



Asian Journal
of
PHARMACEUTICAL RESEARCH
Journal homepage: - www.ajprjournal.com

A REVIEW – MICROEMULSION

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ABSTRACT

The microemulsion formulations consist of one or more surfactants in combination with co-surfactant and drug dissolved in oil. Oils form a distinct core in the interior of the surfactant aggregate, resulting in enhanced solubilizing capacity of the oils with improved drug loading capacities of the microemulsion. It is well established that medium chain fatty acids influence tight junctions of the epithelial cells, and long chain fatty acids stimulate the lipoprotein synthesis and subsequent lymphatic absorption. In system containing comparable amount of oil and water, equilibrium bicontinuous structure is formed in which the oil and the water domain interpenetrate in a more complicated manner. In recent years, numerous studies have suggested that microemulsion [o/w or w/o] as have tremendous potential to enhance the bioavailability of drugs. There the present review focused on microemulsion formulation, advantage and application of microemulsion.

Keywords: Microemulsion, Structure, Advantage, Application.

INTRODUCTION

The solubility potential of microemulsions is a major factor in enhancing absorption of drugs. Mostly microemulsions have favorable solvent properties due to the potential incorporation of large fraction of lipophilic and/or hydrophilic phases. Moreover many, investigations have indicated that the unique structural organization of the phases in microemulsions may contribute to additional solubility regions, increasing the load capacity of microemulsions, compared to nonstructural solutions containing the same fraction of the constituents [1-4].

The concept of microemulsion was proposed by Hoar and Schulman who could make a clear uni-phase solution by slowly titrating a milky emulsion with hexanol [5]. Schulman and his colleagues in 1959 coined the term microemulsion [6]. Microemulsion can be described as system containing water, oil and amphiphile which is a single optically isotropic and thermodynamically stable liquid solution [7].

In other words, microemulsions are thermodynamically stable, transparent, dispersions of oil and water stabilised by an interfacial film of surfactant molecules [8]. These homogenous systems, which can be prepared over a wide range of surfactant concentrations and oil to water ratio, are all fluids of low viscosity.

In recent years, numerous studies have suggested that microemulsion [o/w or w/o] as have tremendous potential to enhance the bioavailability of drugs via topical and systemic routes. Three distinct microemulsions--oil external, water external and middle phase can be used for drug delivery, depending upon the type of drug and the site of action [9,10].

These systems are known to enhance drug solubility, increase the stability, and modify drug release [11,12]. Microemulsion allows the incorporation of hydrophilic as well as lipophilic compound depending on their internal structure [13,14]. These aggregates have been described as reservoir systems, which allow slow release of drugs, thus providing prolonged effects and avoiding high concentration in the blood [15-18]. However with given oil –water-surfactant components are usually formed in narrow specific concentration ranges [19].

For selecting a suitable surfactant / cosurfactant blend, it is important to asses.

- a) The drug solubility in various components
- b) The area of self emulsification region in the phase diagram and
- c) Droplet size distribution.

When surfactants are incorporated into immiscible mixtures of oil and water, the surfactant molecules can locate at the oil /water interface which is thermodynamically very favorable. The surfactant used in these formulations are known to improve the bioavailability by various mechanism including.

- (a) Improved drug dissolution
- (b) Increased intestinal epithelial permeability
- (c) Increased tight junction permeability
- (d) Decreased / inhibition of p-glycoprotein efflux.

Microemulsion structure:

Mostly structures of microemulsions are spherical or cylindrical formed by the aggregates of micelles that are formed by surfactants at the oil/water interface. Micelles are like drops of oil in water and reverse micelles are like drops of water in oil as illustrated in Figure No. 1.

The schematic representation given in Figure No.2 gives an indication of a few of the wide variety of possible self-association structures that surfactants can form in the presence of water, oil or combinations of all three.

The possible structural representations of the three different types of microemulsions which are most probably likely to be formed depending on their individual composition are represented in Figure No.3.

Note that while the oil-in-water (o/w) and water-in-oil composition (w/o) droplets are represented as spheres, they may be also asymmetric in shape, frequently looking like the shape of a prolate ellipsoid. The likely presence of o/w microemulsion droplets is a feature in microemulsions where the volume fraction of oil is low. Conversely, w/o droplets are likely when the volume fraction of water is low and in systems where the amount of water and oil are similar, a bicontinuous microemulsion may result.

The bicontinuous structure or sponge phase is a quite intricate structure. As the name suggests, in this structure, both water and oil are continuous phases. The sponge structure is a good example as the sponge has a continuous structure, but at the same time, it is possible to "fill" the sponge with a liquid. In such a scenario, both the material of sponge as well as the liquid forms a continuous phase. Considering the sponge surface as surfactant, illustration of a bicontinuous structure is presented in Figure No. 3.

Other microemulsion structure is the lamellae, spherulite, interconnected rod-like micelles, vesicles [20] etc as illustrated in Figure No.4. Where in lamellae water and oil consecutive layers are separated by surfactant layers conveniently oriented it presents birefringence and

maintains the order even at diluted concentrations. Lamellae structure is related to the spherulite structure (onion structure). It is possible that spherulites are only out of-equilibrium transient lamellar phases induced by mechanical work [yet to be proved] or by other stimulus.

Factors to be considered during preparation of microemulsion

Three important conditions:

- Surfactants must be carefully chosen so that an ultra low interfacial tension ($< 10^{-3}$ mN/m) can be attained at the oil / water interface which is a prime requirement to produce microemulsions.
- Concentration of surfactant must be high enough to provide the number of surfactant molecules needed to stabilize the microdroplets to be produced by an ultra low interfacial tension.
- The interface must be flexible or fluid enough to promote the formation of microemulsions [21].
- **1.2.3. Theories for microemulsion formulation:**
- Many different theories have been proposed for the formation of microemulsion formulations. Mostly, three approaches have been used to explain microemulsion formation and stability. These are:
 - (i) Interfacial or mixed film theories the emphasis of this theory is to the formation of an interfacial film and the production of ultra low interfacial tensions.
 - (ii) Solubilisation theories - the emphasis of this theory is to the monophasic nature of many microemulsion.
 - (iii) Thermodynamic treatments.
- Some reports have also considered free energy of microemulsion formation and blending elasticity of the film. An admittedly simplified thermodynamic rationalization is presented below.

• However, an admittedly simplified thermodynamic rationalization is presented below. The free energy of microemulsion formation can be considered to depend on the extent to which surfactant lowers the surface tension of the oil–water interface and the change in entropy of the system such that,

$$\Delta G_f = \gamma \Delta A - T \Delta S \quad \text{Equation No.2}$$

Where ΔG = is the free energy of formation,
 γ = is the surface tension of the oil–water interface,
 ΔA = is the change in interfacial area on microemulsification,
 ΔS = is the change in entropy of the system which is effectively the dispersion entropy,
 T = is the temperature.

It should be noted that when a microemulsion is formed the change in ΔA is very large due to the large number of very small droplets formed [22].

Comparison of microemulsions with emulsions:**Potential advantages of microemulsions:**

Microemulsions are potential drug carrier systems for various 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
- This system is reckoned advantageous because of its wide applications in colloidal drug delivery systems for the purpose of drug targeting and controlled release.
- Improvement in oral bioavailability: Microemulsion is a new approach to improve the water solubility and ultimately, bioavailability of lipophilic drugs by solubilised and micro emulsified form in gastrointestinal tract and increase in specific surface area enables more efficient drug transport through intestinal aqueous boundary layer and through the absorptive brush border membrane leading to improved bioavailability.
- Improvement of bioavailability of antifungal and anti-inflammatory drug by topical microemulsion.
- Reduction in Inter-Subject and Intra-Subject Variability: There are several drugs which show large inters subject and intra-subject variation in absorption, leading to decrease performance of drug and patient non-compliance. Microemulsion drug delivery system is a proven approach to overcome inter and intra subject variation.
- As Solid Dosage Form for Oral Administration: Microemulsion can be converted into the various solid dosage forms by adsorbing onto the solid surface.
- Ability to Deliver Peptides that are Prone to Enzymatic hydrolysis in GIT
- Reduction of Food Effects: microemulsion is independent of food and that microemulsion offer reproducibility of plasma profile.
- No Influence of Lipid Digestion Process: Microemulsions are not necessarily digested before the drug is absorbed, as they present the drug in micro emulsified form, which can easily penetrate the mucin, and water unstirred layer [23].

Advantages of microemulsion based systems

- Microemulsions exhibit several advantages as a drug delivery system.
- Microemulsions are thermodynamically stable system and the stability allows self-emulsification of the system whose properties are not dependent on the process followed.
- Microemulsions act as supersolvents of drug. They can solubilize hydrophilic and lipophilic drugs including drugs that are relatively insoluble in both aqueous and hydrophobic solvents. This is due to existence of

microdomains of different polarity within the same single-phase solution.

- The dispersed phase, lipophilic or hydrophilic (oil-in-water, O/W, or water-in-oil, W/O microemulsions) can behave as a potential reservoir of lipophilic or hydrophilic drugs, respectively. The drug partitions between dispersed and continuous phase, and when the system comes into contact with a semi-permeable membrane, the drug can be transported through the barrier. Drug release with pseudo-zero-order kinetics can be obtained, depending on the volume of the dispersed phase, the partition of the drug and the transport rate of the drug.
- The mean diameter of droplets in microemulsions is below 0.22 μm ; they can be sterilized by filtration. The small size of droplet in microemulsions e.g. below 100 nm, yields very large interfacial area, from which the drug can quickly be released into external phase when absorption (in vitro or in vivo) takes place, maintaining the concentration in the external phase close to initial levels.
- Same microemulsions can carry both lipophilic and hydrophilic drugs.
- Because of thermodynamic stability, microemulsions are easy to prepare and require no significant energy contribution during preparation. Microemulsions have low viscosity compared to other emulsions.
- The use of microemulsion as delivery systems can improve the efficacy of a drug, allowing the total dose to be reduced and thus minimizing side effects.
- The formation of microemulsion is reversible. They may become unstable at low or high temperature but when the temperature returns to the stability range, the microemulsion reforms.

Advantages of Microemulsion over Other Dosage Forms

- Increase the rate of absorption
- Eliminates variability in absorption
- Helps solublize lipophilic drug
- Provides a aqueous dosage form for water insoluble drugs
- Increases bioavailability
- Various routes like topical, oral and intravenous can be used to deliver the product
- Rapid and efficient penetration of the drug moiety
- 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.
- Liquid dosage form increases patient compliance.
- Less amount of energy requirement.

Applications of Microemulsions:**➤ Pharmaceutical Applications:**

- Parenteral delivery
- Oral drug delivery

- Topical drug delivery
 - Ocular drug delivery
 - Pulmonary drug delivery
 - Microemulsions in biotechnology
- **Other Applications:**
- Microemulsion in enhanced oil recovery
 - Microemulsions as fuels
 - Microemulsions as lubricants, cutting oils and corrosion inhibitors
 - Microemulsions as coatings and textile finishing
 - Microemulsions in detergency
- Microemulsions in cosmetics
 - Microemulsions in agrochemicals
 - Microemulsions in food
 - Microemulsions in environmental remediation and detoxification
 - Microporous media synthesis (microemulsion gel technique)
 - Microemulsions in analytical applications
 - Microemulsions as liquid membranes
 - Novel crystalline colloidal arrays as chemical sensor materials [24,25].

Figure 1. The structure of micelles. M= Micelles for o/w microemulsion, RM= Reverse micelles for w/o microemulsion

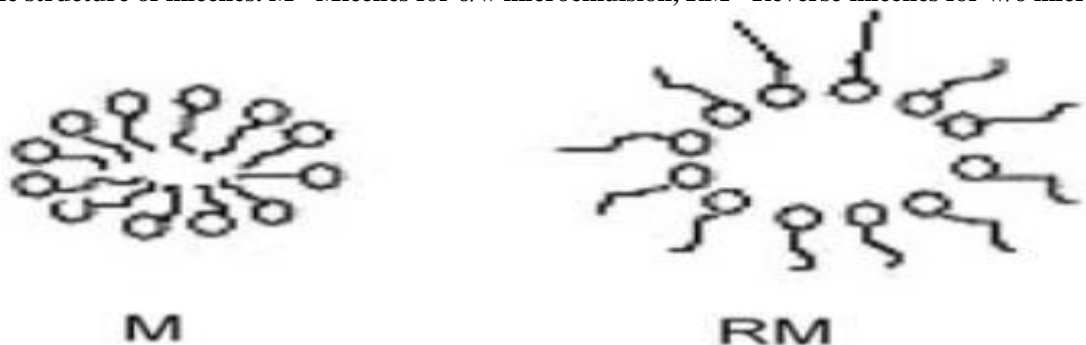


Figure 2. Schematic representation of the most commonly encountered self-association structures in water, oil or a combination thereof

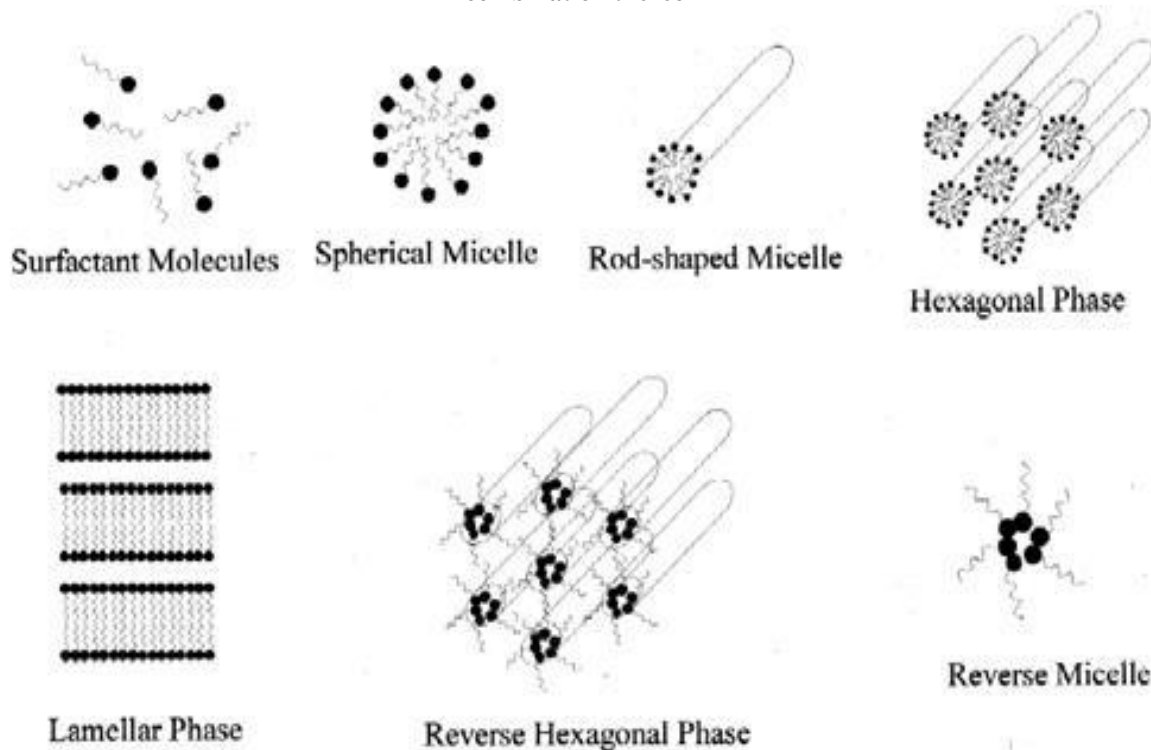


Figure 3. Schematic representation of the four most commonly encountered microemulsion microstructures: (a) oil-in-water, (b) bicontinuous, and (c) water-in-oil microemulsion. (d) bicontinuous structure (sponge phase), (e) Microemulsion Structure

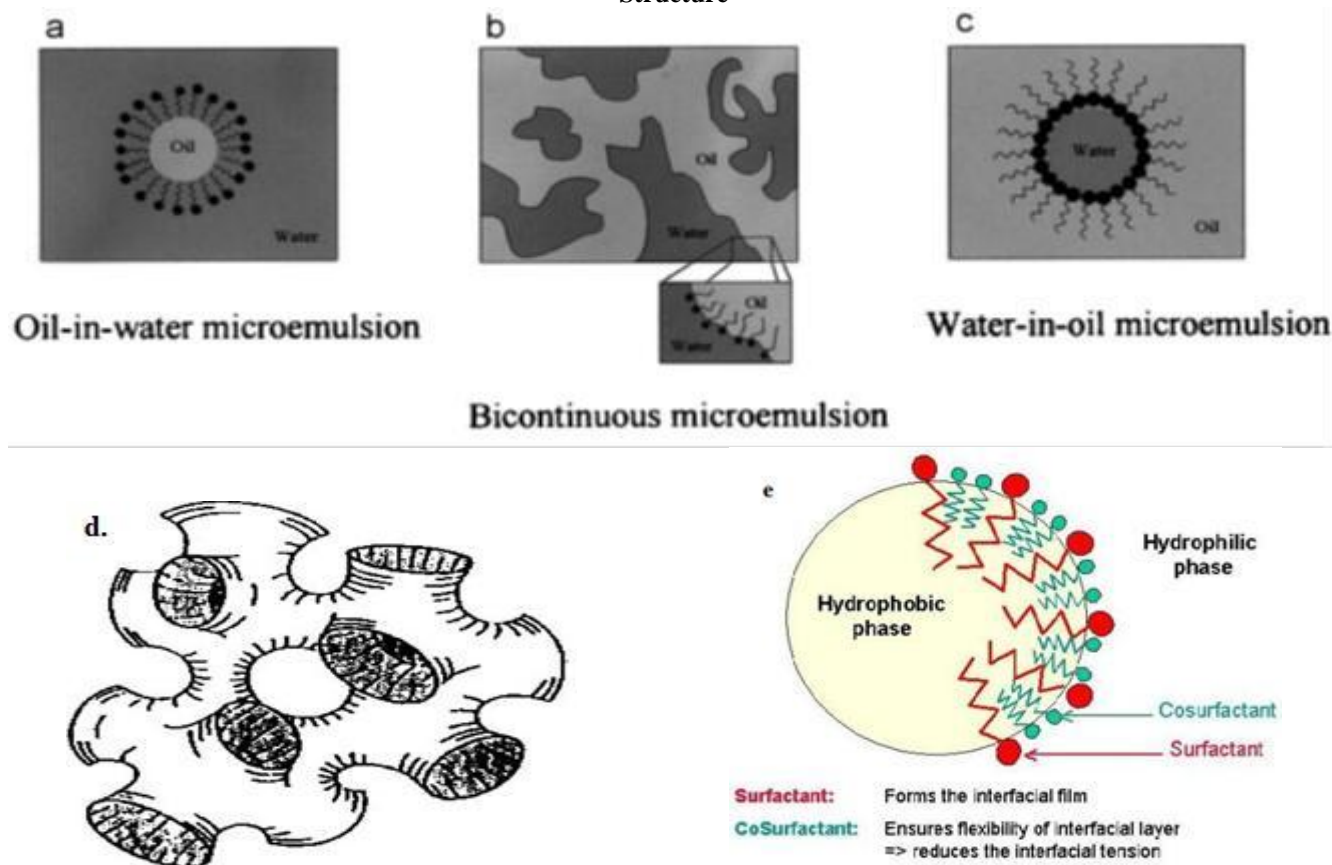


Figure 4. Possible microemulsion structures: The lamellae (L) and the spherulite (S) structures. The surfactant molecules in the spherulite are arranged as onion layers. (A) Vesicles (B) interconnected rod-like micelles

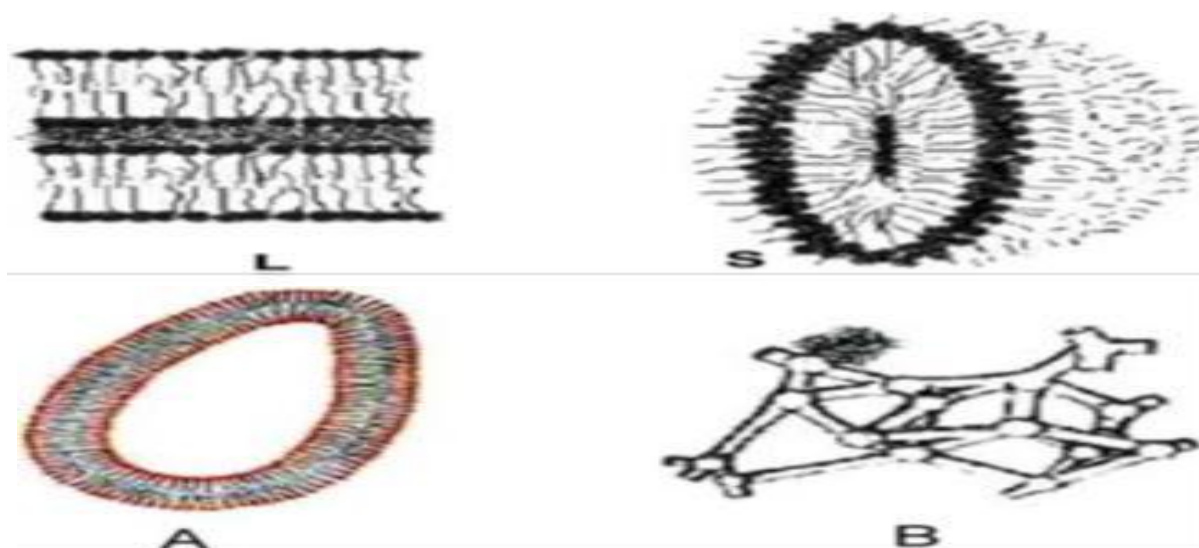


Figure 5. Microemulsion Formation

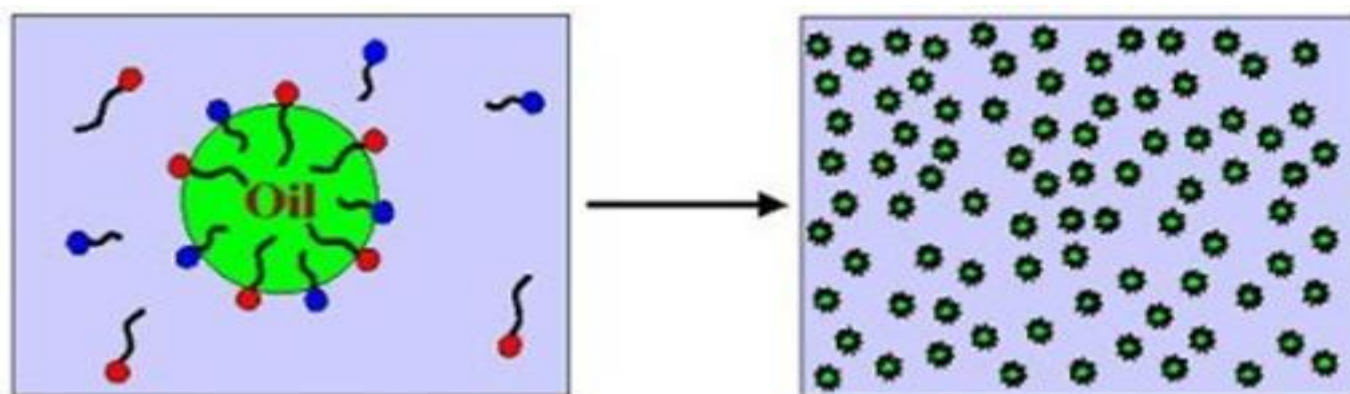


Table 1. Comparison of Microemulsions with Emulsions

Emulsions	Microemulsions
<p>Figure 6. Emulsions structure</p>	<p>Figure 7. Microemulsions structure</p>
Emulsions consist of roughly spherical droplets of one phase dispersed into the other.	They constantly evolve between various structures ranging from droplet like swollen micelles to bicontinuous structure.
Droplet diameter: 1 – 20 μ m.	10 – 100 nm.
Most emulsions are opaque (white) because bulk of their droplets is greater than wavelength of light and most oils have higher refractive indices than water.	Microemulsions are transparent or translucent as their droplet diameter are less than $\frac{1}{4}$ of the wavelength of light, they scatter little light.
Ordinary emulsion droplets, however small exist as individual entities until coalescence or ostwald ripening occurs.	Microemulsion droplet may disappear within a fraction of a second whilst another droplet forms spontaneously elsewhere in the system.
They may remain stable for long periods of time, will ultimately undergo phase separation on standing to attain a minimum in free energy. They are kinetically stable thermodynamically unstable.	More thermodynamically stable than macroemulsions and can have essentially infinite lifetime assuming no change in composition, temperature and pressure, and do not tend to separate.
They are lyophobic.	They are on the borderline between lyophobic and lyophilic colloids.
Require intense agitation for their formation.	Generally obtained by gentle mixing of ingredients.

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