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Review Article

Emulsion Micro Emulsion and Nano Emulsion: A Review

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ABSTRACT
Lipid dosage forms are attractive delivery systems for hydrophobic drug molecules. Emulsion is one of the popular system since many decades. Pharmaceutical applications of emulsions widened especially after micro and nano-emulsion emergence. This paper is an attempt to summarise comparative aspects like definition, theories, types, methods of preparations, advantages, disadvantages and methods of analysis of emulsion, micro-emulsion and nano-emulsion.

Key words: Emulsion, Micro emulsion, Nano emulsion, Surface tension, Zeta potential.

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INTRODUCTION

Emulsions are dispersions made up of two immiscible liquid phases which are mixed using mechanical shear and surfactant. Amphiphilic surface-active molecules are called as 'surfactants' which are responsible to reduce naturally existing attractive forces in the form of surface tension.[1] Choice of surfactant on the basis of hydrophilic-lipophilic balance (HLB) value or critical packing parameter (CPP) helps to develop desired emulsion. Surfactants with low HLB[3-8] values as shown in Figure 1 are useful to form W/O emulsion and that of with high HLB values[8-18] are used to form O/W emulsion.[2-4] critical packing parameter (CPP) is ratio of hydrophilic and hydrophobic parts of surfactant molecule. CPP also gives idea of nature of aggregates.[5] recently two new concepts are emerged in emulsion that is as follows:

Micro-emulsion is clear, thermodynamically stable, isotropic liquid mixture. It is prepared by using oil, water, surfactant and a co-surfactant. It incorporates very small size particles up to nano size as compared to conventional emulsion.[6,7] IUPAC defines micro-emulsion as dispersion made of water, oil, and surfactant(s) that is an isotropic and thermodynamically stable system with dispersed domain diameter varying approximately from 1 to 100 nm, usually 10 to 50 nm.[5-6] Nano-emulsions are very similar to micro-emulsions that are dispersions of nano scale particles but obtained by mechanical force unlike to micro-emulsions which forms spontaneously.[7,8]

1.4.2 Emulsion

Emulsions are dispersions made up of two immiscible liquid phases which are mixed using mechanical shear and surfactant. Particle size of this conventional emulsion grows continuously with time and hence finally separation occurs at gravitational force thus these emulsions are thermodynamically unstable.

Theories: According to the surface-tension theory of emulsification, the emulsifiers or stabilizers lower the interfacial tension between the two immiscible liquids, reducing the repellent force between the two liquids and diminishing the attraction between the molecules of the same liquid[2] The oriented-wedge theory assumes the formation of monomolecular layers of the emulsifying agent which are curved around the droplet of the internal phase of an emulsion. This theory is based on the presumption that certain emulsifying agents orient themselves around a liquid droplet in a manner reflective of their solubility in that particular liquid. The plastic-or interfacial-film theory describes that the emulsifying agent is located at the boundary between the water and oil, forming a thin film by being adsorbed onto the surface of the internal phase droplets. The film avoids the contact and subsequent coalescence of the dispersed phase; a tougher and more pliable film will result in greater physical stability of the emulsion.[2]

- *Surface tension theory*- this theory assumes that, when surface tension between two phases lessens then emulsion can be formed
- *Repulsion theory*- this theory explains a phenomenon by which emulsifying agent forms a film containing globules on one of the immiscible phases with ability to repel each other. Thus immiscible globules remain suspended in the dispersion medium due to these repulsive forces.
- *Viscosity modification*- according to this theory emulsifying agents raises viscosity of the medium and thus miscible viscous suspension of globules is formed.

Types[3]

Following are different types of emulsions

Water-in-oil (w/o)

Oil-in-water (o/w)

Water-in-oil-in-water (w/o/w)

Oil-in-water-in-oil (o/w/o)

Methods of preparations[4]

- **Dry Gum Method**: Triturate mixture of emulsifier and oil with addition of water which will form primary emulsion. Further add water to dilute and mix continuously to form emulsion.
- **Wet Gum Method**: Initially triturate oil with water and then with emulsifier to form primary emulsion. Further add water, dilute and mix to form emulsion.
- ***In Situ* Soap Method**: Take oil and lime water (calcium hydroxide solution). Mix with stirring to form emulsion.
- **Mechanical Method**: Take oil, water and emulsifier together, mix well and stir by machine to form emulsion

Advantages[5]

- To solubilise hydrophobic or oil soluble drugs
- To enhance drug absorption through
- To enhance topical absorption of drugs
- To mask the disagree able taste and odour of drugs
- To enhance palatability of nutrient oils

Disadvantages

- Less stable as compared to other dosage forms
- Possesses short shelf-life
- Creaming, cracking (breaking), flocculation and phase inversion are common problems observed during storage of emulsions (Figure 2)

Micro-emulsion

IUPAC defines micro-emulsion as dispersion made of water, oil, and surfactant(s) that is an isotropic and thermodynamically stable system with dispersed domain diameter varying approximately from 1 to 100 nm, usually 10 to 50 nm.

Theories: Interfacial theory

It is also called as mixed film or dual film theory. Surfactant and co-surfactant together forms complex film (Figure 3) at the oil water interface and thus creates generation of micro emulsion droplets.[6-8]

Solubilization theory

This theory assumes that swollen micellar system forms in the form of micro emulsion. Oil solubilised due to normal micelle formation and water solubilised by reverse micelle formation. Phase diagram (Figure 4) is generally useful to understand this theory assumption.[7-9]

Thermodynamic theory

When interfacial tension between two immiscible phases reduces to zero, causes spontaneous formation of micro emulsions and formed negative free energy helps to make emulsion thermodynamically stable.

Microemulsions are also called as transparent emulsion, swollen micelle and micellar solution. self-microemulsifying drug delivery system (SMEDDS) is also one of the popular term for microemulsion mediated delivery of drugs. The term microemulsion is coined by T. P. Hoar and J. H. Shulman when they used this term to describe multiphase system consisting of water, oil, surfactant and alcohol, which forms a transparent solution in 1953. But discovery of microemulsions confirms well before use in the form white spirit and or liquid waxes.

Types

- According to Winsor, there are four types of micro emulsion phases exists in equilibrium, these phases are referred as Winsor phases.[10-13] they are:
- Winsor I (two phase system): upper oil layer exists in equilibrium with lower (o/w) micro emulsion phase
- Winsor II(two phase system): the upper(w/o) micro emulsion exists in equilibrium with lower excess water.
- Winsor III (three phase system): middle bi-continuous phase of o/w and w/o called) exists in equilibria with upper phase oil and lower phase water.
- Winsor IV (single phase system):it forms homogenous mixture of oil, water and surfactant
- The R-ratio is one of the characterisation concepts which was first proposed by Winsor to explain the influence of amphiphiles and solvents on interfacial curvature. R-ratio compares the affinity for an amphiphile to disperse into oil, to its affinity to dissolve in water. If one phase is favoured, the interfacial region forms a definite curvature. Thus, if R > 1, the interface increases its area of contact with oil while decreasing its area of contact with water. Thus oil becomes the continuous phase and the corresponding characteristic system is type II (Winsor II). Similarly, a balanced interfacial layer is represented by R = 1.

Preparation methods

- **Phase titration method**: Micro emulsion was prepared by dispersing required quantity of drug in appropriate quantity of oil which is required for the solubilisation of drug.[14] The mixture was homogenized and accurately weighed quantity of surfactant: co surfactant blends was added in small portion with stirring to it.[15-18] The blends were mixed thoroughly using magnetic stirrer and drop wise double distilled water added to it with continuous stirring around 10 minute and rate of stirring was optimized as per requirement of particle size.[19]
- **Phase inversion temperature method (PIT):** Phase inversion of micro emulsions means conversion of O/W to W/O system (Figure 5) by adding excess of the dispersed phase or by rising temperature when non-ionic surfactant are used to change spontaneous curvature of the surfactant which brings system near to minimal surface tension and to form fine dispersed oil droplets.[20-22] This method shows extreme changes in particle size which further leads to changes in *in-vivo* and in-vitro drug release pattern.[23-25]

Advantages[25-27]

- It is very easy to prepare and scale up due to spontaneous formation ability
- It is very good system to raise rate of absorption as well as bio avaibility by eliminating interfering variations
- It able to improve solubility of lipophilic drugs
- It is thermodynamically more stable system as compared to conventional system and hence suitable for long term use
- It can be preferred to develop sustained and controlled releases drug system
- It is best system to minimise first pass metabolism.

Disadvantages [28-29]

- Additional use of excess amount of surfactant and co-surfactant increases cost
- Excess concentration of surfactants can lead to mucosal toxicity

Composition

The major components of micro emulsion system are:

1) Oil phase

2) Surfactant (Primary surfactant)

3) Co-surfactant (Secondary surfactant)

4) Co-Solvent

Commonly used components of Micro-emulsion [5-15]

Components	Examples
Oils	Saturated fatty acid-lauric acid, myristic acid, capric acid
	Unsaturated fatty acid-oleic acid, linoleic acid, linolenic acid
	Fatty acid ester-ethyl or methyl esters of lauric, myristic and oleic acid.
	Example: (GlycerylMono-anddicaprate, isopropylmyristate, sunflower oil, soyabean oil, Labrafac ®CC), surfactant (Cremophor ®EL, Labrasol®)

Surfactants	Polyoxyethylene/Polysorbate/Tween 20,40,60,80,; Sorbitan Monolaurate (Span), Soybean lecithin, egg lecithin, lyso lecithin, Sodium dodecyl sulphate (SDS), Sodium bis (2–ethylhexyl) sulphosuccinate (Aerosol OT), Dioctyl sodium sulphosuccinate, Sodium dexoycholate, Labrasol (Polyethylene glycol–8–caprylic acid), TritonX–100
Co-surfactants	Ethanol, propanol, Isopropanol, butanol, pentanol, hexanol, sorbitol, n–pentanoic acid, n–hexanoic acid, n–butylamine, sec, butylamine, 2-aminopentane, 1,2-butanediol, Propylene glycol. Some newly evolved cosurfactants are as follows : Cremophor RH40 (polyoxyl 40 hydrogenated castrol oil), Plurololeique (polyglyceryl–6–dioleate), Plurolisostearique (isostearic acid of polyglycerol), Distearoylphosphatidyl ethanolamine–N–poly (ethyleneglucol)2000 (DSPE–PEG), Poloxamer Polyoxythylene–10–oelyl ether (Brij 96V) Polysorbate 80 (Tween80) Span 20 Sodium monohexyl phosphate Sodium monooctyl phosphate N,N–Dimethyl dodecylamine–N–oxide (DDNO) N,N–Dimethyl octylamine–N–oxide (DONO) Cinnamic alcohol Cinnamic aldehyde

Oil phase

Oil phase is second most important vehicle after water due to its properties to solubilise lipophilic drug molecules and improve absorption through lipid layer present in body.[6] Oil has unique property of penetrating cell wall and hence very useful for lipophilic active drug delivery. Swelling of tail group region of the surfactant is influence by oil phase. Such penetration is to greater extent in case of short chain alkanes as compared to long chainalkanes. [7]

Example

Saturated fatty acids: lauric, myristic and capric acid

Unsaturated fatty acids: oleic acid, linoleic acid and linolenic acid

Fatty acid esters: ethyl or methyl esters of lauric, myristic and oleic acid

Surfactants

During the preparation of the microemulsion,surfactantmustbeableto reducetheinterfacialtensionnearest to zeroto facilitate dispersion of all components. These surfactants can be:

Non-ionic

Anionic

Cationic

Zwitterionic,

Nature of surfactants helps in deciding stability of microemulsion.Dipole and hydrogen bond interactions stabilizes non-ionic surfactant and electrical double layer stabilizes ionic surfactants.

Ionic surfactants are also affected by salt concentration. Hence ionic surfactants being sensitive in stability issues and due to toxicity concern, are generally nor preferable. But non-ionic surfactants can produce nontoxic pharmaceutical dosage forms and hence more popular.[8]

Surfactants with HLB values[3-6] are useful in preparation of W/O micro emulsion and surfactants with higher HLB values[8-18] are useful in preparation of O/W micro emulsion. Surfactants with more than 20 HLB values are acts as co-surfactant to reduce concentrations of surfactants to a acceptable limit and micro emulsion formation.[9-10]

Examples of non-ionicsurfactants:

Polyoxyl 35 castor oil (Cremophor EL)

Polyoxyl 40 hydrogenated castor oil (Cremophor RH 40)

Polysorbate20(Tween20)

Polysorbate80(Tween80)

d-α-tocopherolpolyethylene glycol1000succinate(TPGS)

SolutolHS-15

Sorbitanmonooleate(Span80)

Polyoxyl40 stearate,

PolyglycolyzedglycerideslikeLabrafilM-1944CS,LabrafilM-2125CS, Labrasol, Gellucire 44/14, etc.

Co-surfactants

It is studied that high concentrations of single-chain surfactants are required to reduce the O/W interfacial tension to a level to enable a spontaneous formation of a microemulsion. However, if co-surfactants are added then with minimum concentration of surfactants different curvatures of interfacial film can be formed to generate stable micro emulsion composition. (11-16) Co surfactants raises the fluidity of the interface due to presence of fluidizing groups like unsaturated bonds, then demolishes liquid crystalline or gel structure and alters the HLB value in such way to cause spontaneous formation of micro emulsion.[23-29]

Example:

Short chain alcohols like ethanol to butanol

Short chain glycols like propylene glycol

Medium chain alcohols like amines or acids

Co-solvents

Co-solvents are organic solvents like ethanol, propylene glycol (PG), and polyethylene glycol (PEG) which helps to dissolve relatively high concentrations of surfactants as well as lipid soluble drugs. Hence co-solvents are also considered as co-surfactants.

Nano-emulsion

Nano-emulsions are very similar to micro-emulsions that are dispersions of nano scale particles but obtained by mechanical force unlike to micro-emulsions which forms spontaneously.[7-8]

Theories

The combination of two theories, turbulence and cavitations, explain the droplet size reduction during the homogenization process of nano emulsions.[30-31]

Types[32-33]

Oil-in-water (o/w)

Water-in-oil (w/o)

Oil-in-water-in-oil (o/w/o)

Water-in-oil-in-water (w/o/w)

Preparation methods

- **High energy emulsification method**: ultra sonication and high pressure homogenization
- **Low energy emulsification:** Phase inversion temperature method, solvent displacement method and phase inversion composition method
- **High-Pressure Homogenization:** specially designed high- pressure homogenization instrument is used to produce nano sized particles. At very high pressure (500 to 5000 psi), oil phase and water phase are allowed to force through small inlet orifice.[34] Hence extremely small size particles are created due to strong turbulence and hydraulic shear. But this method requires high temperature and energy. Pressure, homogenization cycles are directly responsible for particle size.[35] Higher the pressure and higher the homogenization cycles, smallest is particle size. This method is easy to scale up.
- **Microfluidization**: In this method also specially designed device called as micro fluidizer is used to create high-pressure (500 to 20000psi). Initially prepare coarse emulsion of by mixing oil and water phase.[36] This device consists of interaction chamber of small micro channels through which coarse emulsion is forced to an impingement area to form nano size fine particles followed by filteration to obtain uniform particles.[37]
- **Ultrasonication**: This method is based on principle that when coarse emulsion is in ultrasonic field and external pressure is increased, cavitations threshold also increases to limit where fine nano size particles are formed.[38]
- **Phase inversion method**: This method uses principle of phase inversion temperature which is the temperature at which phase transition occurs. Low temperature favours O/W emulsions and high temperature favours W/O emulsion. Rapid cooling and heating cycles produces fine particles. Non-ionic surfactant like polyoxyethylene becomes lipophilic at high temperature and hydrophilic at low temperature due to dehydration of the polymer chain.
- **Spontaneous Emulsification**: This method is simple and uses volatile organic solvent composition of oil, water, lipophilic and hydrophilic surfactant. This composition is allowed to mix homogenously by magnetic stirring. Then evaporate the water-miscible solvent under vaccum to obtain nano-emulsion.[39]
- **Solvent Evaporation Technique**: In this technique, initially mix drug with organic solvent using suitable surfactant and prepare O/W emulsion by mixing continuous phase. Then evaporate organic solvent under vacuum or heating or at atmospheric conditions to obtain microspheres loaded with drug followed by centrifugation or filtration.[40]
- **Hydrogel Method**: This method shares similarity with solvent evaporation method. High shear forces are used to form nano-emulsion of drug- solvent which is miscible with the drug anti-solvent.

Parameters	Emulsion[1-5]	Microemulsion[6-15]	Nano emulsion[35-42]
Appearance (Figure 6)	Turbid	Clear	Clear
Particle size	1 to 20 mm	1 and 100 nm	1 and 100 nm
Formation	Mechanical shear	Self assembly	Mechanical shear
Stability	Thermodynamically unstable, Kinetically Stable	Thermodynamically Stable Long shelf life	Kinetically stable/ metastable, thermodynamically unstable
Phases	Biphasic	Monophasic	Monophasic
Viscosity	High	Low	Low (about 1 cP at room temperature)
Preparation cost	Higher cost	Lower cost	Higher cost
Interfacial Tension	High	Ultra Low	Ultra low (less than 10 dyn cm^{-1})
Optical isotropy	Anisotropic	Isotropic	Isotropic
Light scattering	Less scattering	Strong multiple scattering of visible light hence white	Strong multiple scattering of visible light hence white

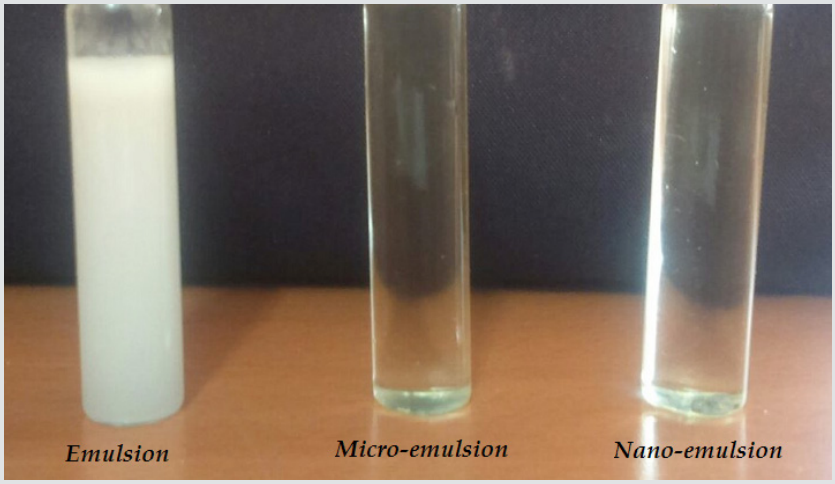

Figure 6: Appearance comparison between emulsion, micro emulsion and nano emulsion.

Concentration of surfactant	High	High (20% by weight)	Low (3-10% by weight)
Types	Oil in Water (O/W) or direct emulsion Water in Oil (W/O) or reverse emulsion	Oil- in- water micro emulsion or winsor I Water – in oil micro emulsion or winsor II Bi-continuous micro emulsion or winsor III Single phase homogeneous mixture or winsor IV	(a) oil in water nano emulsion in which oil is dispersed in the continuousaqueousphase, (b)waterinoilnano emulsion in which water droplets are dispersed in continuous oil phase, and (c) bi-continuous nano emulsions
Formulation methods	Continental or Dry Gum Method Wet Gum Method Bottle or Forbes Bottle Method	Phase Titration Method (Water Titration Method) Phase inversion method	High energy emulsification methods Low energy emulsification methods
Theories	Surface tension theory Repulsion theory Viscosity modification theory Oriented-Wedge Theory Interfacial film theory	Thermodynamic theory Solubilisation theory Interfacial theory	Surface tension theory Interfacial theory
Parameters	Physical appearance Globule size determination Conductivity test Dye-solubility test Refractive index measurement Filter paper test Dilution test Drug content determination Poly disperity determination pH determination Viscosity determination Scattering Techniques Percent Transmittance (Limpidity Test) determination Zeta potential determination *In-vitro* and *in-vivo* drug release determination Stability studies		

Advantages[41-42]

- It is used to improve water solubility and ultimate bioavailability of lipophilic drugs

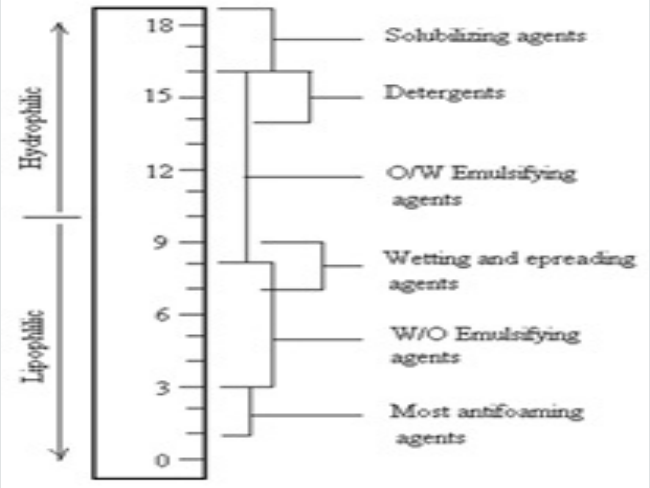

Figure 1: HLB value showing role of surfactants.

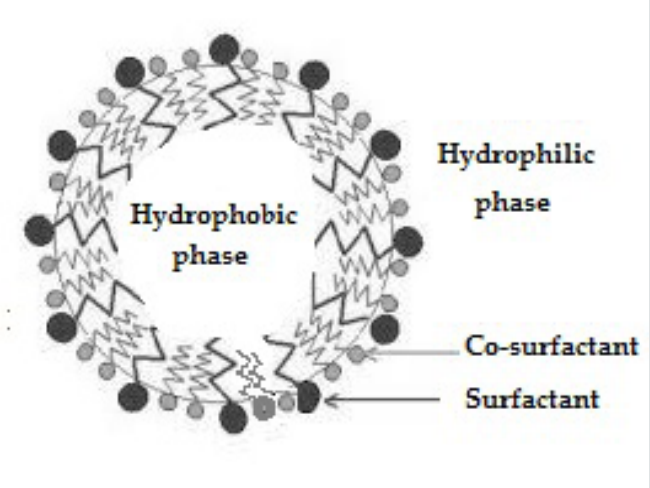

Figure 3: Interfacial theory (film formation).

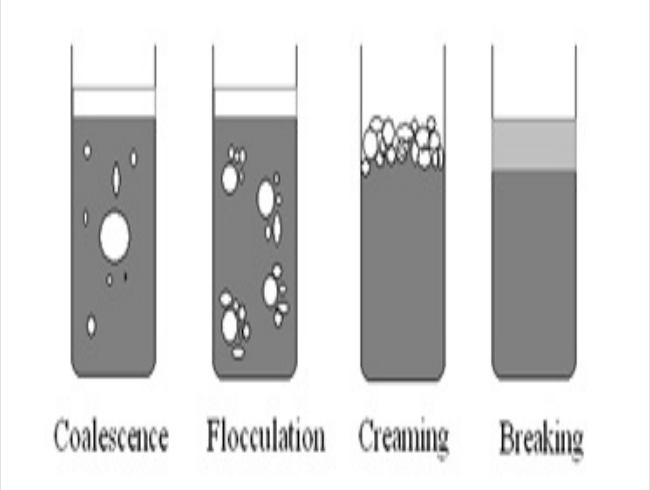

Figure 2: Stability issues with emulsions.

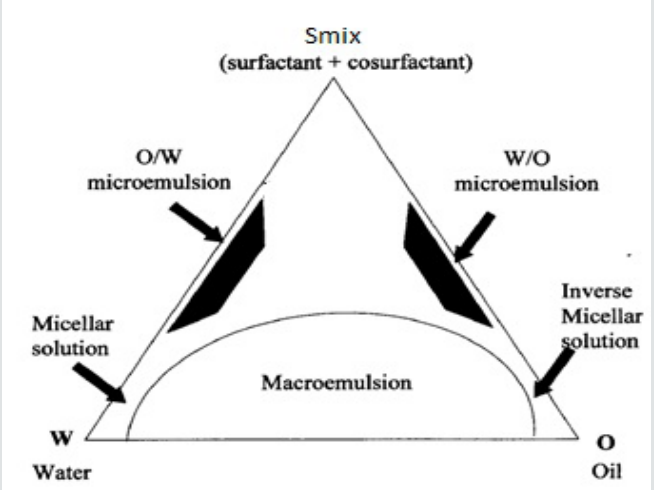

Figure 4: Phase diagram based on solubilisation theory.

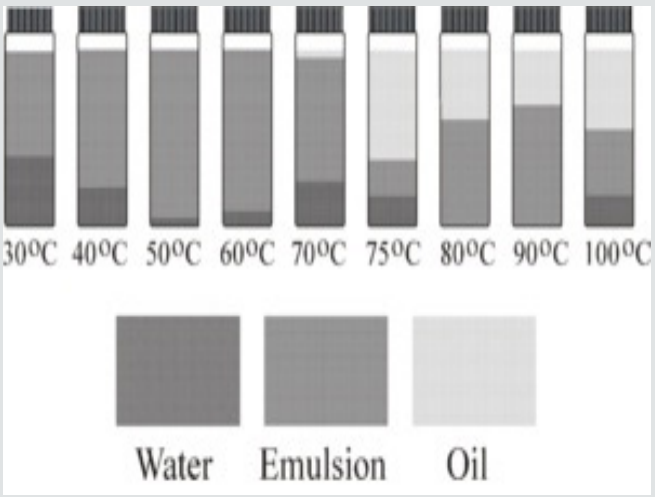

Figure 5: Phase inversion method approach.

- It is preferred dosage form to incorporate GIT irritation causing active drugs.
- It is preferred dosage form to incorporate first pass metabolism mediated degradation prone drugs.
- Stability issues like creaming, flocculation, coalescence, and sedimentation are rarely observed in nano-emulsion

Dis-advantages[43-44]

- The major disadvantage is cost of fabrication of nano emulsion is expensive. Ostwald ripening is the major issue in nano emulsions.

Comparative analysis of emulsion, micro emulsion and nano-emulsion: and Characterisation Parameters for Various Emulsions Following are various parameters useful to evaluate micro emulsions:

Parameters	Discussion
Visual Inspection	Appearance, homogeneity, transparency, optical clarity, and fluidity.[1]
Cross-polarizing Microscope testing	To exclude liquid crystalline systems it is necessary to confirm absence of birefringence by cross polarizing microscope.[1]
Limpidity Test	Limpidity is defined as an acceptable level of visible impurities. Spectrophotometeric determination of percent transmittance directly proportional to limpidity.[1-2]
Globule size	The globule size is very essential aspect to differentiate emulsion, micro emulsion and nano emulsion. It can be determined by light scattering method and or photomicroscope method.[3]
Viscosity	The rheological properties play an important role in stability as viscosity is immediately affected by storage conditions. It can be determined by Brookfield digital viscometer.[2]
pH	The pH of the formulation not only affects the stability of the emulsions but also alters the solubility and bioavailability of the drug through micro emulsion at the site of permeation. P^H meter is useful to determine P^H of emulsions.[3]
Specific gravity	Determine the specific gravity by a capillary gravity bottle method. Gravity settling can be used alone only to treat loose, unstable emulsions; however, for stronger emulsions, gravity settling separates water from oil only when used with other treating methods that increase water droplet size by destabilizing the emulsion and creating coalescence.[4]
Study of microstructure	Electron Microscopy is the most important technique for the study of micro structures of micro-emulsions because it directly produces images at high resolution and it can capture any co-existent structure and micro-structural transitions.[5]
Identification test for type of micro emulsions	Dilutability test: emulsion can be diluted in 1:10 and 1:100 ratios with double distilled water to check if the system shows any signs of separation.[24]
	Staining test: Water soluble dye such as methylene blue or amaranth is when added to emulsion and if drop is observed under microscope, background looks blue/redand globule appears colourless shows o/w emulsion.[24]
Zeta potential measurement	Electrical charges on particles influence the rate of flocculation and as well as bioavailability. Negative, positive or neutral nature depends on excipients and drug's own charges. Zeta potential between + 30 to -30 is acceptable.[5]
Phase Behaviour Studies	Phase behaviour studies are essential for the study of efficiency of different surfactant systems which can be determined by phase diagram. Oil phase, water phase and surfactant/co-surfactant mixture ratios by keeping concentration of one component or the ratio of two components constant provides useful structural organization of final emulsion. One approach to characterize thesemulticomponentsystemsisbymeansof pseudoternary diagrams that combine more than one component in the vertices of the ternary diagram.[6]
Polydispersity	Size, shape and dynamics of the components can be determined by small-angle X-ray scattering (SAXS), small-angle neutron scattering (SANS), static and dynamic light scattering techniques. Modification of the structure and the composition of the pseudophases due to dilution can be overcome by measuring intensity of scattered light at different angles. In dynamic light scattering (DLS) the size distribution of molecules or particles is the property of interest.Here, the distribution describes how much material there is present of the different size "slices." Traditionally, this overall polydispersity has also been converted into an overall polydispersity index PDI which is the square of the light scattering polydispersity. For a perfectly uniform sample, the PDI would be 0.0
Conductivity	O/W emulsions are more conductive, whereas W/O emulsions are non-conductive.
In Vitro Skin Permeation Study	For local use of emulsions, skin permeation study is conducted to find the permeation of drug through skin.The study must be carried out under the guideline compiled by Committee for the Purpose of Control and Supervision of Experiments on Animal (CPCSEA, Ministry of Culture, and Government of India).
	Take the abdominal skins from male Wistar rats weighing 230 ± 20 g (age, 6–8 weeks).Shave hair and excise skin carefully from the abdominal region of each sacrificed rat. Wash the excised rat skins and examine for integrity, and then store at 4°C for 24h in phosphate -buffersaline pH 6.8 (PBS) until permeation experiments. Perform permeation experiments using Franz diffusion cells fitted with excised rat skins having epidermal surface outward. The effective diffusion area is about 3.14 cm2(20mmdiameter orifice). Fill the receptor compartment with 12 ml of PBS. The diffusion cell is to be maintained at 37 ± 1°C using a re-circulating water bath and the solution inreceptor chamber is stirred continuously at 600 rpm throughout the experiment. Place the specified amount of formulation gently in a donor chamber. At 1, 2, 4, 6, and 8 h aliquot of 2 mL, withdraw sample from the receptor compartment for spectrophotometric determination and replace immediately with an equal volume of fresh PBS. Calculate an average value of three readings of *in-vitro* permeation data and plot the average cumulative amount of drug permeated per unit surface area of the skin versus time. Determine the permeability coefficient Kp (centimetresper hour) by using following equation
	Kp ¼ Jss = C donor
	Where, Kp is the permeability coefficient, Jss is the flux, and C donor represents the applied drug concentration in the donor compartment.

Nuclear Magnetic Resonance Studies:	Self-diffusion measurements by Fourier transform pulsed-gradient spin-echo (FT-PGSE) technique provide information on the structure, dynamics and mobility of the particles. Self-diffusion coefficients vary in the range of 9 to 12 m^2/s.6
Stability Tests	Centrifugation stress testing: Stability studies is time consuming process, so accelerated stability test is preferred. Centrifuge micro emulsion at 5000 and 10,000 rpm for 30min to assess phase separation, phase in version, aggregation, creaming and crack in go the formulations. Follow same procedure for previously thermally tested emulsions.(1-4)
	Freeze-Thaw Cycles (FTC): Store samples at 25°C for 24 h followed by 24 h at −5°C.Repeat three times to access any change in stability.
	Determination of thermal stability: Keep 20 ml of drug-loaded emulsions in a 25 ml transparent borosil volumetric contain erat three different temperatures, i.e.4°, 25°and40°C, 1°C in BOD for a period of 1 month.
	Remove samples periodically for visual inspection to observe any physical changes like loss of clarity, coal essence and turbidity etc. Observe the samples for the determination of loss of aqueous phase that is an essential part of the emulsion stability.
	Long Term Stability: For this, store emulsion samples under ambient conditions for 6 months, and examine periodically after 1, 3, and 6 months by visual inspection and measurement of percent transmittance, pH, specific gravity, and rheological evaluation. Follow detail procedure as per ICH guidelines.
In vitro models for intestinal absorption	The parallel artificial membrane permeability assay (PAMPA) uses artificial membrane to predict trans-membrane diffusion. The everted sac and Ussing chamber assay techniques are more superior models than PAMPA as they provide additional information with respect to intestinal metabolism.

CONFLICT OF INTEREST

There is no conflict of interest.

ABBREVIATIONS USED

nm: Nanometer; **mm:** Icrometer; **GIT:** Gastrointestinal tract; **mg:** Milligram, **O/W:** Oil in water; **W/O:** Water in oil; **HLB:** Hydrophilic lipophilic balance; **CPP:** Critical packing parameter; **CP:** Centipoise; **PDI:** Polydispersity index; **PBS:** Phosphate buffer saline; **ICH:** International Conference on Harmonisation; **BOD:** Biological Oxygen Demand.

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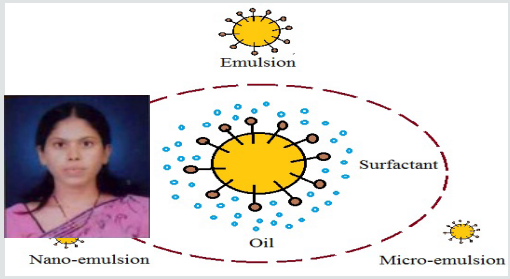
GRAPHICAL ABSTRACT



SUMMARY

- Emulsions (macroemulsion) are dispersions made up of two immiscible liquid phases which are mixed using mechanical shear and surfactant.
- Micro-emulsion is defined as dispersion made of water, oil, and surfactant(s) that is an isotropic and thermodynamically stable system with dispersed domain diameter varying approximately from 1 to 100 nm, usually 10 to 50 nm.
- Nano-emulsions are very similar to micro-emulsions that are disper¬sions of nano scale particles but obtained by mechanical force unlike to micro-emulsions which forms spontaneously.
- Microemulsions and nanoemulsions are promising delivery for poorly water soluble drugs.
- Microemulsion or nanoemulsion mediated topical, transdermal, mucoadhesive and oral delivery of drugs is more promising with benefit of extended release and enhanced bioavaibility.

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Dr. S. L Deore: Is working as Assistant Professor in Govt. College of Pharmacy, Amravati. She has published 03 books and more than 50 research papers. She has grabbed Research Promotion Grant (RPS) and awarded with Career award for Young Teacher (CAYT) by AICTE. Her areas of research are extraction and isolation of phytochemicals, planar chromatography, intellectual property rights, structural elucidation of phytochemicals, neutraceutical development and traditional medicine screening.