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Micro Emulsions: An Overview And Pharmaceutical Applications

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ABSTRACT

Micro emulsions are clear, stable, isotropic mixtures of oil, water and surfactant, frequently in combination with a co-surfactant. Micro emulsions act as potential drug carrier systems for oral, topical, and parenteral administration. They offer the advantage of spontaneous formation, ease of manufacturing and scale-up, thermodynamic stability, and improved drug solubilization and bioavailability. Knowledge of the various methods available to thoroughly characterize a microemulsion system is essential. While microemulsion is used in several fields, in this review the pharmaceutical applications are emphasized. Micro emulsions are one of the best candidates as novel drug delivery system because of their long shelf life, improved drug solubilization with ease of preparation and administration. They have emerged as novel vehicles for drug delivery which allow controlled or sustained release for ocular, percutaneous, topical, transdermal, and parenteral administration of medicaments. The main objective of this review paper is to discuss Micro emulsions as drug carrier system with other possible applications.

Key words:
Microemulsion,
Oil, Water,Vehicle,
Surfactant,Drug Delivery.

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INTRODUCTION

The pharmaceutical term “emulsion” is most time used to indicate preparations prepared for internal use. Emulsions for external use are always given a different title that it focus may indicate their use, e.g. lotion and cream (Christopher and Dawn, 2008). An emulsion may be defined as a biphasic system consisting of two immiscible liquids, one of which (the dispersed phase) is finely and uniformly dispersed as globules throughout the second phase (the continuous phase).Micro emulsions are clear, stable, isotropic liquid mixtures of oil, water and surfactant, frequently in combination with a co-surfactant. The aqueous phase may contain salt(s) and/or other ingredients, and the "oil" may actually be a complex mixture of different hydrocarbons and olefins. In contrast to ordinary emulsions, micro emulsions form upon simple mixing of the components and do not require the high shear conditions generally used in the formation of ordinary emulsions. The two basic types of micro emulsions are direct (oil dispersed in water, o/w) and reversed (water dispersed in oil, w/o) [1-3]. In principle, micro emulsions can be used to deliver drugs to the patients via several routes, but the topical application of micro emulsions has gained increasing interest. The three main factors determining the transdermal permeation of drugs are the mobility of drug in the vehicle, release of drug from the vehicle, and permeation of drug into the skin. These factors affect either the thermodynamic activity that drives the drug into the skin or the permeability of drug in the skin, particularly stratum corneum.Micro emulsions improve the transdermal delivery of several drugs over the conventional topical preparations such as emulsions and gels [4-7]. Mobility of drugs in micro emulsions is more facile [8], as compared to the micro emulsion with gel former which will increase its viscosity and further decrease the permeation in the skin[9]. The superior transdermal flux from micro emulsions has been shown to be mainly due to their high solubilization potential for lipophilic and hydrophilic drugs.

TYPES OF EMULSION

OIL IN WATER EMULSION

If the oil droplets are dispersed throughout the aqueous phase, the emulsion is termed oil-in-water (O/W) as shown in Fig.1. Fats or oils for oral administration, either as medicaments in their own right, or as vehicles for oil soluble drugs, are always formulated as oil in water (O/W) emulsions (Aulton, 1996). They are non greasy and are easily removable from the skin surface and they are used externally to provide cooling effect and internally to also mask the bitter taste of oil. Water soluble drugs are more quickly released from O/W emulsion.

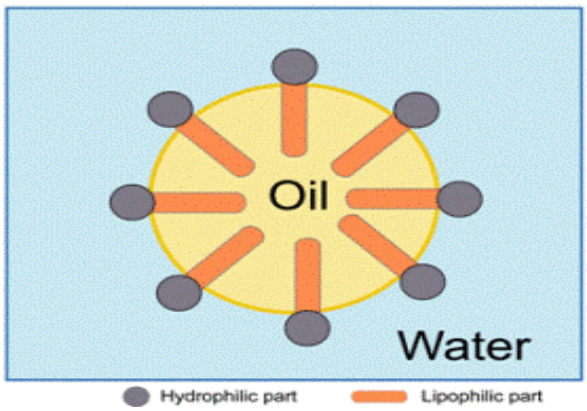
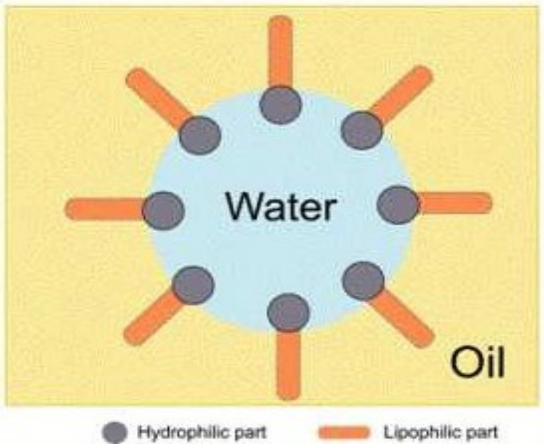


Fig.1: O/W emulsion.

WATER IN OIL EMULSION

A system in which the water is dispersed as globules in the oil continuous phase is termed water-in-oil emulsion (W/O) as shown in Fig.2. Water-in-oil emulsions will have an occlusive effect by hydrating the stratum corneumand inhibiting evaporation of eccrine secretions. It has an effect on the absorption of drugs from W/O emulsions. W/O emulsion is also useful for cleansing the skin of oil soluble dirt, although its greasy texture is not always cosmetically acceptable (Aulton,

1996). They are greasy and not water washable and are used externally to prevent evaporation of the moisture from the surface of skin e.g. cold cream. Oil soluble drugs are more



quickly released from W/O emulsion.

Fig.2: W/O emulsion.

MULTIPLE EMULSIONS

Multiple emulsions are complex systems. They can be considered as emulsions of emulsions, and have been shown been shown to be secured in cosmetic pharmaceutical and separation sciences. It is a complex type of emulsion system in which the oil-in-water or water-in-oil emulsions are dispersed in another liquid medium. In this way an oil-in-water-in-oil (O/W/O) emulsion consists of very small droplets of oil dispersed in the water globules of a water-in-oil emulsion and a water-in-oil-in-water (W/O/W) emulsion consists of droplets of water dispersed in the oil phase of an oil-in- water emulsion. Their pharmaceutical applications include taste masking, adjuvant vaccines, an immobilization of enzymes and sorbent reservoir of overdose treatments, and sometimes for the augmentation of external skin or dermal absorption. Multiple emulsions have been formulated as cosmetics, such as skin moisturizer. Prolonged release can also be obtained by means of multiple emulsions. These systems have some advantages, such as the protection of the ensnared substances and the possibilities of incorporating several actives ingredient in the different compartments. Regardless of their importance, multiple emulsions have limitations because of thermodynamic instability and their complex structure.

MICRO EMULSIONS

Micro emulsions are systems consisting of water, oil and surfactant, which constitute a single optically isotropic and thermodynamically stable liquid solution. A simple way to formulate a micro emulsion was to suggested by Hoar and Schulman. There are two types of micro emulsion, one is O/W and the second is W/O micro emulsion. For preparation of O/W micro emulsion, we start with w/o emulsion using a low hydrophylic- lipophylic balance (HLB) number surfactant .To this emulsion, an aqueous solution of high HLB number surfactant is added while stirring at a certain amount of addition, a 'gel' phase is produced and further addition of surfactant solution, an inversion into O/W emulsion take place. For W/O micro emulsion, one start with O/W emulsion stabilized with an ionic or nonionic surfactant. This emulsion is titrated with a co-surfactant and the emulsion passes through a gel phase, after which further addition of co-surfactant result in the production of W/O micro emulsion. However, a drawback of micro emulsion is the possibility of disruption of the crystalline structure of stratum corneum. These lead to facilitated transdermal transport and skin irritation.

Pickering Emulsion

The solid particles in the colloidal size may be used as emulsion stabilizers. Such particles are known as pickering emulsion. Pickering emulsions are recently employed in many areas like cosmetics, food, pharmaceuticals, oil recovery and waste water treatment.

Basic Differences between Macroemulsion and Microemulsion [10-12]

S.No	Macroemulsion	Microemulsion
1.	They are lyophobic in nature.	They are the border between lyophilic and lyophobic.
2.	Droplet diameter 1 to 20 mm.	Droplet diameter 10 to 100 mm.
3.	Macro emulsion droplets exist as individualentities.	Micro emulsion droplets disappear within Fraction of seconds.
4.	Emulsion droplets are	Micro emulsions are the structures of various droplets like bi-continous to swollen micelles.
5.	Macro emulsions requires quick agitation fortheir formation.	Micro emulsions are obtai b gen mixing ned y tle ingredient s.
6.	Most of the emulsions are opaque (white) inappearance.	Micro emulsions are transparent ortranslucent in nature.

TYPES OF MICRO EMULSIONS [13-16]

Micro emulsions are thermodynamically stable, but are only found under carefully defined conditions. According to Winsor, there are four types of micro emulsion phases exists in equilibria, these phases are also referred as Winsor phases. Theyare,

1. O/W microemulsion or winsorI
2. W/O microemulsion or winsorII
3. Bicontinuousmicroemulsion or winsorIII
4. Single phase homogeneous mixture or winsor IV
5. O/W micro emulsion or winsor I

In Oil-in-water type of micro emulsions droplets of oil is surrounded by a surfactant (and may be co-surfactant) film that forms the internal phase distributed in water, which is the continuous phase. This type of micro emulsion generally has a larger interaction volume than the w/o micro emulsions.

W/O MICRO EMULSION OR WINSOR II

In Water-in-oil type of micro emulsions droplets of water surrounded by a continuous oil phase. These are recognized as "reversemicelles", where the polar headgroups of the surfactant are facing into the droplets of water, with the fatty acid tails facing into the oil phase. A w/o micro emulsionused

orally or parenterally may be destabilized by the aqueous biologicalsystem.

BICONTINUOUS MICRO EMULSION OR WINSORIII

In bicontinuousmicroemulsion system the amount of water and oil present are similar, In this case, both water and oil exist as a continuous phase. An irregular channel of oil and water are combined, and looks like a "sponge-phase". Transitions from o/w to w/o Micro emulsions may pass through this bicontinuous state. Bicontinuous microemulsion, may show non-Newtonian flow and plasticity. These properties make them especially useful for topical delivery of drugs or for intravenous administration.

SINGLE PHASE HOMOGENEOUS MIXTURE OR WINSOR IV

In single phase homogeneous mixture or winsor IV the oil, water and surfactants are homogenously mixed.

INGREDIENTS OF MICROEMULSION [17-19]

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

1. Oilphase
2. Aqueousphase
3. Surfactant
4. Co-solvent

OIL PHASE [20]

Oil is one of the most important components of microemulsion because it can solubilize the required dose of the lipophilic drug and it increases the fraction of lipophilic drug transported via the intestinal lymphatic system. The examples of such phase are cyclohexane, mineral oil, toluene, & vegetable oiletc.

AQUEOUS PHASE

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

SURFACTANT [21]

The term surfactant (surface-active-agent) denotes a substance which exhibits some superficial or interfacial activity & used to lower the surface or interface tension. It has affinity for polar & nonpolar solvents. Surfactants arethe molecules that contain a polar head group and a polar tail. Surfactant molecules self-associate due to various inter- and intra-molecular forces as well as entropy considerations. The surfactant molecules can arrange themselves in a variety of shapes. They can form spherical micelles, a hexagonal phase, lamellar (sheet) phases, rod shaped micelles, reverse micelles, or hexagonal reverse micelles. At low concentrations of dispersed (internal) phase, spherical, isolated droplets are present in the micro emulsions. The various types of surfactants that help in the progressive development of micro emulsion systemare

1. Cationic
2. Anionic
3. Non-ionic
4. Zwitterionicsurfactants.

CATIONIC SURFACTANT

Cationic Surfactants when come in contact with water they come into amphiphilic cation and anion form, most often of halogen type. A very large quantity of this class corresponds to nitrogen compounds such as quaternary ammoniums and fatty amine salts, with one or several long chain of the alkyl type, often coming from natural fatty acids. The most well-known examples from the cationic surfactant class are hexadecyltrimethyl ammonium bromide and didodcecyl ammonium bromide. These surfactants are in general more expensive than anionics.

ANIONIC SURFACTANT

When anionic Surfactants are dissociated in water in an amphiphilic anion, and a cation, which is in general an alkaline metal (Na,K) or aquaternary ammonium. These are the most commonly used surfactants. The anionic charge in these surfactants comes from the ionized carboxyl group. Anionic surfactants account for about 50 % of the world production. Alkalialkanoates, also known as soaps, are the most common anionic surfactants. This is the most well-known type of surfactant when it comes to their shape and function. The three most important anionic groups in all of these surfactants are carboxylate, sulfonate and sulfategroups.

NON-IONIC SURFACTANT

Non-ionic surfactant is stabilized by dipole and hydrogen bond interactions with the hydration layer of water on its hydrophilic surface. They do not ionize in aqueous solution, because their hydrophilic group is of non-dissociable type, such as phenol, alcohol, ester, or amide. A large proportion of these nonionic surfactants are made hydrophilic by the presence of a polyethylene glycolchain.

ZWITTERIONIC SURFACTANT

Zwitterionic surfactants contain both positively and negatively charged groups and form micro emulsions by addition of co-surfactants. Phospholipids, such as lecithin, obtained naturally from soybean or egg are common zwitterionic surfactants. Unlike other ionic surfactants, which is somewhat toxic, lecithin which contains diacylphosphatidylcholine as the major constituent show excellent biocompatibility. Other important class of zwitterionic surfactants is the betaines, such as alkylbetaines, and heterocyclic betaines.

CO-SOLVENT [22]

It has been observed that single-chain surfactants are unable to reduce the o/w interfacial tension sufficiently to form a micro emulsion. The addition of co-surfactants allows the interfacial film to be flexible to take up different curvatures required to form micro emulsion over a wide range of excipients. If a single surfactant film is desired, the lipophilic chains of the surfactant should be sufficiently short, or contain fluidizing groups (e.g. unsaturated bonds). Basic co-surfactants are short chain alcohols (ethanol to butanol), glycols such as propylene glycol, medium chain alcohols, amines or acids. The use of co-surfactant is to destroy liquid crystalline or gel structures that come in place of a micro emulsionphase.

METHOD OF FORMULATION [23,24]

Micro emulsions are prepared when interfacial tension at the oil/water is kept at very low level. Interfacial layer is kept very much flexible and fluid concentration of surfactants should be high enough to give surfactant molecules to be stabilized the

microemulsion at an extremely low interfacialtension. Two main method are reported for the formulation of microemulsion, theseare

1. Phase InversionMethod
2. Phase TitrationMethod

PHASE INVERSION METHOD [25]

In the phase inversion method phase inversion of Micro emulsions 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 micro emulsion to an o/w microemulsion at the inversionpoint.

PHASE TITRATION METHOD [26]

Micro emulsions are formulated by the spontaneous emulsification method (phase titration method) and can be shown with the help of phase diagrams. A mixture of fatty acid and oil is added to a caustic solution to prepare a microemulsion, then after it is titrated with a co-surfactant, an alcohol, until the system turned clear. Micro emulsions 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. It is found that as the chain length of the surfactant increased, Micro emulsions with significant transmittances by visible spectrum can be formed with oils of longer chain lengths. It is also found that different alcohols affect the formation of Micro emulsions in different ways. The best results, in terms of the greatest percent transmittance coupled with the widest range of oil (dispersed in water) concentration, are obtained from short or branchedalcohols.

FACTOR AFFECTING FORMULATION OF MICRO EMULSION SYSTEM [27-29]

PROPERTY OF SURFACTANT

Surfactant contains two group lipophilic and hydrophilic groups. Hydrophilic single chain surfactants such as cetylethyl ammonium bromide dissociate completely in dilute solution and have a tendency to form o/w microemulsion. When the surfactant is in presence of salt or when high concentration of surfactant is used, degree of dissociation of polar groups becomes lesser and resulting system may be w/o type.

Property of Oil Phase

Oil phase also influence curvature by its ability to penetrate & Swell the tail group region of the surfactant monolayer, swelling of tail results into an increased negative curvature to w/o microemulsion.

PACKING RATIO [30]

HLB of surfactant determines the type of microemulsion through its influence on packing and film curvature. The analysis of film curvature for surfactant association`s leading to the formation of microemulsion.

TEMPERATURE [31]

Temperature is extremely important in determining the effective head group size of nonionic surfactants. At low temperature, they are hydrophilic and form normal o/w system. At higher temperature, they are lipophilic and form w/o systems. At an intermediate temperature, microemulsion coexists with excess water and oil phases and forms bicontinuousstructure.

APPLICATION OF MICROEMULSION SYSTEM

MICROEMULSION IN PHARMACEUTICAL

From last two decades there has been a revolution in the utilization of microemulsion systems in a variety of pharmaceuticals.

PARENTERAL DELIVERY [32]

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.

ORAL DELIVERY [33]

Microemulsion formulations offer the several benefits over conventional oral formulation including increased absorption, improved clinical potency, and decreased drug toxicity. Therefore, Micro emulsions have been reported to be ideal delivery of drugs such as steroids, hormones, diuretic and antibiotics.

TOPICAL DELIVERY [34]

Topical administration of drugs can have advantages over other methods for several reasons, one of which is the avoidance of hepatic first-pass metabolism, salivary and degradation of the drug in stomach and related toxicity effects. Another is the direct delivery and targetability of the drug to affected areas of the skin or eyes. Now a day, there have been a number of studies in the area of drug penetration into the skin. They are able to incorporate both hydrophilic (5-flurouracil, apomorphine hydrochloride etc) and lipophilic drugs (estradiol, finasteride, ketoprofenetc) and enhance their permeation. Since formation of microemulsion formation requires high surfactant concentration, the skin irritation aspect must be considered especially when they are intended to be applied for a longer period.

OCULAR AND PULMONARY DELIVERY [35]

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

OTHER PHARMACEUTICAL APPLICATIONS [36-39]

1. Nasaldelivery
2. Drug targeting
3. Cellulartargeting
4. Brain targeting
5. Periodontaldelivery
6. Tumor targeting

CONCLUSION

The role of microemulsion in providing novel solutions to overcome the problems of poor aqueous solubility of highly lipophilic drug compounds and provide high, more consistent and reproducible bioavailability. Till date, Micro emulsions have been shown to be 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. There is still however a considerable amount of fundamental work characterizing the physico-chemical behavior of Micro emulsions that needs to be performed before they can live up to their potential as multipurpose drug deliveryvehicles. Micro emulsions can also be used to achieve drug targeting however challenges remain, primarily because of the layers of barriers that these systems need to overcome to reach to the target. In today's world Microemulsion is accepted as full of potential for novel drug delivery systems. Current research work is focused on the preparation of safe, efficient and more compatible microemulsion constituents which will further enhance the utility of these novelvehicles.

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