobic drug and helps in enhancing the transport of the same via the intestinal lymphatic system. Hence the absorption can be enhanced from the GIT (gastrointestinal tract) by altering the molecular type of the triglyceride. Due to its capacity to permeate and swell the tail fragment of surfactant monolayer the curvature is very much influenced by the oil component (Table 1). The short-chain oils can permeate the tail group region more efficiently than long-chain alkanes and henceforth outcomes in the negative curvature and the clear decrease in HLB.

Table 1. The different types of oils used for the formulation of a microemulsion.

Components	Example
Saturated fatty acids	Capric, myristic, and lauric acids.
Unsaturated fatty acids	Linoleic, linolenic, and oleic acids.
Fatty acid esters	Ethyl or methyl esters of the lauric, myristic and oleic acids.

5.2. Aqueous phase

Based on the expanse of water present in the system, it can be a continuous or dispersed phase. The aqueous phase can comprise hydrophilic active pharmaceutical components and preservatives. In a few cases, the aqueous phase may be comprised of buffer solutions.

5.3. Surfactant

Surfactants are the molecules that help reduce interfacial tension to negligible value and help facilitate the course of dispersion during formulation development. They are also called surface-active agents as they get adsorbed to the surface of the interface of a system and change their interfacial energies. Surfactant screening can be done based on the HLB (Hydrophilic Lipophilic Balance) value, low HLB from 3-6 are considered for the formation of W/O microemulsion, however, higher HLB surfactants from the range 8-18 are favorable for the development of O/W microemulsion system [10] (Table 2). It relays molecular assembly to interfacial packing and film curvature

The different types of surfactants which can aid in microemulsion formation are as follows [11] (Table 3):
Cationic
Anionic
Non-ionic
Zwitterionic surfactant

The stabilization phenomenon for non-ionic surfactants happens by dipole and hydrogen bond interaction whereas for ionic surfactant its via electrical double layer stabilization [12]. Ionic surfactants being sensitive towards salt concentration possess stability issues and the toxicity concern makes it unfavorable for clinical usage. Non-ionic surfactants being non-toxic in behavior are preferred for pharmaceutical dosage forms.

Table 2. HLB values and properties.

Nature	HLB value	Application
Hydrophobic (oil soluble)	2-3	Antifoaming agents
	3-6	w/o Emulsifying agents
Water dispersible	7-9	Wetting and spreading agents
Hydrophilic (water-soluble)	8-16	o/w Emulsifying agents
	13-15	Detergents
	15-18	Solubilizing agents

Table 3. Surface active agents: types and applications.

Type	Structural name	Application
Non-ionic	Polyoxyethylene glycol octylphenol ethers; polyoxyethylene glycol alkylphenol ethers; sorbitan alkyl esters	Wetting agent-coating, spermicide, food ingredients, polishes, fragrance carriers
Anionic	Dioctyl sodium sulfosuccinate; perfluorooctanesulfonate; linear alkylbenzene sulfonates; sodium lauryl ether sulfate, sodium stearate	Wetting agent- coating, toothpaste; Laundry detergents; shampoo; bath products; concrete plasticizer; dishwasher and detergents
Cationic	Benzalkonium chloride; cetylpyridinium chloride; benzethonium chloride; cetyl trimethylammonium bromide; cetyl trimethylammonium chloride	Antifungal, antimicrobial agents, disinfectant and preservative
Zwitterionic	Cocamidopropyl betaine, amphoacetates	Dermatological products-shampoo, cosmetics, and hand dishwashing liquids

5.4. Co-surfactant

Sometimes the single-chain surfactants are not capable alone of reducing the oil/water interfacial tension sufficiently to form a microemulsion system. Medium-chain length is usually used as co-surfactants, which helps in reducing the interfacial tension further, though fluidity of the interface is increased leading to higher entropy of the system. Mobility of the hydrocarbon tail can be enhanced by using medium chain length alcohols and hence allow enhanced oil penetration into this region [13].

6. METHODS OF FORMULATION: PHASE INVERSION & PHASE TITRATION

6.1. Phase titration method.

The development of microemulsion by phase titration method is an impetuous emulsification process and can be demonstrated using a phase diagram [14] (Figure 1). The complex interactions between the various components of the microemulsion system can be studied by using a phase diagram. The study of phase equilibria and delineation of phase boundaries are principal parameters to understand the formation of microemulsion with several association assemblies such as emulsions, micelles, hexagonal, cubic, lamellar depending on the concentration of each component and chemical compositions. The four-component system (quaternary phase diagram) is time-consuming and difficult to interpret [15]. Each corner of the pseudo ternary phase diagram denotes 100% of the specific constituent of the microemulsion system and is used to distinguish w/o or o/w microemulsion by observing oil-rich or water-rich area. Metastable systems can be eliminated by careful observations.

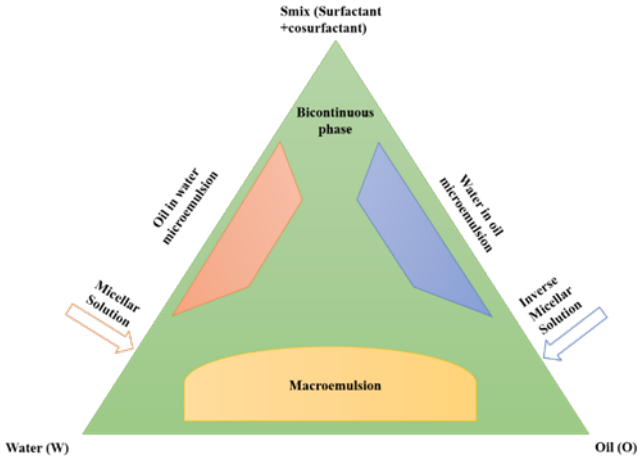

Figure 1. Pseudo ternary phase diagram depicting various emulsion region.

6.2. Phase inversion method.

The addition of dispersed phase in excess or in response to an abrupt change in temperature leads to phase inversion of a microemulsion. This phase inversion results in drastic changes in the physical behavior of microemulsion such as a change in particle size and hence influences the in vivo and in vitro drug release [14]. The transitional phase inversion can be attained by altering the curvature of the surfactant and hence compelling a conversion from o/w microemulsion at lower temperatures to w/o microemulsion at a higher temperature for non- ionic surfactant. The formation of finely dispersed oil droplets takes place during the course of cooling when the system crosses a point of zero spontaneous curvature and insignificant surface tension (phase inversion temperature method). Other parameters such as salt concentration, change in pH and alteration in water volume fraction may also contribute to a spontaneous change in curvature instead of temperature. The spontaneous formation of the microemulsion can be achieved by reducing the interfacial tension between the oil and water phase significantly low. In addition to surfactants can be achieved by controlled usage of lower alkanols such as butanol, pentanol, and hexanol (co-surfactant).

7. PHYSIOCHEMICAL PROPERTIES OF ME SYSTEM

7.1. Physical appearance: The visual appearance inspection can help us determine the properties like flowability, optical clarity, and homogeneity of the microemulsion.

7.2. Cross polarising microscope: to check for the absence of bifringence, to eliminate liquid crystalline system the microemulsion should be analyzed using a cross polarising microscope.

7.3. Percentage transmittance: Also known as limpidity test. The percentage of transmittance is analyzed for the microemulsion using spectrophotometric techniques [16].

7.4. Thermodynamic stability: Stability testing is a time-consuming process hence accelerated stability studies are preferred.

Accelerated stability test includes centrifuging the microemulsion at 6000 rpm for 30 min to check for any phase separation, cracking, creaming and aggregation. The clear samples are taken further for six freeze-thaw cycles. Where microemulsions are subjected to -20°C and +25°C for 48 h each. The clear samples from this step are taken for six heating-cooling cycles, where the microemulsion is subjected to 40 °C and 4°C for 48 h each. The samples are withdrawn at a fixed time interval and checked for any physical changes like loss of clarity, turbidity, droplet size, pH and other parameters.

Long term stability is performed by storing the samples in ambient conditions for six months and periodical inspection of the sample visually, percentage of transmittance, pH, other rheological parameters.

7.5. DLS and zeta measurement: The size of the microemulsion is checked using dynamic light scattering along with the polydispersity index (PDI) which accounts for the homogeneity of the system [17]. The diffusion speed can be measured using the speck pattern formed by irradiating the particle with a laser. The scattering intensity fluctuates with time for a specific angle and is detected using a sensitive APD (avalanche photodiode detector). The change in intensity is analyzed by a digital autocorrelator and produces a correlation function, the curve obtained is used to interpret the size and size distribution of the droplet. Zeta potential is the charge developed by particle/ molecule in a specified medium and emerges due to the surface charge, concentration change and the type of ions in the solution. The stability of the system can be altered by varying the pH, ionic concentration, type of ions, by using additives such as surfactants and polyelectrolytes [18].

7.6. Electrical conductivity: The electrical conductivity is recorded using a conductivity meter by dipping into oil and surfactant mixture which is titrated dropwise with aqueous phase at ambient temperature. The conductivity data helps in determining the type of microemulsion. In the case of the W/O type of microemulsion where the continuous phase is oil, the conductivity is low. Whereas, in O/W type of microemulsion where the water is a continuous phase, the conductivity is higher [19].

7.7. Drug solubility: Drug solubility was ascertained by adding up an excessive amount of the drug to the optimized microemulsion and its individual components. The mixture was vortexed and allowed for continuous stirring for 48- 72 h at 25±1 °C to equilibrate and later centrifuged at 6000 rpm for 10 min. The unbound drug was analyzed by filtering the supernatant through a 0.45µm syringe filter. The absorbance was determined subsequently by appropriate dilution of components at a fixed wavelength with UV double beam spectrophotometer [20].

7.8. *In vitro* drug release study: The *in vitro* drug release study can be performed using modified Franz diffusion cell with a cellulose membrane clamped in between the donor and receptor compartment [21]. The rate of drug release can be determined at fixed time intervals in various simulated fluid (simulated gastrointestinal & simulated intestinal fluid). The donor compartment is filled with drug-loaded microemulsion and drug solution for comparison, the receptor compartment is filled with simulated fluid or phosphate buffer saline. The receptor fluid is constantly mixed using a magnetic bead and fixed sample volume is drawn out from the same and the fresh buffer is replaced immediately. Samples are analyzed for drug content at a specific wavelength using a UV spectrophotometer. The cumulative release of the drug is plotted against time.

8. APPLICATIONS OF ME SYSTEM

8.1. Pharmaceutical

In last one decade a lot of research is carried out on microemulsion for drug delivery through various routes. The research work is summarized (Table 4).

8.1.1. *Oral delivery*

The oral route is progressively used as a delivery vehicle for therapeutic agents. Over 50% of the drug delivery formulations available in the market are based on the oral drug delivery route because of the low cost of therapy, ease of administration and high level of patient compliance. Controlled- release drug delivery system (CRDDS) provides advantages like maintenance of optimal drug concentration with expected and reliable release rates for a prolonged time duration, improvement of activity of duration for short half-life drugs, eradication of side effects, reduced dosing frequency and improved patient compliance [22]. Microemulsion formulations can potentially be used to enhance the oral bioavailability of a hydrophobic drug getting transported to the targeted location. Microemulsion based drug formulations have diverse benefits

over the conventional system when administered parenterally because of the small particle size it passes more gradually compared to the coarse emulsion particle and hence the residence time is longer in the body.

8.1.2. *Topical delivery*

The topical drug delivery system is usually used when other routes like oral, parental, rectal, sublingual of drug dosing fail or in case of confined skin infection like fungal, psoriasis. The drug-loaded formulations can be directly applied to the skin to treat the cutaneous disorder [23]. Human skin is the largest organ, covering around 10% of the total body mass of an average human body. Various extensively used topical agents for instance ointments, creams, and lotions have several drawbacks like stickiness, have less spreading coefficient, exhibit stability issues. The use of clear, transparent and non-sticky gels has increased in cosmetics and pharmaceutical formulation products. Hydrogels are a comparatively recent class of pharmaceutical dosage formulation developed by enmeshment of aqueous or hydroalcoholic fluid in a grid of colloidal particles. These are considered to have a faster drug release compared to ointments and cream formulations [24]. Despite various advantages of gels, a chief constraint is its incompetence to deliver lipophilic drugs as the water-insoluble drug cannot be directly incorporated into the gel-based system. In order to overcome this issue microemulsion based hydrogels are prepared where oil-in-water based formulations are used to entrap lipophilic drug and vice-versa. The use of penetration enhancers can help enhance the penetration of the drug through the skin.

8.1.3. *Ophthalmic delivery*

Drug delivery in the conventional ophthalmic dosage form is a considerable challenge in aqueous form. Drug loss due to lachrymal fluid eye barrier, blood-ocular barrier and lachrymal fluid secretion from the ocular surface is the main hindrance. Low corneal bioavailability and lack of efficacy in the posterior part of ocular tissues are few drawbacks associated with the delivery system. Microemulsions have come froth as an excellent drug delivery carrier with various biopharmaceutical properties, for instance, thermodynamic stability, low surface tension, small droplet size which may lead to drug retention, a prolonged period of action and high ocular absorption [25].

8.1.4. *Nasal delivery*

Microemulsions based nasal drug delivery are used as an alternate route to oral and parenteral routes for systemic delivery. The interest is due to various advantages offered by the nasal cavity such as vascularized epithelium, the large surface area for drug absorption, lower enzymatic activity compared to the systemic circulation, refraining hepatic first-pass metabolism and exasperation of gastrointestinal membrane. It is a non-invasive route and ease of self-medication leads to improved patient compliance.

Although the nasal route of administration of the drug is having certain limitations like nasal mucociliary eviction that restricts the period permissible for drug absorption to happen. In order to overpower the fast clearance, penetration enhancers which can enhance absorption of deficiently absorbable drugs and mucoadhesive systems that enhances the contact period between the drug and the location of absorption can be used.

Table 4. Research work on various routes of drug delivery using microemulsions.

S.No.	Drug Name	Route	Objective/Outcome	Ref. no.
1.	Piroxicam	Oral	Enhanced solubility	[26]
2	Acyclovir	Oral	Enhanced bioavailability	[27]
3	Tamoxifen citrate	Oral	Enhanced Solubility and improved bioavailability	[28]
4	Glipizide	Oral	Enhanced bioavailability and improved drug dissolution	[29]
5	Hydroxysafflor yellow A	Oral	Enhanced oral bioavailability	[30]
6	Ketoconazole	Oral	Enhanced solubility	[31]
7	Quercetin	Topical	Enhanced solubility, pH stability, enhanced skin permeation	[32]
8	Diclofenac	Transdermal	Permeability enhancement	[33]
9	Prilocainne HCl	Transdermal	Enhanced solubility	[34]
10	Estradiol	Transdermal	Enhanced solubility	[35]
11	Ketoprofen	Transdermal	Improved solubility	[36]
12	Terbinafine	Transdermal	Enhanced permeability	[37]

13	Clonixic acid	Transdermal	Improved absorption	[38]
14	Apormorphine HCl	Transdermal	Enhanced permeability	[39]
15	Ligustrazine phosphate	Transdermal	Increased penetration rate	[40]
16	Diphenhydramine HCl	Transdermal	Enhanced penetration	[41]
17	Itraconazole	Transdermal	Sustained release	[42]
18	Repaglinide	Transdermal	Enhanced permeation	[43]
19	Indomethacin	Transde rmal	Enhanced transdermal flux	[44]
20	Chloramphenicol	Ocular	Enhanced permeability	[45]
21	Dexamethasone &Tobramycin	Ocular	Improved bioavailability	[46]
22	Timolol	Ophthalmic	Better absorption	[47]
23	Pilocarpine	Ophthalmic	Low viscosity formulations	[48]
24	Diazepam	Nasal	Increased bioavailability	[49]
25	Nimodipine	Nasal	Enhanced solubility, reduced toxicity, enhanced therapeutic effect	[50]
26	Risperidone	Nasal	higher mucoadhesion and enhanced bioavailability	[51]
27	Clonazepam	Nasal	Delivery to the brain more effectively with internasal administration	[52]
28	Carbamazepine	Nasal	Brain- targeting studies	[53]
29	Fenofibrate	Self-Micro emulsifying	Enhanced solubility	[54]
30	Aceclofenac	Dermatological	Improved solubility	[55]
31	Progesterone	Dermal	Increased chemical stability	[56]
32	Ibuprofen	Topical	Enhanced solubility	[21]
33	Ketoconazole	Topical	Penetration enhancer	[57]
34	Flurbiprofen	Parenteral	Increased solubility	[58]
35	Itraconazole	Parenteral	Enhanced absorption	[59]
36	Glimepiride	Parenteral	Increased solubility and dissolution	[60]

8.2. Biotechnology

Several enzymatic and biocatalytic reactions are directed in aqua-organic, pure organic and biphasic media. Their use is restricted as it can lead to denaturation and inactivation of the biocatalysts. Recently a lot of interest is being engrossed on microemulsions for various applications in the field of biotechnology like enzymatic reactions, bioseparation, and immobilization of proteins. Few examples from literature has been presented in table 5.

Table 5. Research work applications of microemulsion in the field of biotechnology in recent years.

Author (Year)	Scope of study	Major findings	Ref. No.
Weng J et al., 2018	Enzymatic hydrolysis of p-nitrophenyl butyrate using microemulsion.	1. Formulation developed using ionic liquid based microemulsion with Tween 20 without co-surfactant. 2. Enzymatic hydrolysis of p-nitrophenyl butyrate by Candida rugosa lipase was used as model. 3. The enzymatic reaction was measured as a function of Lipase concentration.	[61]
Gharbavi M et al., 2019	Biocompatibility of microemulsion hybridized with bovine serum as nanocarrier.	1. Formulated triacetine microemulsion and bovine serum loaded triacetine microemulsion (T-BSA-ME). 2. Cytotoxicity of MEs systems was investigated on HFF-2 and HEK-293 cells. 3. Biocompatibility of MEs systems was carried out using hemolysis and leukocyte proliferation assay.	[62]
Jalali- Jivan M et al., 2020	Microemulsion as nanoreactor of bioactive compounds.	1. Microemulsions are used for solubilization, separation and encapsulation of bioactive components. 2. Microemulsion liquid membranes are developed as nano-extractor/ nano-reactor vehicles.	[63]

		3. Microemulsion systems can be used for protein extraction and isolation of bioactive compounds.	
Zizzari AT et al., 2021	New perspective in oral peptide delivery	1. The market for peptide drug is constantly growing and its delivery with microemulsion can help enhance oral bioavailability. 2. Microemulsion have ability to improve oral peptide delivery by overcoming absorption barrier. 3. Microemulsion provide protection against metabolism and enhanced permeation through intestinal mucus layer.	[64]
Bose AL et al., 2022	Mixed micelles and bicontinuous microemulsion for enzymatic reactions.	1. Enzyme catalysis was higher in ionic/ non-ionic mixed micelle compared to ionic micelle. 2. Ionic reverse micelles reduced catalytic activities of enzymes through denaturation. 3. Mole ratios of surfactants, of water to total surfactant were crucial parameters.	[65]

8.3. Enhanced oil recovery

Oil and gas production plays a vital role in the socio-economic development of any country. Tertiary methods are also known as Enhanced Oil Recovery (EOR) is the extraction of remaining crude oil from an oil field reservoir that cannot be easily extracted using primary and secondary recovery. The major findings of EOR using microemulsion has been presented in Table 6. The properties of the reservoir fluid system which are affected by Microemulsions -EOR process are interfacial tension (IFT), viscosity and density under reservoir conditions. Microemulsions are homogeneous blends of hydrocarbons and water with huge volumes of surfactants. The study of the phase behavior of microemulsion formed by oil–brine–surfactant/cosurfactant systems is important for EOR [66]. A microemulsion is a competent tool in EOR systems. The microemulsion systems exhibit ultralow interfacial tensions (IFT) [67]. Ultralow interfacial tension is essential to retrieve the confined residual oil [68].

Table 6. Research work applications of microemulsion in the field of Enhanced oil recovery in recent years.

Author (Year)	Scope of study	Major finndings	Ref. no
Pal N et al., 2019	Microemulsion system stabilized by surfactant and implication for EOR	1. Jatropha oil used to synthesize anionic surfactant and study adsorption and micellization properties. 2. Microemulsion demonstrated ultra-low IFT. 3. Microemulsion flooding demonstrated about 30% tertiary oil recoveries.	[67]
Qin T et al., 2020	Nanoparticle stabilized microemulsion for EOR	1. In-situ synthesis of nanoparticles in microemulsions. 2. Synergistic effect reduces oil droplet size and improves the mobilization. 3. Microemulsion reduces capillary force responsible for trapping residual oil.	[69]
Hematpur H et al.; 2021	Microemulsion flooding to increase low viscosity oil recovery.	1. Microemulsion flooding is alternative to surfactant flooding in a chemical EOR. 2. Efficiency of microemulsion flooding is determined through phase behavior analysis.	[70]
Mariyat J et al.; 2022	Microemulsion vs. Nanoemulsion for EOR	1. Droplet size of microemulsion is found to be smaller than nanoemulsion. 2.Microemulsion demonstrated higher efficiency in EOR compared to nanoemulsion. 3. Microemulsion can reduce the interfacial tension to 10^{-4} mN/m, which nanoemulsion cannot.	[71]

8.4. Cosmetics

Cosmetic industries are facing a lot of challenges that can influence the profitability and endurance of a few highly endorsed products. The factors associated with health risks, environmental alarms and merchandise functionality are probable constraints and need to be tackled with innovation to maintain in the global market. Microemulsions epitomize an efficacious approach for the delivery of cosmetic products [72]. Skincare microemulsion system can be prepared using sodium alkyl sulfate, lecithin, dodecyl oligoglucoside,

tetraethylene glycol monododecyl ether, propanol, hexadecane, alkyl dimethyl amine oxide, isopropyl myristate as surfactants, cosurfactants, and oils. Microemulsion formulations are supposed to have a faster uptake in the skin. The key factors which must be considered for the formulation development of microemulsion are cost, safety and suitable choice of ingredients [73]. The introduction of new W/O emulsifiers can help in producing efficient skincare products without an inherent greasy feel. Modified carbomer copolymers or silicone-based copolymers have been incorporated and found to have interesting rheology and enhanced skin moisturization.

Microemulsions are found to be a convenient and effective delivery system for sunscreen products [74] as they are able to attain a wide range of SPF and also are found to have enhanced penetration through skin [75]. Microemulsion based skin moisturizers, antiperspirants, and deodorants have exposed superior properties. The stress laid on the reduction of volatile organic chemicals and preparation of water-based alcohol-free perfumes and fragrances based on microemulsion technology is found to be environmentally friendly. Microemulsion based hair care products are prepared using amino-functional polyorganosiloxane and a metal salt. The hair care products are found to have more desirable properties compared to conventional preparations [76]. Clear and transparent microemulsion based cosmetic products are more appealing to customers compared to opaque or cloudy personal care products. Few applications of microemulsion in cosmetics has been mentioned in Table 7.

Table 7. Research work applications of microemulsion in the field of Cosmetics in recent years.

Author (Year)	Scope of study	Major findings	Ref. no
Chaiyana W et al., 2018	Microemulsion of Camellia assamica	1. Formulated microemulsion having antioxidant and moisturizing effect of Camellia assamica. 2. In-vitro skin moisturizing investigated on piglet skin using Corneometer. 3. Radical scavenging and antioxidant property of CA microemulsion was higher than native oil.	[77]
Ghorbanzadeh M et al.,2019	Micoremulsion based hydrogel for UV protection of skin.	1. Sesame seed oil based microemulsion was formulated using Tween 80/ Span 80 Smix. 2. Microemulsion formulation with droplet in nanometer range demonstrated 6 months of stability. 3. Topical application of hydrogel can prevent skin damage due to UV radiation.	[78]
Ryu KA et al., 2020	Coenzyme Q-10 based microemulsion for skin regeneration	1. Developed a coenzyme Q-10 based microemulsion with improved solubility, penetration and wound healing efficiency. 2. Microemulsion developed using isopropyl myristate, Cremophor EL, Transcutol HP. 3. The droplets confirmed to be nanosized (<20nm) helps in improved penetration.	[79]
Manyala DL et al., 2021	Microemulsion with anionic sodium N-lauroylsarcosinate	1. Triglyceride oils such as caprylic acid, oleic acid and carboxylic acid ester isoamyl acetate were used as oil phase. 2. short chain alcohols like propanol and butanol were used as cosurfactants. 3. Microemulsion using novel amino acid based anionic sodium N-lauroylsarcosinate (SNLS) surfactant was formulated for application in personal care formulations.	[80]
Lee SH et al., 2022	Skin care formulation with essential oil based Microemulsion	1. Essential oils such as peppermint oil, lavender oil and eucalyptus oil have excellent antioxidant and antimicrobial properties and can be used for skin care formulations. 2. Essential oil based microemulsion for skin care formulations demonstrated improved skin permeation, better stability, eco-friendly alternative, and self-preserving.	[81]
Prommaban A et al., 2022	Microemulsion from citrus peel	1. Microemulsions from citrus peels and leaves for reducing irritation, whitening and anti-ageing properties. 2. Citrus oil inhibited collagenase and tyrosinase activities. 3. limonene was the main constituent of the citrus oil.	[82]

9. CONCLUSIONS

Microemulsions have enormous potential in drug delivery systems as well as industrial applications. The role of microemulsion as an innovative candidate to overcome the issues of low aqueous solubility in the case of hydrophobic drugs and problems of consistent and reproducible bioavailability. The ease of preparation and relatively lower cost of commercial production makes it a suitable applicant as a delivery vehicle. It has shown to preserve labile drug, controlled release and reduced patient variability and is demonstrated to formulate dosage form with various routes of administration. Microemulsions can also be used to execute drug targeting though the challenge remains in the system overcoming barriers to reach the target. The other applications of microemulsion such as bioseparation, protein immobilization, skincare products, oil recovery, nanoparticle synthesis are of great interest to researchers. Current research work is more focused on the preparation of safe, effective and compatible microemulsion components which will help improve the effectiveness of these innovative delivery vehicles to a great extent.

Author contributions: Concept – N.T.; Design –N.T.; Supervision – A.S.; Resources – N.T., A.S; Materials – N.T.; Data Collection and/or Processing –N.T.; Analysis and/or Interpretation –N.T.; Literature Search –N.T.; Writing – N.T.; Critical Reviews – N.T., A.S.

Conflict of interest statement: The authors declared no conflict of interest.

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