



MICROEMULSION: PHYTOCHEMICAL USED IN NEW PREPERATIONS

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Article Received on 05/03/2018

Article Revised on 26/03/2018

Article Accepted on 16/04/2018

ABSTRACT

Microemulsion is a clear transparent, thermodynamically stable dispersion of oil and water, stabilized by interfacial film of surfactant frequently in combination with a co-surfactant. Recently there has been a considerable interest for microemulsion formulation, for the delivery of hydrophilic as well as lipophilic drug as drug carriers because of its improved drug solubilisation capacity, long shelf life, ease of preparation and improvement of bioavailability. In this present review, we have discuss biopharmaceutical aspects, advantages, disadvantage, theories, formulations, marketed lipid based formulations, factors affecting formulation and phase behaviour, preparations, characterization and pharmaceutical application of Microemulsion.

KEYWORDS: Microemulsion is a clear pharmaceutical application of Microemulsion.

INTRODUCTION

Microemulsion is a system of water, oil and an amphiphile which is a single optically isotropic and thermodynamically stable liquid solution". In some respects, micro emulsions can be considered as small-scale versions of emulsions, i.e., droplet type dispersions either of oil-in- water (o/w) or of water-in-oil (w/o), with a size range in the order of 5–50 nm in drop radius. Such a description, however, lacks precision since there are significant differences between micro-emulsion and ordinary emulsions (or macroemulsions). In particular, in emulsions the average drop size grows continuously with time so that phase separation ultimately occurs under gravitational force, i.e., they are thermodynamically unstable and their formation requires input of work. The drops of the dispersed phase are generally large (> 0.1 μm) so that they often take on a milky, rather than a translucent appearance. For micro-emulsion, once the conditions are right, spontaneous formation occurs. As for simple aqueous systems, microemulsion formation is dependent on surfactant type and structure. If the surfactant is ionic and contains a single hydrocarbon chain (e.g., sodium dodecylsulphate, SDS) micro-emulsion are only formed if a co- surfactant (e.g., a medium size aliphatic alcohol) and/or electrolyte (e.g., 0.2 M NaCl) are also present. With double chain Ionics (e.g., Aerosol-OT) and some non-ionic surfactants a co-surfactant is not necessary. This results from one of the most fundamental properties of micro- emulsion, that is, an ultra-low interfacial tension between the oil and water phases, γ o/w. The main role of the surfactant is to reduce γ sufficiently – i.e., lowering the energy required to o/w increase the surface area – so that

spontaneous dispersion of water or oil droplets occurs and the system is thermodynamically stable.

Defination and History

Micro emulsions, or μ -emulsions, are isotropic mixtures of oil, water and surfactant; usually with a co-surfactant and the oil being a mixture of different hydrocarbons and olefins.^[1]

The concept of micro-emulsion was introduced by Professor, Jack H. Shulman at Columbia University in 1959. The definition of a microemulsion have varied with time and location, but the more commonly accepted view is that of a "system of water, oil and amphiphile which is a single optically isotropic and thermodynamically stable liquid solution"^[2] and that in a microemulsion the surfactant is located at a certain boundary between the oil and aqueous phases, giving the microemulsion a definite microstructure. The above mentioned surfactant molecules, in most cases, comprise of a polar head which make up a small fraction of the molecular volume and a non-polar tail. These two regions allow them to interact with the polar aqueous phase and the non-polar oil phase. Surfactant molecules associate into different forms, including spherical micelle, rod micelle laminar phase and hexagonal phase, to minimise the Gibbs free energy of the system and to "optimise solvation requirements".

Advantages and Disadvantages

Advantages of Microemulsion as Oral Drug Vehicle

- Increases the rate of absorption.

- Eliminates inter-subject and intra-subject variability in absorption.
- Helps to solubilize lipophilic drug.
- Provides a aqueous dosage form for water insoluble drugs.
- Thermodynamically stable system, so for long time they can remain stable without any type of aggregation or creaming.
- Releases drug in controlled fashion.
- Minimizes first pass metabolism.
- Increases bioavailability.
- Helpful in taste masking.
- Provides protection from hydrolysis and oxidation as drug in oil phase in O/W microemulsion is not exposed to attack by water and air.
- Ease of preparation due to spontaneous formation.
- Scale up process is also easy.^[3]

Disadvantages (limitations) of Microemulsion as Oral Drug Vehicle

- Use of a large concentration of surfactant and co-surfactant necessary for stabilizing the Nano droplets.
- Limited solubilizing capacity for high-melting substances.
- The surfactant must be nontoxic for using pharmaceutical applications.
- Microemulsion stability is influenced by environmental parameters such as temperature and pH. These parameters change upon microemulsion delivery to patients.
- For unique dosage preparation in gelatine capsules, it may produce softening or hardening effect on

capsule shell, so for long term storage it is undesirable.^[3]

Phytochemicals as Micro Emulsion

In modern drug discovery era, various chemically synthesized new molecules are approved by FDA and are coming on the market, having wide therapeutic efficacy, but the adverse effects are associated with this therapy causes serious adverse effects which could be life threatening. Conventional therapy provides non-targetability in tissues and organs due to peak and valley fluctuations, and a frequent dose of administration can produce troublesome for allopathic medicines lead to poor patient compliance. The controlled release drug delivery system provides drug release at a controlled rate and maintains the overall therapeutic concentration of the drug in the body. In ancient times, herbal remedies and natural extract are consumed by people to cure various diseases. These herbal remedies contain hundreds of phytoconstituents present, which is working simultaneously against the disease. In recent times, the interest of people in phytopharmaceuticals has been increasing day-by-day among physicians and patients, and it is evident from the global market of herbal medicine and phytopharmaceuticals that has increased from \$18 billion from 2005 and \$26 from 2011. Various dietary products and supplements are also derived from the natural origin are also gaining more interest in the industry and the global market for phytopharmaceuticals. Some phytoconstituents derived from the natural origin are having a poor solubility and low bioavailability resulting in a narrow therapeutic index, which hinders his novel efficiency, so formulation scientist is working on targeting and controlled drug release of phytoconstituents to provide better therapeutic effect and increased patient compliance.

List of some micro herbal emulsions: Table 1.^[7]

Phytoconstituent	Chemical nature and source	Pharmacological activity	Clinical significance
Curcumin	Diarylheptanoid, obtained from <i>Curcuma longa</i>	Anticancer activity, anti-inflammatory activity	Improved permeation and enhancement ratio via transdermal delivery
Triptolide	Diterpenoid triepoxide, obtained from Chinese herb, <i>Tripterygium wilfordii</i>	Useful in autoimmune disorders, antineoplastic	Microemulsion based hydrogel provides improved percutaneous permeability and better-sustained release profile
Psoralen	Coumarin glycoside, obtained from <i>Psoralea corylifolia</i>	Useful in skin disorders, leprosy, and anti-inflammatory	Topical delivery via microemulsion provides better in vivo anti-inflammatory effect
Silybin	Flavolignans, obtained from <i>Silybum marianum</i>	Broad spectrum activity against human prostate adenocarcinoma cells	Microemulsion vehicle shows prolonged release profile as compared to silymarin solution
Docetaxel	Taxol compound, obtained from <i>Taxus</i> species (<i>Taxus baccata</i> , <i>Taxus brevifolia</i>)	Broad spectrum antimetabolic compound against all types of cancer	Docetaxel microemulsion provides improved apical to basolateral transport across Caco-2 cells
Puerarin	Isoflavone compound, obtained from <i>Radix puerariae</i>	Useful in cardiovascular disorders	AUC _{0-∞} was 15.82-fold higher in microemulsion as compared to puerarin suspension

Pharmaceutical Applications of Micro-emulsion Parenteral Delivery

Parenteral administration (especially via the intravenous route) of drugs with limited solubility is a major problem in 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. The literature contains the details of the many microemulsion systems, few of these can be used for the parenteral delivery because of the toxicity of the surfactant and parenteral use. An alternative approach was taken by Von Corsewant and Thoren in which C3-C4 alcohols were replaced with parenterally acceptable co-surfactants, polyethylene glycol (400) / polyethylene glycol (660) 12-hydroxystearate / ethanol, while maintaining a flexible surfactant film and spontaneous curvature near zero to obtain an almost balanced middle phase microemulsion. The middle phase structure was preferred in this application, because it has been able to incorporate large volumes of oil and water with a minimal concentration of surfactant.^[4]

Oral Delivery

Microemulsion formulations offer the several benefits over conventional oral formulation for oral administration including increased absorption, improved clinical potency and decreased drug toxicity. Therefore, microemulsion have been reported to be ideal delivery of drugs such as steroids, hormones, diuretic and antibiotics. The microemulsion droplets dispersed in the gastrointestinal tract provide large surface area and promote a rapid release of dissolved form of the drug substance and/or mixed micelles containing drug substance, and they may be also responsible for transporting the drug through the unstirred water layer to the gastrointestinal membrane for absorption. In addition to the enhanced dissolution of drugs, another factor contributing to the increasing bioavailability is that lymphatic transport is responsible for a portion of the entire drug uptake as well. The lipid composition of system may be related to facilitate the extent of lymphatic drug transport by stimulating lipoprotein formation and intestinal lymphatic liquid flux.

Pharmaceutical drugs of peptides and proteins are highly potent and specific in their physiological functions. However, most are difficult to administer orally. With 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 parenterally, so require multiple dosing.^{33A} microemulsion

formulation of cyclosporine, named Neoral® has been introduced to replace Sandimmune®, a crude oil-in-water emulsion of cyclosporine formulation. Neoral® is formulated with a finer dispersion, giving it a more rapid and predictable absorption and less inter and intra patient variability.^[5]

Topical Delivery

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 affected area of the skin or eyes. Both O/W and W/O micro-emulsion have been evaluated in a hairless mouse model for the delivery of prostaglandin E1. The micro-emulsion were based on oleic acid or Gelucire 44/14 as the oil phase and were stabilized by a mixture of Labrasol (C8 and C10 polyglycolysed glycerides) and Plurol Oleique CC 497 as surfactant. Although enhanced delivery rates were observed in the case of the o/w microemulsion, the authors concluded that the penetration rates were inadequate for practical use from either system. The use of lecithin/IPP/water microemulsion for the transdermal transport of indomethacin and diclofenac has also been reported. Fourier transform infra red (FTIR) spectroscopy and differential scanning calorimetry (DSC) showed the IPP organogel had disrupted the lipid organisation in human stratum corneum after a 1 day incubation.^[6]

CONCLUSION

Microemulsion is a powerful formulation tools for poorly soluble API's, both for the oral and topical administration routes. The availability of efficient, non-toxic surfactants and co-surfactant now makes them a very attractive and feasible option to overcome the bioavailability problems frequently encountered in the development of modern drugs. Drug delivery through microemulsion is a promising area for continue research with the aim of achieving controlled released with enhancing bioavailability and for drug targeting to various site in the body.

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