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Microemulsion: A futuristic drug delivery approach

Suhail Khan
Noida Institute of Engineering and Technology (Pharmacy Institute), Knowledge Park-II, Institutional Area, Greater Noida (UP) -201306

Sushma Verma
Noida Institute of Engineering and Technology (Pharmacy Institute), Knowledge Park-II, Institutional Area, Greater Noida (UP) -201306
*Corresponding author email: sushmaverma76@gmail.com

Syed Akhlaque Ahmed
Noida Institute of Engineering and Technology (Pharmacy Institute), Knowledge Park-II, Institutional Area, Greater Noida (UP) -201306

Alka Sharma
Noida Institute of Engineering and Technology (Pharmacy Institute), Knowledge Park-II, Institutional Area, Greater Noida (UP) -201306,

Abstract---Microemulsions are the advanced form of the conventionally used emulsions, which is a biphasic dosage form consisting of two immiscible liquids that are brought together with the application of surfactants and cosurfactants. The micron sized globules of microemulsions helps in achieving targeted action with improved availability and stability. The studies related to the microemulsions concluded its potential in delivering various hydrophilic and lipophilic drugs and several leading manufacturers are considering this as ideal formulation for delivering several potent drugs via several routes including oral, ocular, parenteral, topical routes. The advancements occurred during the previous few years in the pharmaceutical sector results in identification of innovative methods for preparing microemulsions and various patents related to the preparation of microemulsions are granted during last decade. This article enlisted the basic information related to the microemulsion along with its component, structure, method of preparation and evaluation parameters. The applications of microemulsion in several sectors of healthcare segment are also discussed in this review and the future scenario is also discussed in the article. Along with this, the article also enlisted the commercially available microemulsion, patent insight of microemulsion and the list

of drugs previously used by the researchers for preparing microemulsion based products.

Keywords---microemulsions, bicontinuous phase, lipophilic, sonication, cosurfactants, interfacial tension, dispersed phase.

Introduction

During the past few years, the incidence rate of several communicable as well as non-communicable diseases increased exponentially, which results in rise in demand of novel drug candidates as well as drug delivery systems so that the optimum effects can be achieved. Due to rapid action and improved convenience, the liquid dosage forms are emerging as ideal approach for delivering a number of essential drugs and continuous innovations in this sector results in the development of more stable and effective formulations. Microemulsion is the advanced form of emulsions, which provides better stability, therapeutic efficacy and many other advantages over the conventionally used emulsions.(Danielsson, 1981; Madhav et al., 2011; Yuan et al., 2006) Theoretically, emulsions are known as biphasic dosage form consisting of two immiscible liquids that are brought together with the help of a surfactant known as emulsifier. (Ansel et al., 2020) As compared to the conventional emulsions, the microemulsions are developed by simple mixing of components and there is no need of high shear force. Further, the emulsions are milky preparations while the microemulsions are clear transparent in appearance while it also has higher kinetic stability. The most common types of microemulsion currently used are oil in water and water in oil type of microemulsions.(Lawrence et al., 2000; Shinoda et al., 1987)

The term microemulsion is first introduced in year 1940s by the chemists named Hoar and Schulman and they prepared it by titrating the conventional milky emulsion with the hexanol.(Hoar et al., 1943) Microemulsions are better alternative over the traditional emulsions, which is mainly due to the small globule size of this formulations that is between the range of 10nm to 160nm.(Derle et al., 2006) The stability of the microemulsion majorly depends upon the nature of emulsifier, which generally consists of a polar end and a nonpolar end due to which it is able to deliver both the hydrophilic as well as hydrophobic drugs. As the particle size is too small, they are not visible through the optical microscope while the flow of particles is observed to be Newtonian. Further, the viscosity of the microemulsion is less as compared to the conventional emulsions.(Nadkar et al., 2010; Vandamme, 2002; K. S. Kumar et al., 2011)

Several advantages of the microemulsions results in its emergence as one of the ideal therapy for the delivery of drug via several routes including parenteral, oral, ocular, otic, topical and many more and hence this system is now considered as ideal drug delivery approach.(Kantaria et al., 2003; Tenjarla, 1999) The major application of microemulsion is in the topical delivery of drugs as it is able in improving the local as well as systemic absorption of the drug. The topical activity of microemulsion mainly depends on its mobility, release rate of drug and penetration of active ingredients. As various studies concluded the optimum

activity of microemulsions, it is believed to consider as ideal formulation for delivering various investigational as well as commercially available active ingredients. (Madhav, et al., 2011; M. Gasco, 1997; M. R. Gasco et al., 1989) The microemulsions also have better loading capacity, which also serves as a unique feature of this formulation and hence encouraging the researchers to work in this sector and demonstrated its action in delivering active ingredients via different routes.(Peltola et al., 2003; Rhee et al., 2001)

Microemulsions are also emerging as ideal alternative for delivering drugs via oral route as it is able to improve the solubility of poorly soluble drugs. Further, the improved thermodynamic activity of microemulsions also helps in improving the absorption rate of the drugs, which ultimately improves the bioavailability of the components. 25,26. As the research and development related work is undergoing at tremendous rate, several novel surfactants were identified during the past few years and many new compounds are expected to enter the market, which will result in development of more stable and efficacious microemulsions in near future.(Kawakami et al., 2002; Mehta et al., 2011)

Currently, three major types of microemulsions are widely used for delivering the active constituents i.e. oil in water type, water in oil and bi-continuous microemulsions.(Acharya et al., 2012) Among these microemulsions, the oil in water type of microemulsions can be used for encapsulation of active ingredients in nano capsules as it can overcome the limitations of other encapsulation processes including the utilization of liposomes, polymersomes, and interfacial polymerization. Along with this, the cost of producing microemulsions is also very low and the method is simpler as compared to other novel formulations with comparative effectiveness.(Bordi et al., 2006; McClements, 2015; Levine et al., 2008; Singh et al., 2018; Watnasirichaikul et al., 2000)

Several innovative approaches are currently explored by the researchers for minimizing the consumption of various excipients, for increasing the drug solubility and bioavailability. The future of microemulsion seems to be very bright as it is emerging as a valuable tool for delivering most of the essential drugs and helps in improving the pharmacokinetic activity of insoluble or poorly soluble drugs. By considering ideal method of developing the microemulsions along with the selection of most suitable emulsifiers, it is now possible to develop highly stable and effective microemulsions, which can overcome most of the limitations related to the conventional microemulsions.(Lawrence, et al., 2000)

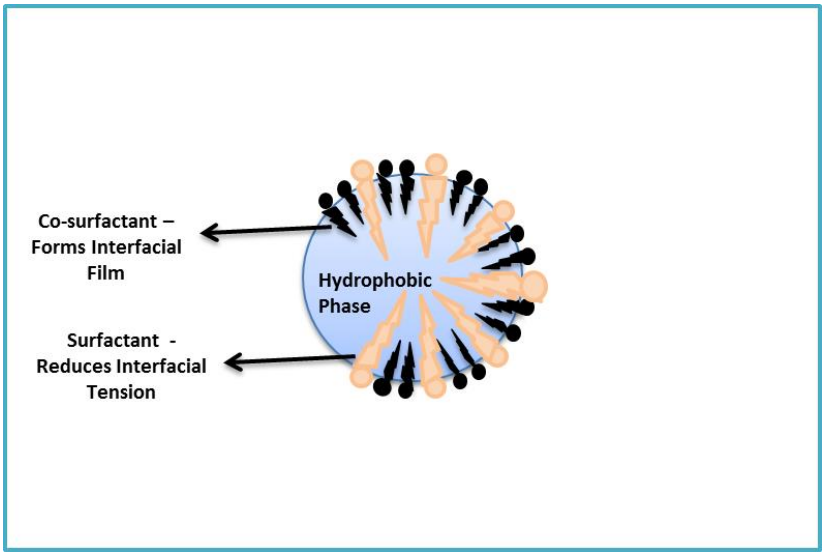

Figure 1. Structure of Microemulsion

Microemulsions - Advantages & Disadvantages

Microemulsions possess several advantages due to which they are widely accepted among the global population. Some of the major advantages are:

- The stability of microemulsions is very high and it provides self-emulsification of the formulation.(K. S. Kumar, et al., 2011)
- Microemulsions are highly soluble preparations, which are able to dissolve both the hydrophilic as well as hydrophobic drug particles and improve the absorption rate of drug. The improved solubility is mainly due to the presence of solvents of different polarity.(K. S. Kumar, et al., 2011)
- As compared to the other liquid dosage forms, the shelf life of microemulsion is better.(M. R. Patel et al., 2007)
- Due to presence of large reservoir of solvent for both hydrophilic as well as hydrophobic drugs, pseudo-zero order kinetics can be achieved.(M. R. Patel, et al., 2007)
- The production of microemulsions is simple and non-expensive as no special equipment is required for its production.(M. R. Patel, et al., 2007)
- The viscosity of microemulsion is also less than the conventional emulsions.(Madhav, et al., 2011)
- Due to small globule size, microemulsions provide more surface area for drug to get absorbed rapidly and hence improve the bioavailability of drug.(Madhav, et al., 2011; M. R. Patel, et al., 2007)
- The occurrence of drug related adverse events is also reduced by using microemulsion as desired effects can be achieved by using minimum drug concentration. (Vyas et al., 2004)
- The formation of microemulsion is reversible process such that its stability fluctuates with change in temperature but it regains its prior form when temperature is stabilized.(Vyas, et al., 2004)

Besides several advantages of microemulsions, some of the disadvantages are also associated with this therapy. Some of the major disadvantages are:

- Large amount of surfactants and co-surfactants are required for the development of microemulsion.(K. S. Kumar, et al., 2011)
- The stability of microemulsion depends upon the several environmental factors including temperature, pH and humidity.(Goswami et al., 2019)
- The solubility of high melting point substance is low in microemulsion and hence delivery of such drugs is matter of concern. (Vyas, et al., 2004; Goswami, et al., 2019)
- Sometimes, phase conversion is also observed.(Shaji et al., 2004)

Types of Microemulsions

As per Winsor, the microemulsions are classified in 4 major categories on the basis of its presence in equilibria.

- **Winsor I**: It is a two-phase system in which the oil layer maintains an equilibrium with the lower (o/w) microemulsion phase.
- **Winsor II**: It is a two-phase system in which the upper water in oil microemulsion develops equilibrium with the lower extra water.
- **Winsor III**: It is a three-phase system in which the middle bi-continuous phase of oil in water or water in oil maintains equilibrium with the upper phase oil and lower phase water.
- **Winsor IV**: It is a single phase system, which involves the development of homogenous mixture of water, oil and surfactants.(Vandamme, 2002; Tenjarla, 1999; Paria et al., 2000; Jha et al., 2011)

Theories of Microemulsions Development

Currently, three major theories can explain the physiochemical properties of microemulsions, which are interfacial or mixed film theory, solubilization theories and thermodynamic theory.

Interfacial Theory

This theory suggested that the surfactants and cosurfactants results in the formation of a complex film at the interface of oil and water and formulate a stable microemulsion. This theory is also known as mixed film and dual film theory.(P. Kumar et al., 1999a; Tang et al., 2007)

Solubilization theory

This theory is based on the fact that the formation of microemulsions is based on the swollen micellar system in which the Solubilization of oil is based on the normal micellar formation while the Solubilization of water is due to the reverse micelle formation.(Talegaonkar et al., 2008)

Thermodynamic Theory

This theory suggested that the formation of microemulsion is based on the reduction of interfacial tension between two immiscible liquids to zero while the negative energy generated during this process provides thermodynamically stability.(Talegaonkar, et al., 2008; Min, 1996)

Components of Microemulsions

The microemulsions are majorly composed of four components i.e. Oil phase, surfactant phase, co-surfactants and co-solvents.

Oils

Oil is one of the two immiscible liquids of the microemulsion, which can solubilize the lipophilic drugs and also able to improve the rate of drug release to the intestinal lymphatic system and hence improve the absorbance of lipophilic drugs. For the preparation of microemulsions, most commonly used oils are saturated fatty acids (Lauric acid, Myristic acid, Capric acid), unsaturated fatty acid (Oleic acid, Linolic acid, Linolenic acid) and fatty acid esters (ethyl or methyl esters of lauric acids, Myristic acid and Oleic acid). The saturated and unsaturated acids also possess permeation enhancing abilities.(Jha, et al., 2011; Sarkhejiya Naimish et al., 2000)

Aqueous Phase

It is the second phase of the microemulsion, which generally consists of hydrophilic active constituents and preservatives. Most of the time water is considered as aqueous phase while some researchers also used buffer solutions as aqueous phase.(Paria, et al., 2000)

Surfactants

Surfactants are the most important constituents of the microemulsion, which maintains the stability of the formulation. It decreases the interfacial tension between the two immiscible liquids and develops a protective film over the globules of the dispersed phase and provides stability to the microemulsion. Currently, the surfactants are divided into 4 classes on the basis of their ionic nature i.e., non-ionic surfactants, zwitter ionic surfactant, anionic surfactants and cationic surfactants. Among all the surfactants, nonionic surfactants are considered ideally for the development of microemulsions as they are non-toxic and orally digestible. It is also observed that the surfactants with low HLB value ideal for the development of water in oil microemulsion while the surfactants with HLB value higher than 8 are ideal for development of oil in water emulsion. (Sarkhejiya Naimish, et al., 2000; Strickley, 2004). Some of the examples of most commonly used surfactants are polyoxyl 35 castor oil, polyoxyl 40 hydrogenated castor oil, polysorbate 20Solutol HS-15, sorbitan monooleate, polyoxyl 40 stearate and different grades of Labrafil M.(Narang et al., 2007)

Cosurfactant

It is observed that the conventional surfactants are not enough for provide sufficient stability to the microemulsions and hence co-surfactants are used to give additional stability, which allows flexibility to the interfacial film of two phases so that it can be used for delivering wide range of active constituents. Generally, the alcohols with short to medium chain length are commonly employed as co-surfactants, which reduce the interfacial tension and improve the flow properties of the microemulsion. In addition to this, the co-surfactants also reduce the chance of forming liquid crystalline and helps in adjusting the HLB. The most widely used co-surfactants are ethanol, butanol, propylene glycols and other short or medium chain acids, amines and alcohol.(Sarkhejiya Naimish, et al., 2000; Roux et al., 1986; P. Ghosh et al., 2006)

Co-solvents

These are the solvents incorporated for enhancing the solubility of both the hydrophilic as well as hydrophobic drugs along with the dissolution of surfactants present in excess amount in microemulsion. The most commonly used co-solvents are ethanol, propylene glycol, polyethylene glycol. Most of the time, the co-surfactants itself acts as co-solvents. (Sarkhejiya Naimish, et al., 2000; Roux, et al., 1986; P. Ghosh, et al., 2006)

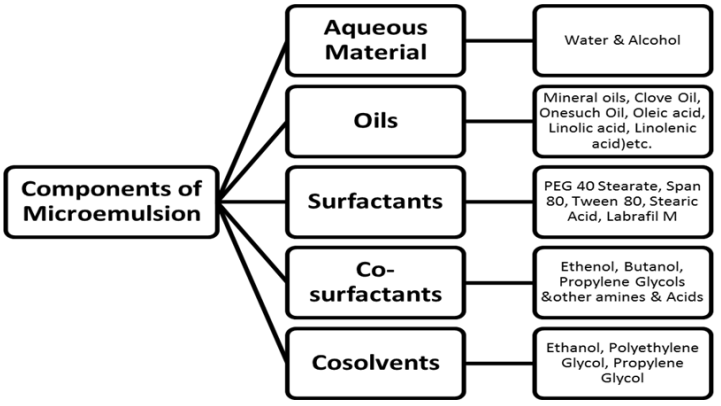

Figure 2. Components of Microemulsion

Microemulsion-Method of Preparation

The microemulsions are generally prepared by following two methods i.e., phase titration method and phase inversion method while some other methods are also implemented for the development of microemulsions.

Phase Titration Method

It involves spontaneous emulsification, which can be explained by studding phase diagrams. The formation of microemulsion depends upon the composition of various structure i.e. micelles, lamellar, hexagonal, cubic and gel or oil emulsion.

All the ingredients are allowed to mix by using magnetic stirrer and after that the water miscible solvent is evaporated to generate microemulsion. The equilibrium maintained between various phases is studied and the ideal method involved generation of pseudo ternary phase diagram. (Talegaonkar, et al., 2008; Shafiq-un-Nabi et al., 2007)

Phase Inversion Method

The phase inversion method involves the formation of microemulsions by using the phase inversion temperature, which is defined as the temperature at which phase transition takes place. It is observed that oil in water emulsion if formed at low temperature while water in oil emulsion will form at high temperature. Rapid and continuous change in temperature results in development of fine particles. It is also observed that most of the nonionic surfactants demonstrated lipophilic properties at high temperature and shows hydrophilic properties at low temperature. Besides the change in temperature, this method also involves the development of microemulsion by adding excess of dispersed phase.(Talegaonkar, et al., 2008)

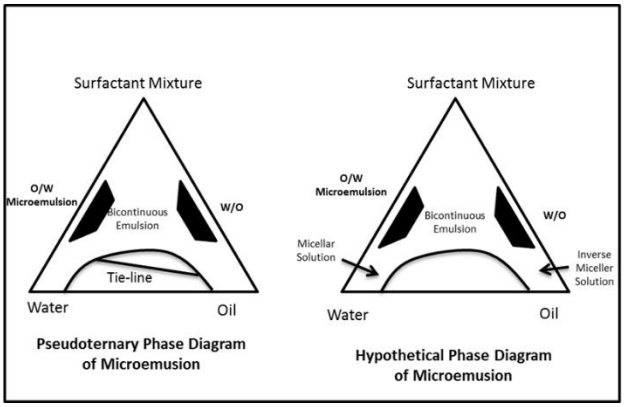

Figure 3. Phase Diagram of Microemulsion

High Energy Emulsification Method

It involves ultrasonic waves along with high pressure homogenization.(Yukuyama et al., 2016)

Low Energy Emulsification

It involves phase inversion temperature method, phase inversion composition method and solvent displacement method.(Yukuyama, et al., 2016)

High pressure Homogenization

It involves the use of a unique instrument developed for serving the purpose of pressurized homogenization for preparing nano-sized particles. For developing microemulsion, the components of formulations are forced to pass under a pressure of 500 to 5000psi through a small orifice which resulted in the

formulation of small size particles or globules. This method required high temperature and energy for the production of microemulsion.(Yukuyama, et al., 2016; Kakkar Thukral et al., 2014)

Microfludization

This method involves the use of micro-fludizer for the generation of high pressure of about 500 to 20000psi. The process of developing microemulsion via this technology involves preparation of coarse emulsion, which is then introduced to the micro-fluidizer to form nano as well as micron sized particles.(Kakkar Thukral, et al., 2014; Ganta et al., 2014)

Ultrasonication

It involves the application of ultrasonic field along with the high pressure, which results in the development of micro sized droplets from the coarse emulsion.(ČERPNJAK et al., 2013)

Solvent Evaporation Technique

In this method, the drug is mixed with the organic solvent in the presence of surfactant and oil in water emulsion is prepared. After that, the organic solvent is allowed to evaporate under external conditions of temperature, pressure or vacuum to develop microemulsion.

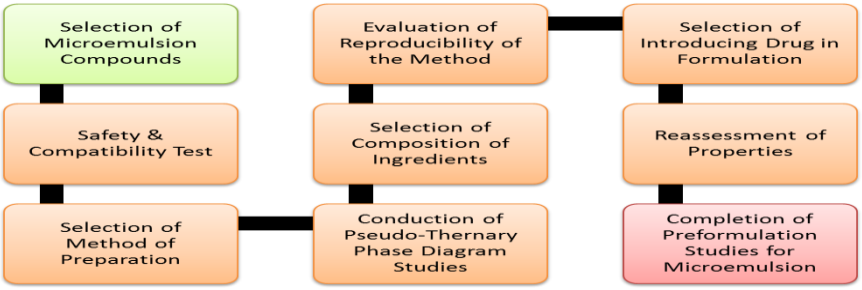

Figure 4. Steps for Preformulation Studies of Microemulsion(Egito et al., 2021)

Evaluation of Microemulsion

- **Visual Examination:** The microemulsion is evaluated for homogeneity, fluidity, appearance and optical clarity.(Malcolmson et al., 1995; Constantinides et al., 1994)
- **Rheology Assessment:** It involves estimation of the viscosity of microemulsion with the use of Brookfield digital viscometer.(Constantinides et al., 1996)
- **Percent Transmittance:** It is also known as Limpidity test, which involves analysis by using spectrophotometer.(Jadhav et al., 2010)
- **Examination under Cross-polarizing Microscope:** This test is performed for detecting the presence of birefringence to prevent the possibility of liquid crystalline systems. (Malcolmson, et al., 1995; Constantinides, et al., 1994)

- **Globule Size Determination:** The determination of globule size is done by using JDS Quasi Elastic Light Scattering Uniphase, US Instruments. This method is based on the principle of light scattering, which makes the process of determining globule size simple and accurate.(P. K. Ghosh et al., 2006)
- **Specific Gravity Test:** For the determination of specific gravity, capillary gravity bottle method is used. First the gravity bottle is washed and dried and then weight of the empty bottle and the bottle with microemulsion is measured, which is then used for the determination of specific gravity.(Bajpai et al., 2014)
- **pH Determination:** pH of the microemulsion is one of the major parameter governing stability of the preparation and it is measured by using micro pH meter.(Bajpai, et al., 2014; Nour et al., 2002; Lucero et al., 1994)
- **Stability Studies:** The stability studies involved centrifugation stress testing, Freeze thaw cycle, long term stability studies.
  - Centrifugation Stress Testing: It is a type of accelerated stability studies in which microemulsion is introduced to centrifugation of about 5000 to 10000 rpm for 30min and presence of physical instabilities including phase separation inversion aggregation etc. are studied.(Brime et al., 2002)
  - Freeze Thaw Cycles (FTC): In this method, the microemulsions are stored at 25°C for a period of 24hours and after that the temperature is change to -5°C and microemulsion is allowed to remain at this temperature for 24 hours. This cycle of altering temperature is continued for three times.(Brime, et al., 2002; A. R. Patel et al., 2007)
  - Long term stability: It is conducted according to the ICH guidelines. The microemulsions are stored for a period of 6 month in a ambient color container and the samples are examined after 1month, 3month and 6month period.(A. R. Patel, et al., 2007)
  - Test for Thermostability: Thermostability test is conducted for evaluating the stability of microemulsion with change temperature. This test involves 20ml of microemulsion, which is stored in 25ml of transparent volumetric flask at three different temperatures i.e. 4°C, 25°C and 40°C for duration of 1 month. After the designated period, physical changes are observed in the microemulsion.(Bajpai, et al., 2014)
- **Study of Micron structure of Microemulsion:** The study of micron structure is performed by using the transmission electron microscope (TEM) and it produces high resolution images to detect micron size structures.(P. Kumar et al., 1999b)
- **Zeta Potential Determination:** It involves measurement of electric charges as it is a major parameter governing the rate of flocculation and bioavailability. Ideally, its range is +30 and -30.(Yaqoob Khan et al., 2006)

- **In-Vitro Drug Permeation Studies:** This test involves determination of permeability coefficient and flux in the case of topically applied microemulsion. For performing this test, the human cadaver skin from the abdomen is excised and stored at 4°C and the epidermis from this skin is separated. The skin is then washed and the dried skin sample is stored at 20°C. Besides this, the dorsal skin of mice can also be used. The

permeability is measured by using Franz Diffusion cell apparatus and the skin is placed between two compartments of the cell. The samples are withdrawn from the receiver compartment at regular interval for measuring the permeation rate.(Von Corswant et al., 1998)

- **Bioavailability Studies:** This study involves the determination of amount of drug that reaches the systemic circulation via microemulsion. For conducting this test, the male Sprague–Dawley rats are used, which are anesthetized and hair from the abdominal surface are removed. After that, microemulsion is applied to the skin surface. After duration of 10min, 30min and 60min, the rat is killed and the exposed skin is used to determine the bioavailability. Further, the skin is cleaned with the help of gauze soaked in 0.05% sodium lauryl sulfate solution. The exposed area is cut and weighed and the difference in weight is then measured after extracting the drug in the solvent. (Von Corswant, et al., 1998)
- **Skin Irritation Test:** this test is also conducted for the topically applicable microemulsion. A required area of skin is cleaned and microemulsion is applied to hat area, which is then covered with the help of gauze or a polyethylene film, after 24 hours, the exposed area is observed for presence of any edema, irritation or any redness.
- **Identification Tests for Type of Microemulsion:**
  - **Dilution Test**: This test involves the addition of continuous phase in the microemulsion i.e. if aqueous phase is added excessively to the microemulsion and the emulsion doesn't break, this means the microemulsion is of oil in water type otherwise it is water in oil type.(Rasal et al., 2010)
  - **Staining Test:** This test involved the addition of water-soluble dye in the microemulsion and then the preparation is observed in microscope. The background shows color in case of o/w emulsion while the globules ae colored in case of w/o emulsion.(Rasal, et al., 2010; D. Patel et al., 2009)
  - **Dilutability Test:** During this test, the microemulsion is diluted in ratio of 1:10 or 1:100 and it is then observed for any cracking or separation.(Rasal, et al., 2010; D. Patel, et al., 2009)

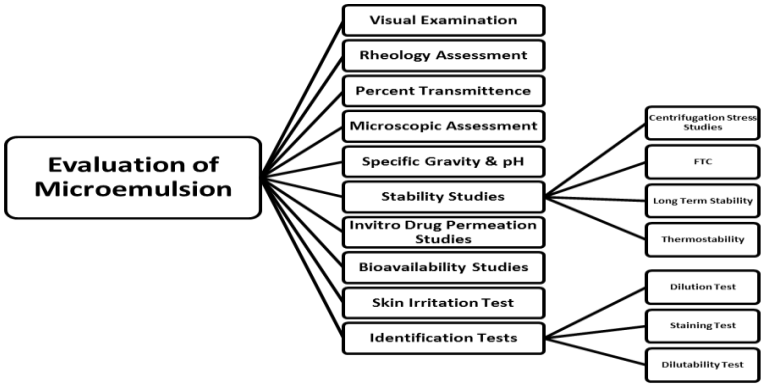

Figure 5. Evaluation Parameters for Microemulsion

Applications of Microemulsions

Microemulsions are currently serving as ideal formulation for delivery of wide range of lipophilic as well as hydrophilic drug constituents via various routes including parenteral delivery, oral drug delivery, topical delivery and ocular drug delivery.

Microemulsion in Parenteral drug delivery

Microemulsions are able to overcome the limitations related to the delivery of drugs with low solubility via parenteral route and maintain required concentration of drug at the target site. The microemulsions also have advantage in terms of the residence time as the fine particles of microemulsions are cleared at slow rate as compared to the coarse particles of the conventional emulsions. Another major advantage of microemulsion as parenteral formulation is that it has higher stability as compared to other novel formulations. Further, the choice of surfactants is one of the leading parameter for the development of parenteral microemulsions as several surfactants are toxic in nature.(Von Corswant, et al., 1998)

Microemulsion in Oral Delivery

Oral route is the most convenient route for the delivery of drugs and various formulations are available in the market. Microemulsion is emerging as ideal formulation for the oral administration as it improves the absorption, bioavailability, clinical potency and low toxicity and hence the drugs such as steroids, hormones, diuretics and antibiotics are ideally given by using microemulsions. Along with this, the bioavailability of the proteins and peptides is about 10% when administered as conventional oral dosage forms and hence unable to achieve the desirable therapeutic effects. Microemulsions are able to improve the bioavailability of the peptides and improve the stability of the preparation when introduced via the oral route.(H.-O. Ho et al., 1996; Kovarik et al., 1994)

Topical Administration via Microemulsion

The acceptance of topical administration is increasing continuously due to its convenience nature and high patient compliance. Both the oil in water as well as water in oil microemulsions are used for delivering the active ingredients via topical route of administration, which results in targeted delivery of drug as well as the systemic absorption of the active ingredients. Besides the advantages of microemulsions, the topical administration sometimes leads to the irritation but the number of benefits is encouraging the researcher to consider microemulsion as novel formulation.(H. O. Ho et al., 1998; Dreher et al., 1997)

Ocular Delivery via Microemulsion

Microemulsions are also used for as vehicle for ocular delivery and oil in water type is the most commonly studied microemulsion for ocular delivery. It can serve as ideal formulation for delivering poorly soluble drugs and helps in increasing

absorption and provides extended release of drugs. One of the examples of ocular microemulsion involves pilocarpine along with lecithin, PEG and propylene glycol, which shows low viscosity and refractive index and hence it is replacing the conventional ocular formulations.(Haβe et al., 1997)

Intranasal Administration & Brain Targeting

It helps in bypassing the first pass metabolism and result in improvement in bioavailability of the drug. (Goswami, et al., 2019) Intranasal route is ideal for delivering the drugs to brain as it is non-invasive, cheap and most convenient route and the drug reaches the brain after penetrating the brain barriers.(Wermeling et al., 2001; Dorman et al., 2002)

Periodontal Delivery

Microemulsions are also able to deliver the drug to a group of drugs affecting the gums, periodontal ligaments, cementum, and the supporting bone. Previous studies concluded that the microemulsions containing the anesthetic drugs and non-toxic surfactants are able to overcome the pain within the oral cavity along with the periodontal scaling and root. It is able to overcome the limitations of conventional doses such as jelly, ointment and spray. (Muzaffar et al., 2013)

Cellular & Tumor Targeting

Microemulsions are able to deliver the targeted therapies as composition and structure of microemulsions is assisting the drug to reach the target effectively and several studies are currently investigating the role of microemulsions in the targeted drug delivery.(Shiokawa et al., 2005)

Application of Microemulsions in biotechnology

Microemulsions are used in biotechnological studies related to the enzymatic activities. The microemulsions are able to conduct enzymatic reactions such as synthesis of esters, peptides and sugar acetyl transestrification, hydrolysis reaction and steroid transformation. As various enzymatic and biocatalyst reactions are undergone in the organic medium and hence the microemulsion can fulfill the demand of ideal vehicle.(Paul et al., 2001)

Other applications

- Microemulsions are able to improve the penetration rate of Lycopene and hence improve the absorption and availability.
- The transdermal penetration of Nimesulide is increased by administering via microemulsion.
- Microemulsions are also used in other industries as fuel, lubricant, corrosion inhibitors, coating and textile finishing.
- It is also used for developing porous media synthesis for analytical application.
- Microemulsions are also used in cosmetic industries, agrochemicals, food industries, oil recovery, detergent industry etc.(Paul, et al., 2001)

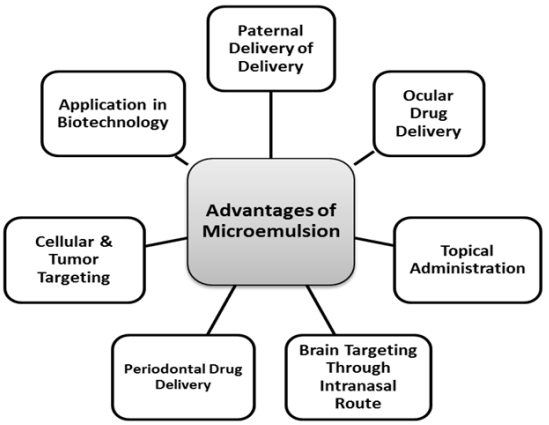

Figure 6. Advantages of Microemulsion

Future Scenario

Recently, several advancements have occurred in the field of microemulsion as many new surfactants are identified for developing an ideal form of this preparation. Along with this, various new methods are also identified by the researchers for developing microemulsions as well as nano-emulsions. These advancements result in overcoming of the limitations such as poor aqueous solubility and improve the absorption and bioavailability of the drug. Further, the newer methods are helping in reducing the overall cost of the production and marketed price of the final product. In future, the market penetration of microemulsion is believed to increase and its major application is observed in delivering the drugs via parenteral route. Further, the conventional chemotherapeutic drugs are also expected to deliver in the form of microemulsions as it will improve the bioavailability of these drugs and reduce the adverse events. Currently, the researchers of the leading pharmaceutical and biotechnological companies are focusing to develop more stable, compatible and safer microemulsion and many new products of this category are expected to enter the market in near future.(Muzaffar, et al., 2013; Zhang et al., 2020)

Table 1
Marketed Microemulsions with Active Ingredient, Indication & Manufacturer

S. No.	Brand Name	Active Ingredient	Indication	Manufacturer	Reference
1	Restasis	Cyclosporine A	Eye Inflammation	Allergan	(Luschmann et al., 2014)
2	Diazemuls	Diazepam	Fungal Infection	Brawn Mclsungen	(Collins-Gold et al., 1990)
3	Limethason	Dexamethasone	Arthritis	Green Cross	(Lu et al., 2008)

4	Etomidat	Etomidate	Anesthesia	Dumex	(Tamilvanan, 2008)
5	Lipfen	Flurbiprofen	High Cholesterol	Green Cross	(Park et al., 1999)
6	Liple	Prostaglandin-El	Impotency	Green Cross	(Abolmaali et al., 2011)
7	Diprivan	Propofol	Anesthesia	AstraZeneca	(Abolmaali, et al., 2011; Cai et al., 2012)
8	Douxoseborrhea	Phyto-sphingosine	Cleansing	Sogeval	(Kovalik et al., 2012)
9	Retamax	Retinol	Skin Care	Skin Health Inc.	(Praça et al., 2020)
10	White Glow	SPF25	Sunburn	Lotus Herbal	(Strickley, 2007)
11	Tray Bell	Cocoa Extract	Hair Nourishment	Alcantra	(Praça, et al., 2020; Strickley, 2007)
12	Norvir	Ritonavir	HIV Antiviral	AbbVie	(Gibaud et al., 2012)
13	Lipire	Fenofibrate	Hypertension	Emedi	(S. Sharma et al., 2015)
14	Convule	Valproic Acid	Epilepsy	Opsonin Pharma	(Strickley, 2007)
15	Fortovase	Saquinavir	HIV	Roche Laboratories	(Gibaud, et al., 2012)

Table 2
List of Drugs being used in Previous Studies for Developing & Evaluating Microemulsion

S. No.	Drug Used	Objective	Indication	Reference
1	Aceclofenac	Formulation of Aceclofenac Microemulsion for topical delivery	Pain	(Lee et al., 2005)

2	Penciclovir	Development of Penciclovir Microemulsion via dermal route.	Herpes Simplex Virus	(Zhu et al., 2008)
3	Silymarin	Formulation of Silymarin containing microemulsion for dermal delivery	Cirrhosis	(Panapisal et al., 2012)
4	Amphotericin B	Formulation, characterization and Optimization of Amphotericin B Microemulsion for Topical Use	Anti-Fungal	(Butani et al., 2014)
5	Tretinoin	Formulation Design & Development of Tretinoin Microemulsion	Anti-Inflammatory	(Moghimipour et al., 2012)
6	Griseofulvin	Development, Characterization & optimization of Griseofulvin Microemulsion	Skin infections	(Aggarwal et al., 2013)
7	Propofol	Design & Evaluation of Propofol Microemulsion	Anesthesia	(Li et al., 2012)
8	Naproxen	Design & Optimization of Naproxen Microemulsion	Pain	(Moghimipour et al., 2013)
9	Sertaconazole	Formulation, Characterization & Evaluation of Sertaconazole Microemulsion	Tinea pedis	(Sahoo et al., 2014)
10	Econazole	Formulation and Evaluation of Econazole Microemulsion for percutaneous delivery	Skin Infections	(Ge et al., 2014)
11	Voriconazole	Formulation & Optimization of Voriconazole Microemulsion for Ocular Delivery	Eye Infection	(R. Kumar et al., 2014)
12	Atorvastatin	Formulation, Optimization & Characterization of Atorvastatin loaded Microemulsion	Antihyperlipidemic	(B. Sharma et al., 2015)
13	Carbamazepine	Formulation & Characterization of Carbamazepine via transdermal route	Epilepsy	(R. B. Patel et al., 2013)
14	Ofloxacin	Preparation & evaluation of Ofloxacin containing microemulsion via ocular route	Eye Infection	(Üstündag-Okur et al., 2014)
15	Mustard Oil	Formulation of mustard oil emulsion	Anti-	(V. Ghosh

		for bactericidal activity	bacterial	et al., 2012)
16	Adapalene	Formulation of Adapalene Microemulsion for trans follicular delivery	Acne	(Bhatia et al., 2013)
17	5-fluorouracil	Formulation of novel ionic liquid based microemulsion of 5-fluorouracil	Anticancer	(Goindi et al., 2014)

Table 3
Patents Related to the Composition, Preparation & Utilization of Microemulsions

S. No.	Title of Patent	Patent Number	Outcome	Reference
1	Microemulsion process and composition	US8460641B2	It involves the composition of microemulsions for dermal delivery along with the method of preparation.	(Larm et al., 2013a)
2	Microemulsion cleaning composition	US7902123B2	It comprises of composition of surfactants, co-surfactants and co-solvents governing the cleaning activity.	(Harrison et al., 2011)
3	Alcohol-free microemulsion composition	US20060165739A1	It involves the composition of alcohol free microemulsion along with the method of preparation.	(Komesvarakul et al., 2006)
4	Gel-microemulsion formulations	US7064114B2	A composition of gel microemulsion, which can be used as spermicidal method and also as antimicrobial formulation.	(Yiv et al., 2006)
5	Linker-based lecithin microemulsion delivery vehicles	US9918934B2	This patent involves biocompatible microemulsion for controlled delivery of lecithin with surfactants of HLB less than 5.	(Acosta-Zara et al., 2018)
6	Atom transfer radical polymerization in microemulsion and true emulsion polymerization processes	US8273823B2	It involves the microemulsion polymerization involving catalyst, an ATRP initiator and an aqueous solution.	(Matyjaszewski et al., 2012)
7	Microemulsion flowback	US970188	This patent involves the	(Nguyen,

	aid composition and method of using same	8B2	microemulsion flowback aid along with the methods of improving the recovery of oil.	2017)
8	Aqueous two-phase emulsion gel systems for zone isolation	US770352 7B2	Method of preparing water-in-water emulsion containing polymers or oligomers, which is then used to develop of emulgel by removing one polymer.	(Sullivan et al., 2010)
9	Single phase microemulsions and in situ microemulsions for cleaning formation damage	US809164 6B2	It involves the application of single phase microemulsion in cleanup and removal of non-polar materials.	(Quintero et al., 2012)
10	Water-in-volatile silicone emulsion gel cosmetic	US200601 65616A1	This patent involves the alkanol-ammonium salts of alkyl-sulphonates containing microemulsions for antidandruff.	(Brock et al., 2006)
11	Pharmaceutical compositions based on a microemulsion	US201000 34880A1	This patent involves transdermal, transmucosal pharmaceutical composition of microemulsion containing one biological active constituent.	(Sintov et al., 2010)
12	Microemulsion to improve shale gas production by controlling water imbibition	US201100 21386A1	It consists of methods of treating tight gas and subterranean formations by forming microemulsion.	(Ali et al., 2011)
13	Nano capsules containing microemulsions	US107584 90B2	This patent is based on the formulation of nano capsules containing microemulsion.	(Petit et al., 2020)
14	Microemulsion and sub-micron emulsion process and compositions	US844986 7B2	It involves the composition of sub-micron and microemulsions for dermal delivery along with the method of preparation.	(Larm et al., 2013b)
15	Composition of microemulsion and method for advanced recovery of heavy oil	US818318 2B2	It consists of composition of microemulsion involving combination of surfactants and co-surfactants.	(Oliveira et al., 2012)

Conclusion

By analyzing various parameters and advantages related to the microemulsion, it is concluded that it has potential to emerge as ideal formulation for delivering a wide range of drugs via different routes including oral, topical, ocular, otic, parenteral etc. Microemulsion overcomes the limitations of the conventional emulsions and improves the bioavailability of both the hydrophilic as well as lipophilic drugs. Further, the commercial success of the available microemulsions is also encouraging the researchers of the leading pharmaceutical companies to work in this sector and many new microemulsions are expected to get approve in near future. Along with this, the advancement in technology related to the method of preparation of microemulsion and the identification of new emulsifier is also indicating towards the development of more stable and safer microemulsions, which further boosts the acceptance of this formulation among the population. As the nanotechnology-based products are demonstrating wide range of applications in the therapeutic sector, the microemulsions are currently replacing most of the liquid dosage forms in delivering drugs more effectively with improved safety profile.

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