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MICROEMULSION - A PROMISING DRUG DELIVERY STRATEGY - A REVIEW

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ABSTRACT

Microemulsions are clear, thermodynamically stable systems. They were used to solubilize drugs and to improve drug availability. Microemulsions have emerged as novel vehicles for drug delivery which 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. While microemulsions are used in several fields. this article we focus on the microemulsion in pharmaceutical use requires to understanding of the types, characters, and application of microemulsion.

KEYWORD: Microemulsion, advantages, disadvantages, Applications.

INTRODUCTION

Emulsions are pharmaceutical preparations consisting of at least two immiscible liquids; typically, oil and water. A microemulsion is defined as a dispersion consisting of oil, surfactant, co surfactant and an aqueous phase. It is a single optically isotropic and thermodynamically stable liquid solution with a droplet diameter usually within the range of 10– 100 nm. Microemulsions have a number of special properties such as enhanced drug solubility, good thermodynamic stability, ease of manufacturing and permeation enhancement ability over conventional formulations, which have been exploited in drug delivery systems, pharmaceutics, and food industries.[1]

Microemulsions are macroscopically isotropic mixtures of at least a hydrophilic, a hydrophobic and an amphiphilic component. Their thermodynamic stability and their nanostructure are two important characteristics that distinguish them from ordinary emulsions which are thermodynamically unstable. Microemulsions were first observed by Schulman and Winsor in the 1950s. Then, the term “microemulsions” has been used to describe multi-component systems comprising non-polar, aqueous, surfactant, and cosurfactant components. Conventional microemulsions can be classified oil-in-water, (o/w), water-in-oil (w/o) and bicontinuous phase microemulsions.[2]

All microemulsions are fluids with low viscosity. Depending upon their structure, microemulsions are of different types as water-in-oil (w/o), oil-in-water (o/w) or bicontinuous systems. Ultra-low interfacial tension exists between water and oil phases. Due to the presence of both lipophilic and hydrophilic domains, a wide range of lipophilic and hydrophilic drugs can be incorporated in these systems. Enzymatic hydrolysis and oxidation is prevented trough these flexible delivery systems. The solubilization and bioavailability of lipophilic drugs is improved. These systems can be used for topical, intravenous and oral delivery as well as for the sustained and targeted delivery. The oral bioavailability of many poorly soluble drugs is enhanced.[3]

Microemulsions are currently the subject of many investigations because of their wide range of potential and actual utilizations. The high capacity of microemulsions for drugs makes them attractive formulations for pharmaceuticals.

Types

According to Winsor, there are four types of micro emulsion phases exists in equilibrium, these phases are referred as Winsor phases. they are:

- Winsor I (two phase system): upper oil layer exists in equilibrium with lower (o/w) micro emulsion phase
- Winsor II (two phase system): the upper(w/o) micro emulsion exists in equilibrium with lower excess water.
- Winsor III (three phase system): middle bi-continuous phase of o/w and w/o called) exists in equilibria with upper phase oil and lower phase water.

- Winsor IV (single phase system): it forms homogenous mixture of oil, water and surfactant.[4]

Characterization of micro-emulsion

There are various techniques by which micro-emulsions are characterized. Because the micro-emulsions are very complex, they have various components involved in their systems, they have a very large variety of structures and also there are various limitations attached to their methods of characterization, it is very difficult to characterize micro-emulsions, but their characterization data is very much important used for their viable manipulation. Hence, corresponding revisions by means of the grouping of numerous methods remain essential to acquire an impressive sight of the structure and the Physico-chemical assets of the micro-emulsions. Physico-chemical characterization of microemulsion will be studied on the basis of follwing components.

- The dimension and the microstructure of the microemulsion.
- Phase behavior and phase stability.
- The local molecular rearrangement.
- The surface features like charge distribution and the specific area.
- Shape.
- Interface and changing aspects.

From these assets, Interface and changing aspects and the particle size are very much important as many general properties of the micro-emulsions are governed by them. There are various parameters on which the drug release from the micro-emulsions depends such as droplet size, Oil liquid section magnitude relation.[5]

Phases Involved in Micro-emulsion Formulation

Water phase

Depending upon the amount of water present in the system, water may form water pool or work as a dispersion medium in micro-emulsion system.

Oil phase

The oil phase must be chosen appropriately, since it governs the selection of the other ingredients for the micro emulsion and there are two main factors that need be considered before selecting the appropriate oil phase. Firstly, the solubilizing potential of the oil for the selected substance must be seen and secondly, the chosen must be 103 such that the micro emulsion forming region is enhanced. Oils with shorter hydrocarbon chains are easier to micro-emulsify as compared to oils with long hydrocarbon chains. An oils ability to solubilizing lipophilic groups is directly proportional to the chain length of the oil. Thus, the selected oil should be such that it is capable of solubilizing the API, and facilitating the formation of micro emulsions with desired characteristics.

Composition

The Major component in micro emulsion system are

1) Oil phase
2) Surfactant (primary surfactant)
3) Co-surfactant (secondary surfactant)
4) Co-solvent

Table 1: Component of microemulsion system.[6]

Component	Example
Oil	saturated fatty acid- lauric acid, carpic acid unsaturated fatty acid-oleic acid, linolic acid, linolenic acid fatty acid ester-ethyl or methyl ester of lauric, oleic acid and myristic acid
Surfactant	1)polyoxyethylene/polysorbate/tween 20,40,60,80 2)sorbitan monolaurate, eggs lecithin 3-sodium dodecyl sulphate
Co-surfactant	1)ethanol, proranol, butanol, isopropanol, pentanol, hexanol 2)polyoxyethylene-10-oelyl ether 3)sodium monohexyl phosphate 4-cinnamic alcohol, cinamic alcohol.

Advantages of Microemulsion

Microemulsions are potential drug carrier systems for various 6 routes of administration. These are having advantages when compare to the other dosage forms.

- ✓ These are thermodynamically stable and require minimum energy for formation.
- ✓ Ease of manufacturing and scale-up
- ✓ Improved drug solubilisation and bioavailability.
- ✓ This system is reckoned advantageous because of its wide applications in colloidal drug delivery systems for the purpose of drug targeting and controlled release.
- ✓ Liquid dosage form increases patient compliance.
- ✓ Provides protection from hydrolysis and oxidation as drug in oil phase in O/W microemulsion is not exposed to attack by water and air.
- ✓ Various routes like tropical, oral and intravenous can be used to deliver the product.
- ✓ Provides a aqueous dosage form for water insoluble drugs.
- ✓ Less amount of energy requirement.
- ✓ Increase the rate of absorption.

Microemulsion is having wide applications in colloidal drug delivery systems for the purpose of drug targeting and controlled release.[7]

Disadvantages F MICROEMULSIONS16-18

- ✓ The main problem in a microemulsions application is a high concentration and a narrow range of physiologically acceptable surfactants and cosurfactants.

- ✓ It has limit potential topical application due to their toxic and irritant properties of component.
- ✓ Large surfactant concentration (10-40%) determines their stability. It is poor palatability due to the lipid content leading to the poor patient compliance. Moreover, due to their water content, Microemulsions cannot be encapsulated in soft gelatin or hard gelatin capsules.[8]

Method of Preparation

1. Phase Titration Method

Microemulsions are prepared by the spontaneous emulsification method (phase titration method) and can be depicted with the help of phase diagrams. Construction of phase diagram is a useful approach to study the complex series of interactions that can occur when different components are mixed. Microemulsions are formed along with various association structures (including emulsion, micelles, lamellar, hexagonal, cubic, and various gels and oily dispersion) depending on the chemical composition and concentration of each component. The understanding of their phase equilibria and demarcation of the phase boundaries are essential aspects of the study. As quaternary phase diagram (four component system) is time consuming and difficult to interpret, pseudo ternary phase diagram is often constructed to find the different zones including microemulsion zone, in which each corner of the diagram represents 100% of the particular component. The region can be separated into w/o or o/w microemulsion by simply considering the composition that is whether it is oil rich or water rich. Observations should be made carefully so that the metastable systems are not included.[9]

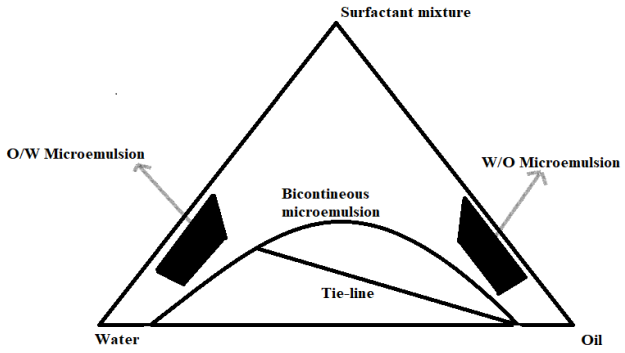

Figure 1: Pseudoternary phase diagram of oil, water and surfactant.

Phase Inversion Method

In the phase inversion method phase inversion of microemulsions occurs by addition of excess amount of the dispersed phase. During phase inversion quick physical changes occur including changes in particle size that can affect drug release both in vivo and in vitro. For non-ionic surfactants, this can be completed by changing the temperature, forcing a transition from oil in water microemulsion at low temperatures to water in oil microemulsion at higher temperatures (transitional phase inversion). During cooling, the system crosses a point of zero spontaneous curvature and minimal surface tension, promoting the formation of finely dispersed oil droplets. This method is also known as phase inversion temperature (PIT) method. Other than temperature, other parameters such as pH value or salt concentration may be considered more effectively instead of the temperature alone. Additionally, a transition in the spontaneous radius of curvature can be obtained by changing the water volume fraction. By successively adding water into oil, initially water droplets are formed in a continuous oil phase. By increasing the water volume fraction changes the spontaneous curvature of the surfactant from initially stabilizing a w/o microemulsion to an o/w microemulsion at the inversion point.[10]

Theories of Microemulsion Formation and Stabilization

There are three main theories of microemulsion formation and stabilization.

1. Mixed film theory, the interfacial film is considered as a duplex film, having different properties on the water and oil side of the interface. According to this theory the micro-emulsion has been capable to form instantaneous and spontaneously generate a negative interfacial tension in the surfactant and co-surfactant in working together. The film, which may consist of surfactant and cosurfactant molecules, is considered as a liquid ‘‘two dimensional’’ third phase in equilibrium with both oil and water. Such a monolayer could be a duplex film, i.e. giving different properties on the water side and oil side.

2. solubilization theory considers microemulsions as swollen micellar systems, i.e. solutions with solubilized water or solubilized hydrocarbon; in effect, one-phase systems. The formation of microemulsion is oil soluble phase and water phase by micelles or reverse micelles. In micellar it gradually become larger and swelling to a certain size range results.

3. thermodynamic theory proposes that the free energy of formation of microemulsion, ΔGm, consists of different terms, such as interfacial free energy, 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 the microemulsion formation.[11]

Applications of microemulsion

Microemulsion in pharmaceuticals

Parenteral administration: Parenteral administration (especially via the intravenous route) of drugs with limited solubility is a major problem in the pharmaceutical industry because of the extremely low amount of drug actually delivered to a targeted site. Microemulsion formulations have distinct advantages

over macroemulsion systems when delivered parenterally because of the fine particle, microemulsion is cleared more slowly than the coarse particle emulsion and, therefore, have a longer residence time in the body. Both O/W and W/O microemulsion can be used for parenteral delivery.

Oral administration: Oral administration of microemulsion formulations offer several benefits over conventional oral formulation including increased absorption, improved clinical potency, and decreased drug toxicity. Therefore, microemulsion has been reported to be an ideal delivery of drugs such as steroids, hormones, diuretic and antibiotics.

Pharmaceutical drugs of peptides and proteins are highly potent and specific in their physiological functions. However, most are difficult to administer orally. With on oral bioavailability in conventional (i.e. non-microemulsion based) formulation of less than 10%, they are usually not therapeutically active by oral administration. Because of their low oral bioavailability, most protein drugs are only available as parenteral formulations. However, peptide drugs have an extremely short biological half life when administered by parenteral route, so require multiple dosing.

Topical administration: Topical administration of drugs can have advantages over other methods for several reasons, one of which is the avoidance of hepatic first pass metabolism of the drug and related toxicity effects. Another is the direct delivery and targetability of the drug to the affected area of the skin or eyes.

Ocular and pulmonary delivery: Ocular and pulmonary delivery for the treatment of eye diseases, drugs are essentially delivered topically. O/W microemulsions have been investigated for ocular administration, to dissolve poorly soluble drugs, to increase absorption and to attain prolong release profile.

For instance microemulsions containing pilocarpine were formulated using lecithin, propylene glycol and PEG 200 as co-surfactant and iso-propyl myristate (IPM) as the oil phase. The formulations were of low viscosity with a refractive index lending to ophthalmologic applications.[12]

Table no:2 List of Recent Research Reported on Microemulsion.

Author Name	Method of Preparation	Drug	Components	Report
Khalid SH et al.,[13] (2018)	Water titration method	Miconazole Nitrate	Oils**:** oleic acid, eucalyptus oil, isopropyl myristate, soyabean oil, sweet almond oil, miglyol, coconut oil and olive oil Surfactants: tween 20, tween 80, tween 40, Span 20 and Span 80 co-surfactants: propylene glycol, PEG-400, glycerine and Labrasol	They concluded that the Microemulsion is a suitable vehicle to increase the solubility and topical delivery of miconazole nitrate with enhanced antifungal activity.
Yu S et al.,[14] (2019)	water titration method	carnosic acid	Oils: α-tocopherol Surfactants: Tween 20 and lecithin co-surfactants: Propylene glycol (PG)	Found that the photostability of carnosic acid was dramatically improved when it was encapsulated in MEs.
Mu G et al.,[15] (2019)	Phase inversion method	Bimatoprost	Oil: Isopropyl myristate Surfactants: Pluronic F68, Tween 20	Their work explored the successful application of bimatoprost microemulsion to improve the uptake of bimatoprost in the contact lenses and improve the drug release kinetics using soaking method.
Liu T et al.,[16] (2020)	Phase inversion method	Travoprost	Oil:I sopropyl myristate Surfactant: Tween 80 co-surfactants: isopropyl alcohol	Their work successfully demonstrates the application of a microemulsion system to improve travoprost loading in the contact lens along with improvement in the swelling and optical properties of the contact lenses with improvement in the drug uptake and the release profile.
GUL R et al.,[17]	water titration	Salbutamol Sulphate	Oil: oleic acid	Developed Salbutamol sulphate as

(2020)	method		Surfactant: polysorbate 20 co-surfactants: ethanol	a component of Micro emulsion-based gel has a good affinity for the membranes and enhancement of drug released in the cellulose membrane and reported ME was potential novel delivery systems to improve the release and stability of salbutamol
Das S et al.,[18] (2020)	water titration method	resveratrol	Oil: Tea tree oil Surfactant: Tween 80 co-surfactants: diethylene glycol monoethyl ether	Investigated to provide additional multiple skin care benefits depending on the efficacy of the oils. is known for its anti-oxidant efficacy. the developed resveratrol-loaded microemulsion gels by using Tea tree oil to provide long lasting multiple skin care benefits.
Tao J et al.,[19] (2018)	water titration method	7,2′,4′-trihydroxyflavanon	Oils: Peanut oil,Rapeseed oil, Sunflower oilOlive oil ,Soybean oil Aqua coconut oil Surfactants: Tween80 Kolliphor EL, Kolliphor RH 40 Co-surfactants: Propylene glycol Glycerol PEG 400	In this study, a food grade water in oil (O/W) microemulsion to improve the solubility and stability of 7,2′,4′-trihydroxyflavanone. The results showed that the solubility of 7,2′,4′-trihydroxyflavanone in the aqua coconut oil mi- croemulsion was up to 22.380 ± 0.336 mg/mL, which is approximately a 2000-fold solubility increase compared with that in water (0.011 mg/mL).
Gungor S et al., [20] (2018)	water titration method	Voriconazole and sertaconazole	oil: oleic acid surfactant: Tween 80 co-surfactant: ethanol	They suggested that therapeutic drug levels covering the MIC of most fungi could be reached by topical application of the formulated microemulsions, due to the enhanced permeation of drug containing microemulsion oil globules through the fungal cell wall, thereby inhibiting the ergosterol synthesis and causing the fungal cell death, confirmed against Candida species.
Grunhu M et al., [21] (2018)	Aqueous titration method	Octyl p-methoxycinnamate	0il: Ocimum basilicum Surfactant; DME co-surfactants: Ethyl alcohol	In this work an Ocimum basilicum essential oil based O/W microemulsion as a vehicle for a chemical UVB filter (OMC) and with a potential use as anti-inflammatory and mosquito repellent was investigated.
Maulvi FA et al., [22] (2020)	water titration method	Lidocaine tripotassium phosphate	Oil: Capmul MCM C8 EP Surfactant: Pluronic F127 co-surfactants: polyethylene glycol 400	Their work revealed the application of tailored lidocaine-tPP-complex loaded microemulsion as a potential strategy for proving prolong local anaesthesia.
Dhaval M et al., [23] (2020)	phase titration method	Sparfloxacin	oil: oleic acid Surfactants: Tween 20, tween 80, co-surfactants: polyethylene glycol,	Prepared microemulsified based in-situ gel system of sparfloxacin to improve its solubility and permeability through the cornea.

Baboota S et al.,[24] (2018)	water titration method	Duloxetine	Oils: pecol, olive oil, capryol 90, capmul MCM Surfactant: tween 80, tween 20, labrasol, labrafil co-surfactants: propylene glycol 600, Transcutol P, Plurol oleique, propylene glycol 400	Results revealed that permeability of duloxetine microemulsion was found to be significantly higher (1.5 times) when compared to duloxetine suspension
Shrestha S et al.,[25] (2017)	water titration method	Terbinafine HCL	Oils: oleic acid, liquid paraffin, propylene glycol Surfactants: surfactants like tween 80 and tween 20 co surfactant: Tween 80	Developed a novel drug delivery system with enhanced therapeutic efficacy by improving the solubility, permeability and hence bioavailability of terbinafine using microemulgel.

Table no:3 Microemulsions based marked products.

SL.NO	Brand Name	Composition	Manufactured by
1.	Sandimmune Neoral®	Cyclosporin	Novartis
2.	Fortovase®	Saquinavir	Roche Laboratories
3.	Norvir®	Ritonavir	Abbott Laboratorories
4.	Restasis	Cyclosporine A	Allergan
5.	Diazemuls	Diazepam	Braun Melsungen
6.	Limethason	Dexamethazone Palmitate	Green Cross
7.	Etomidat	Etomidate	Dumex (Denmark)
8.	Lipfen	Flurbiprofen	Green Cross
9.	Liple	Prostaglandin-E1	Green Cross
10.	Propofol	Propofol	Baxter Anesthesia
11.	Fluosol-DA	Perflurodecalin + Perflurotripropylamine	Green Cross
12.	Vitalipid	Vitamins A, D, E and K	Kabi

Review of litreture

Azeem *et al* (2009)., reviewed in detail about the microemulsions, which are isotropic, thermodynamically stable transparent (or translucent) systems of oil, water, and surfactant, frequently in combination with a cosurfactant with a droplet size usually in the range of 20–200 nm. They also reviewed the exploration of microemulsion for transdermal drug delivery with possibility of low surface tension in conjunction with enormous increase in the interfacial area due to nanosized droplets of the microemulsion that ultimately influences the drug permeation across the skin. Their study explored microemulsion as transdermal drug delivery vehicles with emphasis on components selection for enhanced drug permeation.[26]

Munir et al (2007)., studied Microemulsions are based on oil, water and surfactants and mostly in combination of co-surfactant. The resultant mixture is a stable heterogeneous system and has advantage over the conventional emulsion as well as over solution formulations. For topical, oral and parenteral administration, microemulsion acts as a potential carrier system. The main reason of selecting the microemulsion as drug delivery system is that it is easy to prepare, have ability to incorporate hydrophobic drug, stable and it exhibits more physical stability as compared to other vesicular systems. Their purpose of this study was the applications of microemulsions and to understand the important facts of this novel delivery system.[27]

Oliveira MB et al (2015)., Developed and characterized Fluconazole -loaded microemulsions for topical administration. of Fluconazole as prominent alternative to combat Cutaneous leishmaniasis. Fluconazole -loaded microemulsions improved the fluconazole safety profile that was they evaluated using red cell haemolysis and in vitro cytotoxicity assays with J-774 mouse macrophages. Their results suggested that fluconazole -loaded microemulsions exhibited treat to cutaneous leishmaniasis.[28]

Tirnaksiz F, et al (2012)., They reported topical water-in-oil type microemulsion containing Metronidazole and compared its effectiveness with a commercial gel product in the treatment of rosacea. They have conducted a randomized, double-blind, baseline-controlled, split-face clinical trial for the treatment of patients for both microemulsion and marketed gel, found that statistically significant difference in reduction of the main symptoms of rosacea for the patients treated with the

microemulsion. Finally they concluded, the microemulsion containing Metronidazole was found to be more effective in reducing the symptoms of rosacea compared to the commercial gel product.[29]

CONCLUSION

Microemulsions is the attractive technology platform for the pharmaceutical formulators as it has excellent solubilization properties, transparency and the relatively simple formulation process. There is still a considerable amount of fundamental work characterizing the physico-chemical behaviours of microemulsions that need to be performed before they can live to their potential drug delivery vehicle. It can able to protect labile drug, 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. Current study was concentrated on the making of safe, economical and extra Companionable micro-emulsion elements which are able to any improve the value of those innovative vehicles. So microemulsion is the one of the promising drug delivery system.

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