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Review Article

MICROEMULSIONS - A POTENTIAL CARRIER FOR DRUG DELIVERY

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ABSTRACT

Microemulsions (MEs) have attracted much interest over the past years as potential drug delivery systems because of their transparency ease of in preparation and long-term stability. MEs provide sustained or controlled drug release for different routes of administration including parenteral administration. It shows advantages in the drug delivery like greater absorption of drugs, alteration of the kinetics of the drug release and decreased toxicity are several advantages in the delivery process. In this article, the ME preparation techniques and applications were discussed in detail.

Keywords: Hydrophilic Lipophilic balance, Phase behavior, surfactants, Differential scanning calorimetry.

INTRODUCTION

The microemulsion (MEs) concept was introduced as are molecularly dispersed. Most of the researchers in 1940's who generated a clear single-phase solution by Titratinga milky emulsion with hexanol. Schulman *et al.* (1959) subsequently coined the term ME [1,2].

The MEs definition provided by Danielson and Lindman in 1981 will be used as the point of reference.

These systems have an advantage over "conventional emulsions" is that they are thermodynamically stable liquid systems and are spontaneously self-forming. Moreover, the radius of MEs is as small as <100 nm, which indicates that the nanoscale effect of MEs will enhance either the penetration into or absorption by cells. To develop MEs (MEs), an important parameter take into account is the hydrophilic-lipophilic balance (HLB) of the surfactant or surfactant mixture. It is related to the contribution of both hydrophilic and hydrophobic fragments of a surfactant molecule. In general, surfactants with HLB values between 8 and 20 are able to form O/W MEs, while W/O MEs are formed when the HLB range is 4-7 [3,4].

It is also known that using mixed surfactants or adding can reduce the surface tension between oil and water when preparing ME. Choice of the surfactant is critical for the formulation of MEs. The HLB of surfactant may be adjusted by a short-chain alcohol, or adding either a non-ionic surfactant for the preparation of stable MEs is known that a single surfactant is not sufficient to form single-phase MEs and an adequate mixture of surfactants may be required to optimize the MEs formation.

The use of mixtures of nonionic surfactants is an interesting approach from the pharmaceutical point of view since such surfactants are generally regarded as low toxicity and irritancy and therefore, considered to be acceptable for oral administration. In addition, the use of mixtures allows the individual concentration of each surfactant to be decreased, which may increase the biocompatibility of the final formulations. Therefore, Tween80 was mixed with the hydrophobic surfactants of the Span series to provide surfactant blends to screen and select the best surfactant mixture to prepare oil-in-water (o/w) MEs [5,6].

Injectable emulsions must meet many of the same requirements that pertain to all parenteral products. These requirements include physicochemical stability (physically and chemically stable), endotoxin free, sterilizable, maximum globule size (<1 or 2 mm), and biological stability (low incidence of side-effects, sterile and non-antigenic and all components metabolized or excreted).

Unique to parenteral emulsions are strict requirements for globule size and surface charge. These two aspects are important in the manufacture and control of emulsions.

All injectable emulsions are their strict globule size requirement, as this has a direct effect on both toxicity and stability [7,8].

Advantages of MEs over other dosage forms

1. Increase the rate of absorption
2. Eliminates variability in absorption
3. Helps solubilize lipophilic drug
4. Provides an aqueous dosage form for water insoluble drugs
5. Increases bioavailability
6. Various routes such as tropical, oral, and intravenous can be used to deliver the product
7. Rapid and efficient penetration of the drug moiety
8. Helpful in taste masking
9. Provides protection from hydrolysis and oxidation as a drug in oil phase in o/w ME is not exposed to attack by water and air
10. Liquid dosage form increases patient compliance
11. Less amount of energy requirement.

PARENTERAL DELIVERY

MEs are commercially feasible, simple and convenient novel vehicles for delivery of medicaments which can enhance drug absorption with reduced systemic side effects. They can be used to optimize drug targeting without a concomitant increase in systemic absorption. Appropriate excipient selection and safety evaluation especially of the co-surfactants crucial in the formulation of MEs. They can be potential drug delivery systems for the delivery of more than one medicament simultaneously [9].

O/w emulsions are currently employed as safe and efficacious vaccine adjuvant in various vaccine products already approved for human use or in clinical trials. The leading o/w emulsions developed for vaccine applications, such as MF59 and AS03, are squalene-based (AS03 also contains - tocopherol).

The formulation of lipophilic and hydrophobic drugs into parenteral dosage forms has proven to be difficult. O/w MEs are beneficial in the parenteral delivery of sparingly soluble drugs where the administration of suspension is not desirable. They provide a means of obtaining relatively high concentration of these drugs which usually requires frequent administration. Other advantages are that they exhibit a more physical stability in plasma than liposomes or other vesicles and the internal oil phase is more resistant against drug leaching. Several

sparingly soluble drugs have been formulated into o/w ME for parenteral delivery MEs can also be used as intravenous delivery systems for the fat soluble vitamins and lipids in parenteral nutrition [10].

Advantages of parenteral emulsions

- The MEs have the advantage of a very small dispersed-phase diameter, which can impart thermodynamic stability. For many drugs, insufficient aqueous solubility and/or water hydrolysis are the major formulation challenges. By incorporating the drug in the interior oil phase, these problems can be reduced. Use of conventional co-solvent systems can be avoided as well as the associated undesirable effects caused by precipitation of the drug at the injection site. Moreover, protein binding and hydrolytic degradation of drugs such as barbiturates12 do not occur as long as the drug remains in the oil phase, thus further contributing to an improved therapeutic index for emulsion formulations compared with aqueous solutions. While in many cases incorporation of a drug into the oil phase of an emulsion might not reduce the hydrolysis rate sufficiently to permit the development of a liquid product that is stable at room temperature.
- Another advantage of parenteral emulsions is the potential to provide for sustained release. Delayed absorption for the drugs with the large partition coefficient can be achieved using MEs. The phase volume ratio between the lipid and aqueous phases in the delivery system decides the fraction of the drug available for the absorption. For example, if the volume of the aqueous phase is much larger than that of the oil phase, a large partition coefficient will result in a small fraction of the drug being available for absorption and hence a sustained release effect [11] (Tables 1-3).

THEORIES OF ME FORMATION

Various theories concerning ME formulation, stability and phase behavior have been proposed over the years. For example, one explanation for their thermodynamics stability is that the o/w dispersion is stabilized by the surfactant present and their formation involve the elastics properties of the surfactant films at the o/w interface, which involves, the curvature and the rigidity of the film. These parameters may have pressure and temperature dependence (the salinity of the aqueous phase). Which may be used to infer the region of stability of the ME, or to delineate the region where three coexisting phase occur [13,14].

Phase behavior

The first unifying classification of the phase behavior accounting for the different phenomena observed in ternary oil-water-amphiphile

Table 1: Potential micro emulsion systems for drug of varying physicochemical and biological properties

Solubility in		Membrane permeability	Potential micro emulsion system	Possible advantages
Aqueous solution	Organic solution			
+++	+	+	w/o	Protection against enzymatic and hydrolytic degradation Enhanced bioavailability
+++	+++	+++	w/o or o/w	Protection against enzymatic and hydrolytic degradation
+	+++	+	o/w	Improved solubilization and rate of solution
+	+++	+++	o/w	Improved solubilization and rate of solution

+++: High, +: Low, w/o: water- in-oil, o/w: oil-in-water

Table 2: Components available for parenteral microemulsions [12]

General class	Examples	Commercial name
Polysorbates	POE-20-sorbitan monooleate	Tween 80, chrillet 4
	POE-20-sorbitanmonolaurate	Tween 20, chrillet 1
Sorbitan esters	Sorbitan mono laurate	Span 20, chrill 1
PEO-PPO-Block co-polymers	Poloxamer 188	Pluronic/lutrol F68
POE alkyl ethers	POE-10-oleyl ether	Brij 96 V
POE castor oil	POE-35-castor oil	Cremphor EL, Etocs 35 HV
POE hydrogenated castor oil	POE-40-hydrogenated castor oil	Cremphor RH 40, HCO-40, Croduret 40 LD
	POE-60-hydrogenated castor oil	Cremphor RH 60, HCO-60
POE - stearate	PEG - 660-12-hydroxystearate	Solutol HS 15
Phospholipids	Soybean lecithin	
	Egg lecithin	
	Diolelyl phosphatidyl choline	
	Di steraoylphosphatidyl glycerol	
	PEGylated phospholipids	
	Di myristoyl phosphatidyl choline	
Fixed oils	Soyabean oil, castor oil	
MCT's	Triglycerides of capric/caprylic acid	Miglylol 810, 812, labrafac CC Croadamol GTCC, Captacs 300, 355
Fatty acid esters	Ethyl oleate	Crodamol EO
	IPM	
	IPP	
Vitamins	Vitamin E	
Short chain alcohols	Ethanol, benzyl alcohol	
Alkane diols and triols	PG	
	Glycerol	
PEG	PEG 400	
Glycol ethers	Tetrahydrofurfuryl PEG ether (tetra glycol or glycofurol)	
Pyrrolidine derivatives	N-methyl pyrrolidone	Pharmasol
	2-pyrrolidone	Sulphur P
Bile salts	Sodium deoxycholate	

Applications in veterinary products only, PG: Propylene glycol, PEG: Polyethylene glycols, IPP: Isopropyl palmitate, IPM: Isopropyl myristate

Table 3: Some marketed products in parenterals

Drug name	Route	Purpose/result
Flurbiprofen	Parenteral	Increased the solubility
Itraconazole	Parenteral	For better absorption

system was published by Winsor in 1948. On the basis of an extensive experimental study of different mixtures, Winsor distinguishes among four general type of phase behavior, schematically represented (Fig. 1).

One phase system
Winsor IV: These mixtures can be water (S1) or oil dispersible (S2), or gel (G) or a mixture of G with S1 or S2, respectively.

Two phase system
Winsor I: (Direct) micelles in water in equilibrium with an oil phase.
Winsor II: Reverse micelles in oil in equilibrium with an aqueous phase.

Three phase system
Winsor III: Most of the surfactant in a middle phase is in equilibrium with an upper organic phase and a lower aqueous phase. The middle phase may also be water - oil - dispersible.

Even though some particular system exhibits a phase behavior that is not accounted for classified in Winsor classification, it remains an important tool for the description of amphiphillic aggregation in multi-component systems.

ME FORMULATION DEVELOPMENT [15]

Much of the interest in the use of MEs as vehicles arises from their unique physical properties, in particular their thermodynamic stability and ease of preparation, Although this interest has recently been further stimulated by the introduction, in Europe and America by Sandoz (Basel, Switzerland), of a very successful oral ME pre-concentrate formulation of cyclosporine called Neoral. MEs, has been extensively studied in the pharmaceutical sciences as a means of enhancing the solubility and controlling the delivery of protein and peptide drugs.

MEs are defined as systems which comprise of a mixture of water, hydrocarbons and amphiphilic compounds which form thermodynamically stable, homogeneous (heterogeneous at molecular scale), optically isotropic solutions.

METHOD OF PREPARATION OF ME

Phase titration method
MEs are prepared by the spontaneous emulsification method (phase titration method) and it is depicted with the help of phase diagram. Construction of phase diagram is studied by complex series of interaction occurred by different components mixture. A quaternary phase diagram (four component system) is time-consuming and difficult to interpret, pseudo ternary phase diagram is often constructed to fine the different zones including MEs zone, in which each corner of the diagram represents 100% of the particular component [8]. Gibbs phase diagrams can be used to show the influence of changes in the volume fractions of the different phases on the phase behavior of the system.

Phase inversion method
Phase inversion of MEs is carried out on addition of excess of the dispersed phase or in response to temperature. During phase inversion, drastic physical changes occur including changes in particle size that can ultimately affect drug release both *in vitro* and *in vivo* [10]. These methods make use of changing the spontaneous curvature of the surfactant. For non-ionic surfactants, this can be achieved by changing the temperature of the system, forcing a transition from an o/w ME at low temperatures to a w/o ME at higher temperatures (transitional phase inversion).

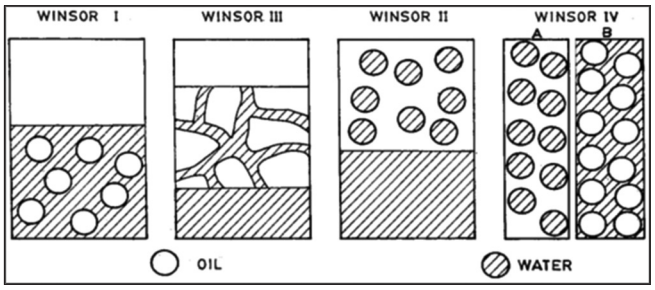

Fig. 1: Phase behavior in accordance with Winsor system

Preparation of ME
The drug is dissolved in the hydrophilic part of ME. Oil and the water phases can be combined with a surfactant is then added at slow rate with gradual stirring until the system is formed. The amount of surfactant to be added and the percent of oil phase that can be incorporated shall be determined with the help of pseudo-ternary phase diagram. Homogenization and micro fluidizer ultra-sonication can finally be used to achieve the desired size range for dispersed globules.

Construction of phase diagram
Pseudo-ternary phase diagram of oil, water and surfactant mixture are constructed at fixed surfactant ration. Phase diagram is obtained by mixing of the ingredients which shall be pre-weighed into glass vial and titrated with water and stirred well at room temperature. Formulation of monophonic/biphasic system is confirmed by visual inspection. In case turbidity appears by a phase separation then the sample is considered as biphasic. In case, monophonic mixture is visualized by stirring then the sample is marked as a point in phase diagram. The area covered by the point is considered as the ME region.

COMPONENTS OF ME

Oil phase
The selection of oil mainly depends on the drug solubility. It will minimize the volume of the formulation to deliver the therapeutic dose of the drug in an encapsulated form. Oil having maximum solubilizing potential for the drug is selected for the formulation of the ME to achieve maximal drug loading. Oils with long hydrocarbon chains (or high molecular volume) such as olive, peanut, soybean, canola, and sunflower are difficult to micro emulsify, whereas oils with shorter (or low molecular volume) such as medium chain triglycerides, medium chain mono- and diglycerides are easier to micro emulsify. The capacity of solubilizing lipophilic moieties usually increases with the chain length of the oil.

Oils mainly used for the formulation of ME are as follows:
1. Saturated fatty acid-lauric acid, myristic acid, capric acid
2. Unsaturated fatty acid-oleic acid, linoleic acid, linolenic acid
3. Fatty acid ester-ethyl or methyl esters of lauric, myristic and oleic acid.

The oil component influences curvature by its ability to penetrate and hence swell the tail group region of the surfactant monolayer. Short chain oils have better-penetrating efficiency to the tail group region than long chain alkenes, and hence, swell this region to a greater extent, resulting in increased negative curvature (and reduced effective HLB). Saturated (for example, lauric, myristic and capric acid) and unsaturated fatty acids (for example, oleic acid, linoleic acid and linolenic acid) have penetration enhancing a property of their own and they have been studied since a long time. Fatty acid esters such as ethyl or methyl esters of lauric, myristic and oleic acid have also been employed as the oil phase [1]. Lipophilic drugs are preferably solubilized in o/w MEs (Fig. 2).

Note the greater the extent of oil penetration when the film curves toward water (i.e. the region of reserve curvature).

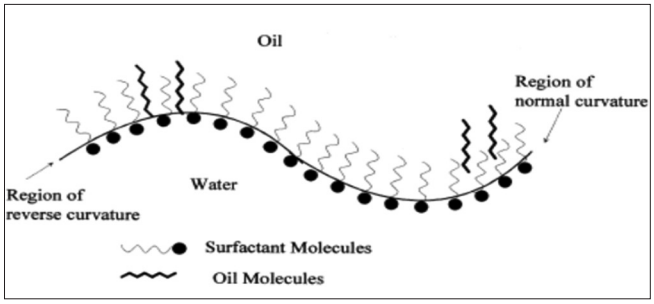

Fig. 2: Penetration of oil molecules between the hydrophobic chains of the interfacial surfactant monolayer in a bicontinuous micro emulsions

Depending on the nature of the oil, in particular, its size relative to the hydrophobic chain of the surfactant, the oil may penetrate to varying extents into the surfactant tails of the interfacial monolayer. For a bicontinuous ME a similar effect has been proposed to occur in both o/w and w/o ME.

Aqueous phase

The aqueous phase, in practice, is almost never just water because most formulations dictate the use of several additives such as buffers, isotonic agents, antibacterial compounds, and many others that might in some cases affect the ME. Salinity might strongly affect MEs made of anionic surfactants. Low pH might also damage the ME, mainly if esters of fatty acids are used as surfactants and/or oils, and, therefore, it is always recommended to keep the ME as close as possible to neutral pH.

The aqueous phase should be augmented by incorporation of ionic or osmotic agents, antioxidants, buffers and preservatives as required. Because emulsified oil exerts no osmotic effect, isotonic adjustment (to 280-300 mosm/kg) will be important for large-volume parenterals such as the injectable fat emulsions. Glycerol has been preferred by the manufacturers of soybean oil emulsion. In addition to contribution to tonicity, glycerol in combination with propylene glycol has been shown to reduce the globule size and improve the creaming stability of o/w emulsions. Ionic agents (sodium chloride) and reducing sugars (glucose) should be avoided because of the potential interaction between reducing sugars and protein contaminants which results in brown discolouration and/or phase separation of the emulsion.

Surfactants

Surfactants belong to a group of substances that meet certain characteristics like: Good surface activity, are able to form condensed interfacial films and their diffusion rates to interface are comparable to emulsion forming time. According to their structure, surfactants are classified in:

1. Anionic (e.g. sodium stearate, potassium laurate, alkyl sulfates like sodium dodecyl sulfate, and sodium sulfosuccinate).
2. Nonionic (nonylphenol with ethylene oxide units, poly glycol, fatty acid esters, and lecithin).
3. Cationic (quaternary ammonium salts and amine hydrochlorides); zwitter ionic/amphoteric (amino acids, phospholipids, and derivatives of quaternary ammonium compounds) or polymeric and silicone surfactants which could be either of the above.

A surfactant is chosen for a certain application mostly by trial and error, although the best way is to learn how to use HLB value which only applies to nonionic surfactants.

Each oily material requires a different strength of emulsifier to ensure the stability of its emulsion. This is referred to as the HLB requirement for that oil. Vegetable oils are the easiest to emulsify, mineral oils are moderately difficult while silicone oils are the most difficult to stabilize. Matching HLB and the chemical structure of oil and emulsifying agent is an ideal situation. Such information, however, is only available for a limited number of compounds. Blending surfactants (by varying their composition in the mixture) also allow the selection of an optimum HLB for a given application.

Based on the Bancroft's rule, it is possible to change or invert an emulsion from o/w type to w/o type by inducing changes in surfactant HLB and critical packing parameter (CPP) values. Making the emulsifier more oil soluble tends to produce a w/o emulsion and *vice versa*.

This is accomplished by:

i. Altering the order of the addition of the phases (e.g. adding water to oil and emulsifier will produce a W/O emulsion, while adding oil to water and emulsifier, an O/W emulsion is obtained).
ii. Variations in the phase volume ratio (e.g. if the o/w ratio is increased, an w/o emulsion is obtained, and *vice versa*).
iii. Temperature variations and the presence of electrolytes and other additives like alcohols, disrupt the water molecules around nonionic and ionic surfactants, respectively, altering surfactant solubility and, therefore, inducing inversion (e.g. increasing the temperature of an o/w emulsion, makes the nonionic surfactant more hydrophobic and the emulsion could invert to w/o).

Emulsion inversion is particularly useful when the final emulsion is subjected to specifications that are not attainable with more conventional emulsification methods, as for instance in the case of tiny droplets of very viscous oils.

Surfactants facilitate emulsification by reducing interfacial tension and stabilization by introducing double layer forces and/or solvation forces between dispersed particles. Such solution-like systems form spontaneously when the components are brought together in a proper ratio and when the interfacial tension is around 10^{-3} mN m^{-1}.

Optimization of process variables of ME [16]

Preparation of ME involves various process variables, out of which the followings were selected:

a. Effect of the oil concentration
b. Effect of co-surfactant concentration
c. Effect of type of oil.

Optimizations by selective parameters or experimental designs allow to conclude that, with respect to composition variables, generally there is an optimum surfactant mixture composition, or HLB, and that the higher the oil surfactant ratio the greater the droplet size. The preparation variables, like addition, agitation or cooling rate, generally do not have a significant influence if the system is optimized with respect to composition.

CHARACTERIZATION

Characterization of ME requires macro analytical tools, such as viscosity, conductivity, dielectric, differential scanning calorimetry, together with scattering advanced techniques (dynamic light scattering [DLS], small-angle X-ray scattering [SAXS], small-angle neutron scattering [SANS]) and spectroscopic advanced methods (high resolution-nuclear magnetic resonance [NMR], PSEG-NMR) and electronic microscopy (transmission electron microscopy [TEM] and cryo-TEM). Some of the major methods relevant to the characterization of the MEs include viscosity and conductivity measurements as well as more advanced methods such as pulsed gradient spin echo (self-diffusion) NMR. Other sophisticated methods such as time corrected single-photon counting methods (photo physics of a fluorescent drug) have also been utilized.

The commonly used techniques for structural information are SANS, SAXS and DLS.

Stability studies of the emulsion

- Physical examination: Visual observation for creaming, coalescence, oil separation, and color change
- Chemical analysis: Determination and characterization of the drug

substance, oil, emulsifier(s) and adjuvant's present, as well as degradation of related substances, including, in particular, free fatty acids, lyso lecithin and oxidative degradation products
- pH determination
- Globule size and surface charge
- Preservative test
- Sterility test
- Progeny test
- Centrifugation test
- Freeze thaw cycles.

Shelf-life stability of MEs, both as a function of time and storage temperature was routinely evaluated by visual inspection of the samples initially on a daily and later on a weekly basis. Stable systems were identified as those free of any physical change, such as, phase separation, flocculation, and/or precipitation. The particle size of the MEs upon storage was also determined to assess ME stability in terms of drastic changes in the mean droplet diameter due to droplet coalescence and/or aggregation. Stability was monitored at 4°C, ambient temperature, 37 and 50°C [17].

The small droplets adhere to membranes at a greater extent as well as transport bioactive molecules in a more controlled fashion. Using the ME vehicles, water-insoluble and oil-soluble components from different plant extracts can be co-solubilized to attain synergistic effect for a specific therapeutic goal.

CONCLUSIONS

MEs can be considered as an effective vehicle for the solubilization of certain drugs and as protecting medium for the entrapped of drugs from degradation, hydrolysis, and oxidation. MEs provide prolonged release of the drug and prevent irritation despite the toxicity of the drug.

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