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Review Article

NANOEMULSION IN ENHANCEMENT OF BIOAVAILABILITY OF POORLY SOLUBLE DRUGS: A REVIEW

Ajay Thakur*, Manpreet Kaur Walia and S.L. Hari Kumar

Rayat and Bahra Institute of Pharmacy, Sahauran, Kharar, Punjab -140104, India

ABSTRACT

Nanoemulsions have the potential in pharmaceutical industries because of the transparency at high droplet volume fraction, higher rate of bioavailability or diffusion and increased shelf life of the pharmaceuticals. Nanoemulsions are clear, thermodynamically stable, isotropic liquid mixtures of oil, water, surfactant and co-surfactant. These are oil-in-water (o/w) type of emulsions with the average droplet size ranging from 5nm to 100 nm. Reduction in droplet size to nanoscale leads to change in physical properties such as optical transparency & unusual elastic behavior. Nanoemulsions have widespread applications in different fields such as pharmaceutics, food technology. Nanoemulsion offers a promising vehicle for increasing the aqueous solubility of poorly water-soluble drugs. Nanoemulsions have many advantages; for instance, enhance drug solubility, perfect thermodynamic stability, ease of manufacturing and permeation over conventional formulations that convert them to important drug delivery systems. The design & development of nanoemulsions aimed at controlling or improving required bioavailability levels of therapeutic agents. This review mainly discussed about the importance of nanoemulsions over other dosage forms, preparation methods, characterization of nanoemulsions and applications.

Keywords: Nanoemulsion, Poorly soluble drug, Method of preparation, Characterization, Application in drug delivery.

INTRODUCTION

The term "Nanoemulsion" refers to a thermodynamically stable isotropically clear dispersion of two immiscible liquids, such as oil and water, stabilized by an interfacial film of surfactant molecules. A Nanoemulsion is considered to be a thermodynamically or kinetically stable liquid dispersion of an oil phase and a water phase, in combination with a surfactant. The dispersed phase typically comprises small particles or droplets, with a size range of 5 nm-200 nm, and has very low oil/water interfacial tension. Because the droplet size is less than 25% of the wavelength of visible light, Nanoemulsions are transparent. The Nanoemulsion is formed readily and sometimes spontaneously, generally without high-energy input. In many cases a cosurfactant or cosolvent is used in addition to the surfactant, the oil phase and the water phase.

Three types of Nanoemulsions are most likely to be formed depending on the composition

- **O/W Nanoemulsion**
  Wherein oil droplets are dispersed in the continuous aqueous phase
- **W/O Nanoemulsions**
  Wherein water droplets are dispersed in the continuous oil phase
- **Bi-continuous Nanoemulsions**
  Wherein microdomains of oil and water are interdispersed within the system.

In all three types of nanoemulsions[1], the interface is stabilized by an appropriate combination of surfactants and/or co-surfactants.

Components of Nanoemulsion

Main three components of Nanoemulsions are as follows:

- Oil (table 1)
- Surfactant (table 2)
- Co-surfactant (table 3)

Nanoemulsions are colloidal dispersions composed of an oil phase, aqueous phase, surfactant and cosurfactant at appropriate ratios. Unlike coarse emulsions micronized with external energy nanoemulsions are based on low interfacial tension. This is achieved by adding a cosurfactant, which leads to spontaneous formation of a thermodynamically stable Nanoemulsion. The droplet size in the dispersed phase is very small, usually below 140 nm in diameter, which makes the nanoemulsions transparent liquids.[2] in principle, nanoemulsions can be used to deliver drugs to the patients via several routes, but the topical application of nanoemulsions 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. Nanoemulsions improve the transdermal delivery of several drugs over the conventional topical preparations such as emulsions[3,4] and gels.[5,6] Mobility of drugs in nanoemulsions is more facile[4,6,7], as compared to the nanoemulsion with gel former which will increase its viscosity and further decrease the permeation in the skin.[5] The superior transdermal flux from nanoemulsions has been shown to be mainly due to their high solubilization potential for lipophilic and hydrophilic drugs. This generates an increased thermodynamic activity towards the skin.[4,7,8] Nanoemulsions may affect the permeability of drug in the skin. In this case, the components of nanoemulsions serve as permeation enhancers. Several compounds used in nanoemulsions have been reported to improve the transdermal permeation by altering the structure of the stratum corneum. For example, short chain alkanols are widely used as permeation enhancers.[9-11] It is known that oleic acid, a fatty acid with one double bond in the chain structure, perturbs the lipid barrier in the stratum corneum by forming separate domains which interfere with the continuity of the multilamellar stratum corneum and may induce highly permeable pathways in the stratum corneum.[12-14] Isopropyl myristate (IPM) is used as a permeation enhancer in transdermal formulations, but the mechanism of its action is poorly understood.[15] Nonionic surfactants are widely used in topical formulations as solubilizing agents but some recent results indicate that they may affect also the skin barrier function.[16] It is of interest to explore the effects of these components in the organized Nanoemulsion structures. A unique attempt was made[17] to emulsify coconut oil with the help of polyoxyethylene 2-cetyl ether (Brij 52) and isopropanol or ethanol, forming stable isotropic dispersion thus paving way for use of plant and vegetable oil to be used as oil phase in Nanoemulsion.

The surfactants used to stabilise such systems may be:

(i) Non-ionic
(ii) Zwitterionic
(iii) Cationic
(iv) Anionic surfactants

A combination of these, particularly ionic and non-ionic, can be very effective at increasing the extent of the Nanoemulsion region.

Examples:

(i) Non-ionic include polyoxyethylene surfactants such as Brij 35 (C12E35) or sugar esters such as sorbitan monooleate (Span 80).
(ii) Zwitterionic surfactants include Phospholipids are a notable example and exhibit excellent biocompatibility.
(iii) Cationic surfactants include Lecithin preparations from a variety of sources including soybean and egg are available commercially and contain diacylphosphatidylcholine as its major constituent.[18-21] Quaternary ammonium alkyl salts form one of the best known classes of cationic surfactants, with hexadecyltrimethyl ammonium bromide

(CTAB) and the twin-tailed surfactant didodcecylammonium bromide (DDAB) are amongst the most well known.

(iv) Anionic surfactant include sodium bis-2-ethylhexylsulphosuccinate (AOT) which is twin-tailed and is a particularly effective stabiliser of w/o microemulsions.[22]

Attempts have been made to rationalise surfactant behaviour in terms of the hydrophile-lipophile balance (HLB)[23], as well as the critical packing parameter (CPP).[24,25] Both approaches are fairly empirical but can be a useful guide to surfactant selection. The HLB takes into account the relative contribution of hydrophilic and hydrophobic fragments of the surfactant molecule. It is generally accepted that low HLB (3–6) surfactants are favoured for the formation of w/o nanoemulsions whereas surfactants with high HLBs (8-18) are preferred for the formation of o/w nanoemulsion systems. Ionic surfactants such as sodium dodecyl sulphate which have HLBs greater than 20, often require the presence of a cosurfactant to reduce their effective HLB to a value within the range required for nanoemulsion formation. In contrast, the CPP relates the ability of surfactant to form particular aggregates to the geometry of the molecule itself.

In most cases, single-chain surfactants alone are unable to reduce the oil /water interfacial tension sufficiently to enable a microemulsion to form, a point made in a number of pertinent microemulsions reviews.[26-30] Medium chain length alcohols which are commonly added as cosurfactants, have the effect of further reducing the interfacial tension, whilst increasing the fluidity of the interface thereby increasing the entropy of the system.[27,28] Medium chain length alcohols also increase the mobility of the hydrocarbon tail and also allow greater penetration of the oil into this region.

PREPARATION METHODS OF NANO-EMULSIONS

The drug is be dissolved in the lipophilic part of the nanoemulsion i.e. oil and the water phases can be combined with surfactant and a cosurfactant is then added at slow rate with gradual stirring until the system is transparent. The amount of surfactant and cosurfactant to be added and the percent of oil phase that can be incorporated shall be determined with the help of pseudo-ternary phase diagram. Ultrasonicator[31] can finally be used so to achieve the desired size range for dispersed globules. It is then being allowed to equilibrate. Gel may be prepared by adding a gelling agent to the above nanoemulsion. Carbomers (crosslinked polyacrylic acid polymers) are the most widely used gelling agent.

Factors to Be Considered During Preparation of Nanoemulsion

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 nanoemulsions.
- 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 nanoemulsions.

Construction of Phase Diagram

Pseudo-ternary phase diagrams of oil, water, and co-surfactant/surfactants mixtures are constructed at fixed cosurfactant/surfactant weight ratios. Phase diagrams are obtained by mixing of the ingredients, which shall be pre-weighed into glass vials and titrated with water and stirred well at room temperature. Formation of monophasic/biphasic system is confirmed by visual inspection. In case turbidity appears followed by a phase separation, the samples shall be considered as biphasic. In case monophasic, clear and transparent mixtures are visualized after stirring; the samples shall be marked as points in the phase diagram. The area covered by these points is considered as the nanoemulsion region of existence.

Several methods have been suggested for the preparation of nanoemulsion. Here some methods are discussed which are freely used for the nanoemulsion preparation.

Phase Inversion Method

In this method, fine dispersion is obtained by chemical energy resulting of phase transitions occur through emulsification method. The adequate phase transitions are produced by changing the composition at constant temperature or by changing the temperature at constant composition, phase inversion temperature (PIT) method was introduced by Shinoda *et al.* based on principle of the changes of solubility of polyoxyethylene-type surfactant with temperature. This surfactant becomes lipophilic as increase in temperature because of dehydration of polymer chain. At low temperature, the surfactant monolayer has a great positive spontaneous curvature forming oil swollen micellar solution phase.[33]

Sonication Method

Sonication method is best way to prepare nanoemulsions. In sonication method the droplet size of conventional emulsion or microemulsions are reduced with the help of sonication mechanism. This method is not applicable for large batches, but only small batches of nanoemulsions can be prepared by this method.[34]

Ultrasonic System

In ultrasonic emulsification, the energy input is provided through so called sonotrodes (sonicator probe) containing piezoelectric quartz crystals that can be expand & contract in response to alternating electrical voltage. As the tip of sonicator probe contacts the liquid, it generates mechanical vibration and therefore cavitations occurs, which is the main phenomenon responsible for ultrasonically induced effects. Cavitation is the formation and collapse of vapour cavities in a flowing liquid. Such a vapour cavity forms when the local pressure is reduced to that of at the temperature of the flowing liquid because of local velocity changes. The collapse of these cavities causes powerful shock waves to radiate throughout the solution in proximity to the radiating face of the tip, thereby breaking the dispersed droplets. Within the ultrasound range, the power available varies inversely with the frequency and only powerful ultrasound (0-200kHz) is able to produce physical and chemical changes such as emulsification.

Ultrasound can be used directly to produce emulsion, but since breaking an interface requires a large amount of energy, it is better to prepare coarse emulsion before applying acoustic power. Due to small product throughput the ultrasound emulsification process mainly applied in laboratories where emulsion droplet size as low as 0.2 micrometer can be obtained.[35]

Microfluidizer

It is possible to produce emulsion at much higher pressures up to approximately 700 Mpa, in the nozzle of microfludizer that is the heart of this device (the interaction chamber) two jets of crude emulsion from two opposite channels collide with one another. The process stream is delivered by a pneumatically powered pump that is capable of pressurizing the in-house compressed air (150-650 Mpa) up to about 150 Mpa. Forcing the flow stream by high pressure through microchannels toward an impingement area creates a tremendous shearing action, which can provide an exceptionally fine emulsion.[36]

Jet Disperser

Forcing the flow stream by high pressure through microchannels towards an impregnated area creates a tremendous shearing action, which can provide an exceptionally fine emulsion. In general, initial forces in turbulent flow along with cavitations are predominantly responsible for droplet disruption in microfludizer. Disruption in laminar elongation flow is also possible, especially when emulsion has high viscosity.

In the jet disperser two or more jets of crude emulsion each from opposing bores collide with one another but at a different design than microfludizer, the diameter of the bores in jet dispersers are typically 0.3-0.5mm. Finally an "orifice plate" is the simplest construction form for a homogenizing nozzle. The diameter of orifice bore is of same order of magnitude as the jet dispersers and inlet head diameter of orifice plate is typically 10-60nm, in jet dispersers & orifice plates, droplets are disrupted predominantly due to laminar elongation flow ahead of the bores. Unlike

radial diffusers, the nozzle is microfludizer; jet dispersers and orifice plate contain no moving parts, so they can be used at high pressures up to 300-400 Mpa.[37]

ADVANTAGES OF NANOEMULSIONS

- Nanoemulsion is the approach to improve water solubility and ultimate bioavailability of lipophilic drugs.[38]
- Nanoemulsions have been reported to make the plasma concentration profiles and bioavailability of drugs more reproducible.[38,39]
- Fine oil droplets empty rapidly from the stomach and promote wide distribution of the drug throughout the intestinal tract and thereby minimizing irritation.[40]
- Nanoemulsions have a higher solubilization capacity than simple micelle solutions and their thermodynamic stability offers advantages over unstable dispersions such as emulsions and suspensions.[41]
- They also provide ultra low interfacial tension and large o/w interfacial areas.[41]
- Nanoemulsions may possess high kinetic stability and optical transparency resembling to microemulsions.[42]
- The structures in the nanoemulsions are much smaller than the visible wavelength, so most nanoemulsions appear optically transparent, even at large loading.[42]
- Nanoemulsions have potential to deliver peptides that are prone to enzymatic hydrolysis in GIT.[43]
- Nanoemulsions have higher surface area and higher free energy than macro emulsions that make them an effective transport system.[44]
- Problems of inherent creaming, flocculation, coalescence, and sedimentation are not seen in nanoemulsions, which are commonly associated with macroemulsions.[45]
- It is non-toxic and non-irritant so can be easily applied to skin and mucous membranes.[46]
- Nanoemulsions are formulated with surfactants, which are approved for human consumption so they can be taken by enteric route.[47]
- It is do not damage healthy human and animal cells, so nanoemulsions are suitable for human and veterinary therapeutic purposes.[48]

DISADVANTAGES OF NANOEMULSIONS

- The formulation of nanoemulsions is an expensive process due to size reduction of droplets is very difficult as it required a special kind of instruments and process methods.
- Homogenizer (instrument required for the nanoemulsions formulation) arrangement is an expensive process. More ever microfluidization and ultrasonication (manufacturing process) require large amount of financial support.
- The stability of nanoemulsions is quite unacceptable and produces a big problem during the storage of formulation for the longer time.
- Ostwald ripening is the main problem associated with unacceptability of nanoemulsions formulations. Ostwald ripening is due to the high rate of curvature of small droplet show greater solubility as compared to large drop with a low radius of curvature.[49,50]

PHYSICOCHEMICAL CHARACTERIZATION OF NANOEMULSIONS

- **Particle Size Analysis**

  A Photon Correlation Spectrometer is used to monitor the particle size of nanoemulsions. Light scattering are monitor 90° angle and 25°C.

- **Rheological Measurements**

  Rheological measurements will perform at 25±0.1°C using a Bohlin rheometer equipped with a cone/plate apparatus 40 mm per 4°. For each sample, continuous variation of shear rate γ will applied and the resulting shear stress σ will measured. Viscosity of dispersions with Newtonian

flow properties will be calculated according to the relation: $\eta=\sigma/\gamma$.

- **Refractive Index**

  Refractive index will be determined at 25°C using refractometer.

- **Surface Tension**

  Surface tension measurements will carry out at 20°C using a thermostatically controlled processor tensiometer K100.

- **pH and Osmotic Pressure**

  pH of the formulation will measured at 25°C using digital pH meter and the osmotic pressure will measured using Micro Osmometer.[51,52]

APPLICATION OF NANOEMULSIONS

Nanoemulsions containing pharmaceutically active agents can be utilized for the production of pharmaceutical preparations, the nanoemulsion being mixed, as the active component, with a solid or liquid vehicle suitable for therapeutic administration. If desired, a special galenic form can be imparted to the mixture. The following galenic forms of administration can be considered, in this connection: Ampoules, especially sterile injection and infusion solutions; solutions, especially oral liquids, eye drops and nose drops which can contain various auxiliary substances in addition to the nanoemulsion; aerosols without metering feature, and dosing aerosols, which can contain propellant gas and stabilizers besides the nanoemulsion; hydrophilic and hydrophobic gels and ointments containing the nanoemulsion; o/w or w/o creams containing the nanoemulsion; lotions and pastes containing the nanoemulsion.

Ocular Delivery

Oil in water emulsions are being explored for improved topical lipophilic drug delivery to the eye. Lipophilic drug loaded o/w ocular emulsions provide equivocally a better balance between ocular bioavailability improvement and patient comfort following topical instillation into the eye e.g. Piroxicam, pilocarpine, indomethacin, cyclosporine A.[53]

Percutaneous Route

Many drugs exhibit low skin penetration, which results in poor efficacy. As opposed to common chemical skin penetration enhancers, organic solvents, which are generally associated to some degree with skin irritation, toxicity and sensitization, a solvent free topical vehicle based on drug entrapment in the o/w emulsion droplets of submicron size is more efficacious in terms of percutaneous absorption with possibly devoid of adverse effects. In addition, the uniqueness of the large internal hydrophobic core of o/w submicronized emulsion droplets allows high solubilization capacity for water insoluble topically active medicaments and also aids in carrying water, an excellent softener, to the skin e.g. NSAIDs, diazepam, α-tocopherol, antifungal drugs (econazole or miconazole nitrate), EMLA (Eutectic mixtures of local anaesthetic) has proven to be a useful medication for children. It is an emulsion containing a mixture of lidocaine and prilocaine. This cream gives an effective deep sedation.[53]

Nasal Route

The nasal route has received great attention due to number of advantages over parenteral and oral administration especially by-passing the liver. Nanoemulsions increase absorption by solubilizing the drug in the inner phase of an emulsion and prolonging contact time between emulsion droplets and nasal mucosa e.g. a lipid soluble rennin-inhibitor was incorporated into an o/w emulsion. Enhanced and prolonged in vivo nasal absorption was observed in emulsion compared to aqueous suspension. Other drugs which have been formulated for nasal delivery are insulin and testosterone.

Pulmonary Delivery

A novel pressurized aerosol system has been devised for the pulmonary delivery of salbutamol using lecithin-stabilized microemulsions formulated in trichlorotrifluoroethane.[54]

Use of Nanoemulsions in Cosmetics

Nanoemulsions have recently become increasingly important as potential vehicles for the controlled delivery of cosmetics and for the optimized dispersion of active ingredients in particular skin layers. Due to their lipohilic interior, nanoemulsions are more suitable for the transport of lipophilic compounds than liposomes. Similar to

liposomes, they support the skin penetration of active ingredients and thus increase their concentration in the skin. Another advantage is the small-sized droplet with its high surface area allowing effective transport of the active to the skin. Furthermore, nanoemulsions gain increasing interest due to their own bioactive effects. This may reduce the trans-epidermal water loss (TEWL), indicating that the barrier function of the skin is strengthened. Nanoemulsions are acceptable in cosmetics because there is no inherent creaming, sedimentation, flocculation or coalescence observed within macroemulsions. The incorporation of potentially irritating surfactants can often be avoided by using high-energy equipment during manufacturing.[55]

Antimicrobial Nanoemulsions

Antimicrobial nanoemulsions are oil-in-water droplets that range from 200-600 nm. They are composed of oil and water and are stabilized by surfactants and alcohol. The nanoemulsion has a broad spectrum activity against bacteria (e.g., *E. coli*, *Salmonella*, *S. aureus*), enveloped viruses (e.g., *HIV*, *Herpes simplex*), fungi (e.g., *Candida*, *Dermatophytes*), and spores (e.g., *Anthrax*). The nanoemulsion particles are thermodynamically driven to fuse with lipid-containing organisms. This fusion is enhanced by the electrostatic attraction between the cationic charge of the emulsion and the anionic charge on the pathogen. When enough nanoparticles fuse with the pathogens, they release part of the energy trapped within the emulsion. Both the active ingredient and the energy released destabilize the pathogen lipid membrane, resulting in cell lysis and death.[56]

CONCLUSION

To date nanoemulsions 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. Although high energy emulsification method is traditionally used for the preparation of nanoemulsion formulation but low emulsion emulsification method now create an attraction due to their wide application and advantages as a formulation and stability aspects. The applications of nanoemulsion are limited by the instability. Stability of formulation may be enhanced by controlling various factors such as type and concentration of surfactant and co surfactant, type of oil phase, methods used, process variables and addition of additives used over the inter phases of nanoemulsion formulation.

Table 1: List of oils used in nanoemulsions

Name	Chemical Name
Captex 355	Glyceryl Tricaorylate/Caprate
Captex 200	Propylene Dicaprylate/Dicaprate Glycol
Captex 8000	Glyceryl Tricaprylate (Tricaprylin)
Witepsol	90:10 % w/w c12 Glyceride tri: diesters
Myritol 318	c8/c10 triglycerides
1sopropyel myristate	Myristic acid isopropyl ester

Table 2: List of surfactant used in nanoemulsions

S. No.	Solubilizing,surfactants,emulsifying agents adsorption enhancers
1	Capryol 90
2	Gelucire 44/14, 50/13
3	Cremophor RH 40
4	Imwitor 191, 308(1), 380, 742, 780 K, 928, 988
5	Labrafil M 1944 CS, M 2125 CS
6	Lauroglycol 90
7	PEG MW > 4000
8	Plurol Oleique CC 497
9	Poloxamer 124 and 188
10	Softigen 701, 767
11	Tagat TO
12	Tween 80

Table 3: List of Co-Surfactant used in nanoemulsions

S. NO	Co-surfactant
1	TranscutolP
2	Glycerin,Ethylene glycol
3	Propylene glycol
4	Ethanol
5	Propanol

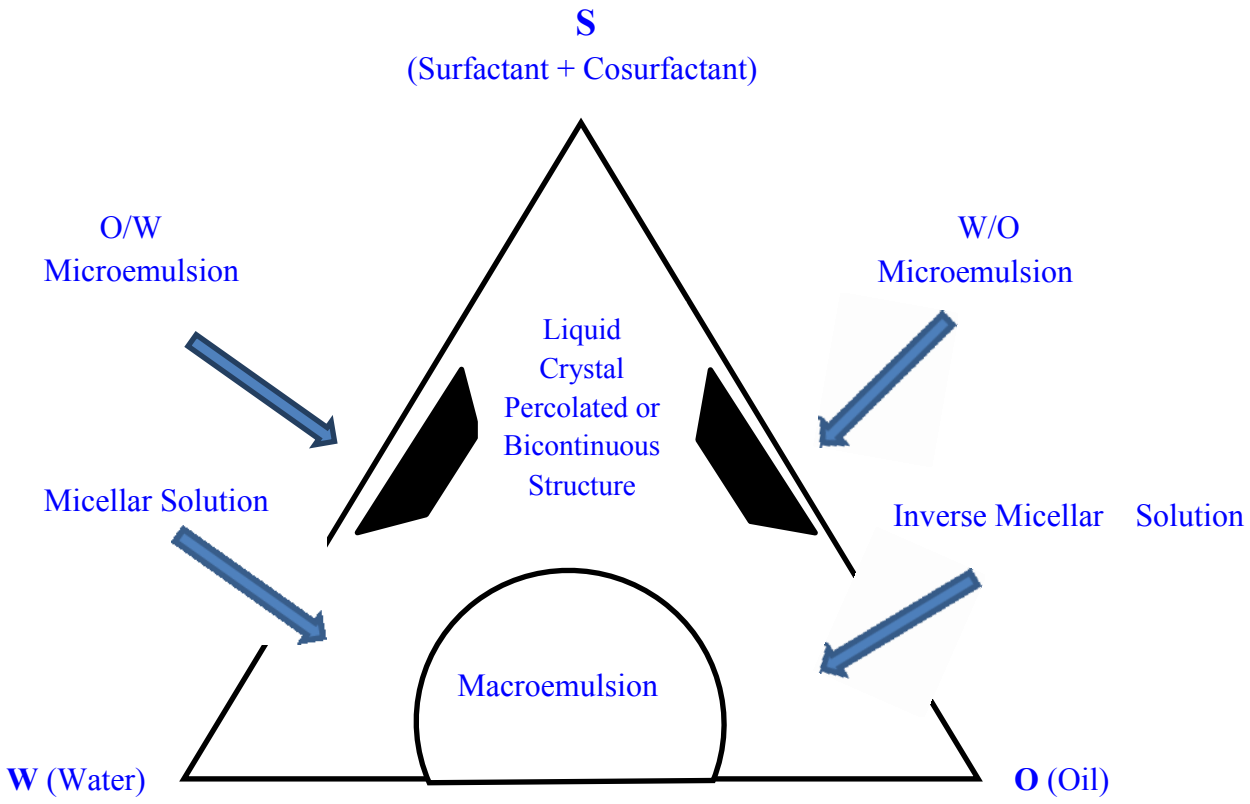

Table 1: Hypothetical Phase Regions of Microemulsion Systems[32]

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