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Review on Nanoemulsion Drug Delivery System

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ABSTRACT

Nanoemulsions are emulsions that are submicron in size and function as drug carriers to enhance the delivery of medicinal medicines. They are the most cutting-edge nanoparticle systems for the targeted or regulated systemic distribution of active medicinal ingredients. These are isotropic thermodynamically stable systems that combine two immiscible liquids (oil and water) into a single phase using the proper surfactants. The normal size range for nanoemulsion globules is between 10 and 100 nm, with a limited size distribution. For the future of biotechnologies, diagnostics, pharmacological treatments, and cosmetics, nanoemulsions hold out a lot of potential. The purpose of this study is to examine the benefits and drawbacks of nanoemulsions as well as various preparation methods, characterisation techniques, and sub-micron emulsion applications like different administration methods, chemotherapy, cosmetics, etc.

INTRODUCTION:

Nanoemulsions, also known as submicron emulsions, ultrafine emulsions, and miniemulsions, are isotropic dispersions of two immiscible liquids, such as water and oil, stabilised by an interfacial film made of a suitable surfactant and co-surfactant to form a single phase. They are submicron sized colloidal particulate systems that are considered to be thermodynamically and kinetically stable. Such nanoemulsions have been employed with a variety of surfactants, both ionic and non-ionic, with various properties. They were mostly utilised as cationic (quaternary ammonium halide), anionic (potassium laurate, sodium lauryl sulphate), zwitterions (quaternary ammonium halide), and nonionic (sorbitan esters, polysorbates) surfactants. Early nanoemulsions were of the oil-in-water (O/W) type, with droplet sizes averaging between 50 and 1000 nm. Recent classifications of nanoemulsions into three groups include the O/W type (water is dispersed in the oil phase), water-in-oil (W/O) type (oil is distributed in the aqueous phase), and bi-continuous (the system contains interdispersed microdomains of water and oil). By changing the components of the emulsions, these three kinds can be transformed. O/W and W/O emulsions coexist in one system concurrently in multiple emulsions, another form of nanoemulsion. Both hydrophilic and lipophilic surfactants are applied simultaneously to stabilise these two emulsions. [1-5]

Emulsions are dispersions comprised of two immiscible liquid phases that are blended together with the aid of mechanical shear and a surfactant. Surfactants, which are amphiphilic surface-active molecules, are in charge of reducing naturally occurring attractive forces in the form of surface tension. The development of the desired emulsion is aided by the selection of the surfactant based on the hydrophilic-lipophilic balance (HLB) value or the critical packing parameter (CPP). Surfactants with low HLB3-8 values are beneficial for creating W/O emulsions, whereas those with high HLB8-18 values are employed to create O/W emulsions. The ratio of a surfactant molecule's hydrophilic and hydrophobic components is known as the [2-4] critical packing parameter (CPP). The CPP also reveals the type of aggregates. Recently, two new ideas in emulsion have surfaced. Micro-emulsion is an isotropic, transparent, thermodynamically stable liquid mixture. Oil, water, a surfactant, and a co-surfactant are used to prepare it. Compared to a typical emulsion, it contains particles that are as tiny as nanoscale.6,7 The term "micro-emulsion" is used by the IUPAC to describe a dispersion of water, oil, and surfactant(s) that is isotropic and thermodynamically stable, with a dispersed domain diameter that ranges

approximately from 1 to 100 nm, typically 10 to 50 nm.[5-6] Nano-emulsions are dispersions of nanoscale particles, much like micro-emulsions, but they are produced mechanically as opposed to micro-emulsions, which develop naturally.[7,8]

Nanoemulsions advantages compare to otherdosage forms

1. Takes away variations in absorption.

2. Increases absorption rates.

3. Aids in lipophilic drug solubilization.

4. Offers aqueous dose forms for medications that are not water soluble.

5. Enhances bioavailability

6. The substance can be delivered via a variety of methods, including topical, oral, and intravenous.

7. Quick and effective medication molecule penetration.

8. Aids in flavour masking.

9. As a medication in the oil phase of an o/wemulsion, it offers protection against hydrolysis and oxidation.

10. Less energy is necessary.

11. Patient compliance is increased by liquid dose form.

12. Nanoemulsions are thermodynamically stable systems, and this stability allows the system to self-emulsify so that its characteristics are not influenced by the method used.

13. Nanoemulsions transport both hydrophilic and lipophilic substances.

14. Using Nanoemulsion as a medication delivery system increases a medicine's effectiveness, allowing the overall dose to be decreased and minimising adverse effects. [6]

Disadvantages of Nanoemulsion

1. The stabilisation of the Nanodroplets requires the use of a high concentration of cosurfactants and surfactants.

2. Limited ability to dissolve materials with high melting points.

3. The surfactant used in pharmaceutical applications must not be harmful.

4. Environmental factors like temperature and pH have an impact on the stability of nanoemulsions. When patients get nanoemulsion, these variables alter.[7].

Components of Nanoemulsion

Main three components of Nanoemulsions are

1. Oil

2. Surfactant/Co surfactant

3. Aqueous phase[8,9]

Nanoemulsions are colloidal dispersions com- posed of an oil phase, aqueous phase, surfactant and cosurfactants at appropriate ratios. Unlike coarse emulsions micronized with external energy nanoemulsions are based on lowinterfacial tension. This is achieved by adding cosurfactants, which leads to spontaneous formation of a thermodynamically stable nanoemulsion. The droplet size in the dispersed phase is small, usually below 140 nm in diameter, which makes the nanoemulsions transparent liquids. They are used to deliver there are various ways to deliver medications to patients, but topical administration of nanoemulsions has drawn a lot of attention. The mobility of the drug inside the vehicle, the release of the drug from the vehicle, and the permeation of the drug into the skin are the three key elements that affect transdermal permeation of pharmaceuticals. Thus, they outperform conventional topical treatments like emulsions and gels in terms of transdermal drug delivery. Compared to nanoemulsions containing gel, which will enhance their viscosity and further reduce skin permeability, medicines move more easily in nanoemulsions. It has been established that nanoemulsions' higher transdermal flow is primarily a result of their strong drug solubilization capacity for both lipophilic and hydrophilic compounds. This increases the thermodynamic activity in the direction of the skin. They could have an impact on how easily a medicine penetrates the skin. In this situation, the nanoemulsion's constituent parts act as permeation promoters. Several substances used in nanoemulsions have been reported to enhance trans-dermal penetration by changing the stratum corneal structure. Short chain alkanols, for instance, are frequently utilised as permeability enhancers. By forming distinct domains that

interfere with the continuity of the multilamellar stratum corneum and may result in highly permeable pathways, the fatty acid oleic acid, which has one double bond in its chain structure, disrupts the lipid barrier in the stratum corneum.[9-11]

Factors affecting on the nanoemulsion

1. The surfactant is the most crucial component of the Nanoemulsion, according to 1. They shouldn't create "micro-emulsions" phases of lyotropic liquid crystal. Phases that are typically utilised with the co-surfactant are systems with short chain alkanes, alcohols, water, and surfactants.

2. To prevent Oswald ripening, the composition must be appropriate, and the dispersed phase must be almost completely insoluble in the dispersion medium.

3. Surfactant overuse makes it possible to cover new nanoscale surfaces quickly during emulsification, which prevents induced coalescence.[12]

Types of nanoemulsion[3]

Following are different types of emulsions

i. Water-in-oil (w/o)

ii. Oil-in-water (o/w)

iii. Water-in-oil-in-water (w/o/w)Oil-in-water-in-oil (o/w/o**)**

Methods of preparations[4]

• **Using dry gum:** Triturate an oil and emulsifier combination with the addition of water to create a main emulsion. To create an emulsion, add more water to dilute and mix continually.

• **Wet Gum Method**: To create a primary emulsion, first triturate oil with water, and then add an emulsifier. To create an emulsion, add more water, dilute it, and combine.

• Calcium hydroxide solution and oil are used in the in situ soap method. Emulsion is created by mixing and stirring.

• **Mechanical Method:** To create an emulsion, combine the oil, water, and emulsifier. Mix thoroughly.

Advantages[5]

- To make hydrophobic or oil-soluble medicines more soluble.
- To improve medication absorption.
- To improve topical medication absorption
- To cover up the unpleasant flavour and scent of medications.
- To make nutrients more palatable.
- **Using dry gum**: Triturate an oil and emulsifier combination with the addition of water to create a main emulsion. More water to dilute and stir the mixture.

Disadvantages

- Less stable than alternative dose types
- Has a limited shelf life
- Creaming, cracking (breaking), flocculation, and phase inversion are frequent issues seen during emulsion storage.

Micro-emulsion

A micro-emulsion, according to the IUPAC, is a dispersion of water, oil, and surfactant(s) that is an isotropic and thermodynamically stable system with a dispersed domain diameter ranging roughly from 1 to 100 nm, often 10 to 50 nm.

Theories: Theory of interfaces

Dual film theory and mixed film theory are other names for it. At the oil-water interface, surfactant and co-surfactant combine to produce a complex film (Figure 3), which causes the formation of micro-emulsion droplets.[6-8]

Theory of solubilization

According to this view, swelling micellar system develops as a microemulsion. Water is dissolved through reverse micelle production, while oil is dissolved by regular micelle creation. It is often helpful to grasp this theoretical assumption.[7-9]

Theory of thermodynamics:

When there is no longer any interfacial tension between two immiscible phases According

to IUPAC, a micro-emulsion is a dispersion composed of water, oil, and surfactant zero that spontaneously produces micro-emulsions and generates negative free energy that aids in the thermodynamic stability of the emulsion.

Transparent emulsion, swelling micelle, and micellar solution are other names for microemulsions. Another common name for the micro emulsion-mediated delivery of pharmaceuticals is self-micro emulsifying drug delivery system (SMEDDS). In 1953, T. P. Hoar and J. H. Shulman developed the word "micro emulsion" to describe a multiphase system made up of water, oil, surfactant, and alcohol that produces a transparent solution. However, the detection of microemulsions shows prior usage of liquid waxes or white spirit.

Types

• The Winsor phases are four different types of micro-emulsion phases that exist in equilibrium, according to Winsor.They are: [10–13]

• In the Winsor I (two phase system), the top oil layer and bottom (o/w) micro emulsion phase coexist in equilibrium.

• In the Winsor II (two phase system), the top (w/o) micro emulsion and lower surplus water are in balance.

• The Winsor III (three phase system) contains a central bi-continuous phase of water and oil that is in equilibrium with the upper and lower phases of the system.

• Winsor IV (single phase system): it creates a uniform combination of oil, water, and surfactant.

• Winsor initially proposed the R-ratio as one of the characterization notions to describe how amphiphiles and solvents affect interfacial curvature. Comparison of the affinity for an amphiphiles.

• According to Winsor, there are four different sorts of micro emulsion phases, from those that are ephemeral to oil and those that prefer water for dissolution. The interfacial area produces a distinct curve if one phase is preferred. As a result, if R > 1, the interface's area of contact with oil grows while its area of contact with water shrinks. As a result, oil

becomes the continuous phase, and type II (Winsor II) characteristic systems are appropriate. Similar to this, R = 1 represents an interfacial layer that is balanced.

Preparation methods

- **Phase titration method**: The required amount of medicine was mixed with the right amount of oil, which is necessary for the solubilization of the drug, to create a micro emulsion.14 The mixture was homogenised, and co-surfactant blends were precisely weighed and added in small amounts while being stirred.[15-18] The mixtures were completely blended using a magnetic stirrer, and then double-distilled water was added to them while it was being continuously stirred for around 10 minutes, at an optimum pace depending on the desired particle size.[19]

- **PIT or the phase inversion temperature technique:** Phase inversion of microemulsions is the process of changing an O/W system to a W/O system by adding too much dispersed phase or by increasing temperature when non-ionic surfactants are employed to modify the surfactant's spontaneous curvature, which results in the formation of an emulsion technology to create finely distributed oil droplets with minimum surface tension.[20-22] Extreme variations in particle size are demonstrated by this approach, and these changes also affect the pattern of drug release both in vivo and in vitro.[23-25]

Advantages[25-27]

- It can increase bioavailability and rate of absorption by removing interfering variations, and it can also improve the solubility of lipophilic drugs.
- It is also thermodynamically more stable than conventional systems, making it suitable for long-term use.
- It can be preferred to develop sustained and controlled release drug systems.
- It is the best system to minimise side effects.

Disadvantages[28-29]

• Using more surfactants and co-surfactants results in higher costs.

• Mucosal toxicity can result from an excess of surfactants.

Composition:

The following are the main parts of the micro emulsion system:

1) Oil phase
2) Surfactant (Primary surfactant)
3) Co-surfactant (Secondary surfactant)
4) Co-Solvent

Oil phase

Due to its abilities to solubilize lipophilic drug molecules and enhance absorption via the body's lipid layer, oil phase is the second most significant transport medium after water.6 Oil's particular ability to penetrate cell walls makes it ideal for the delivery of lipophilic active drugs. Oil phase has an impact on the surfactant's tail group area swelling. Compared to long chain alkanes, short chain alkanes have a larger degree of this penetration. 7 Example

Lauric, Myristic, and Capric Acid are Saturated Fatty Acids.

Oleic, linoleic, and linolenic acids are examples of unsaturated fatty acids.

Lauric, myristic, and oleic acid ethyl or methyl esters are examples of fatty acid esters.

Surfactants

Surfactant must be able to lower the interfacial tension closest to the surface during the preparation of the microemulsion.[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 to enable the dispersion of all components, to zero. Among these surfactants are:

Non-ionic ionic anionic cationic Zwitter. The nature of the surfactants influences the stability of the microemulsion. Ionic surfactants are stabilised by electrical double layers, while non-ionic surfactants are stabilised by dipole and hydrogen bond interactions.

The concentration of salt also has an impact on ionic surfactants. As a result, ionic surfactants are typically not preferred due to their sensitivity to stability problems and potential toxicity. However, non-ionic surfactants are more often used because they may provide benign medicinal dosage forms.[8]

When creating a W/O microemulsion, surfactants with HLB values of 3–6 are helpful, whereas surfactants with higher HLB values of 8–18 are helpful when creating an O/W microemulsion. Surfactants with more than 20 HLB values work as co-surfactants to lower surfactant concentrations to a permissible limit and the development of micro emulsions.9–10 Polyoxyl 35 castor oil (Cremophor EL), Polysorbate 80 (Tween 80), and others are non-ionic surfactants.

Co-surfactants

According to research, substantial concentrations of single-chain surfactants are necessary to lower the O/W interfacial tension to a point where a microemulsion can spontaneously develop. However, if co-surfactants are included, then varied curvatures of interfacial film may be generated with the least amount of surfactant concentration to provide a stable micro emulsion composition. (11-16) Due to the presence of fluidizing groups such unsaturated bonds, cosurfactants increase the fluidity of the interface. They subsequently dissolve liquid crystalline or gel structures and change the HLB value in a way that results in the spontaneous creation of micro 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 pres- sure homogenization

- **Low energy emulsification:** Phase inversion temperature method, solvent displacement method and phase inversion composition meth-od

- **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, ho- mogenization 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 filtration 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 vac- cum 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.

- **Ultrasonication** and high-pressure homogenization are two methods of high energy emulsification.

- **Phase inversion** temperature method, solvent displacement method, and phase inversion composition method are all examples of low energy emulsification techniques.

- **High-Pressure Homogenization:** To create nanosized particles, a specifically made high-pressure homogenization apparatus is utilised. Oil phase and water phase are permitted to push via a tiny input aperture at extremely high pressure (500 to 5000 psi).[34] Therefore, severe turbulence and hydraulic shear result in the creation of exceedingly tiny size particles. However, this approach demands a lot of heat and energy. The direct causes of particle size are pressure and homogenization cycles.[35] The smaller the particle size, the higher the pressure and homogenization cycles. Scaling up this methodology is simple.

- **Microfluidization**: Using a specifically created instrument known as a micro High pressure is produced with a fluidizer (500 to 20,000 psi). First, make a coarse emulsion by combining the water and oil phases.[36] This device consists of an interaction chamber with a series of tiny microchannels through which a coarse emulsion is driven to generate fine nanoparticles in an impingement region before being filtered to produce homogenous

particles.[37]

When a coarse emulsion is placed in an ultrasonic field and the external pressure is raised, the cavitation threshold likewise rises to restrict the formation of tiny, nanoscale particles.[38]

- **The phase inversion method:** employs the phase inversion temperature, or the temperature at which a phase shift takes place. O/W emulsions are better at low temperatures, whereas W/O emulsions are better at high temperatures. Quick heating and cooling High pressure is produced with a fluidizer (500 to 20,000 psi). First, make a coarse emulsion by combining the water and oil phases.36 This device consists of an interaction chamber with a series of tiny microchannels through which a coarse emulsion is driven to generate fine nanoparticles in an impingement region before being filtered to produce homogenous particles.[37]

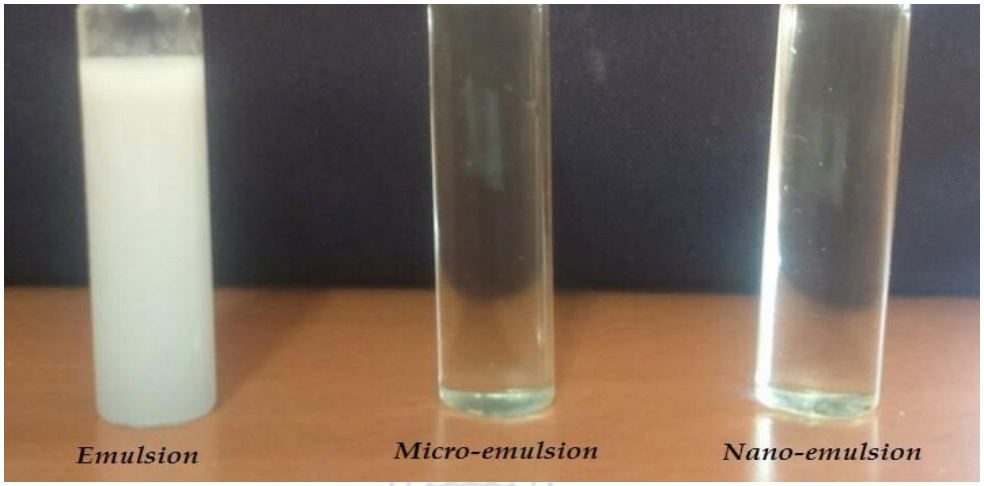
When a coarse emulsion is placed in an ultrasonic field and the external pressure is raised, the cavitation threshold likewise rises to restrict the formation of tiny, nanoscale particles.[38] The phase inversion method employs the phase inversion temperature, or the temperature at which a phase shift takes place. O/W emulsions are better at low temperatures, whereas W/O emulsions are better at high temperatures. Quick heating and cooling tiny particles are produced by cycles. Due to the dehydration of the polymer chain, non-ionic surfactants like polyoxyethylene become lipophilic at high temperatures and hydrophilic at low temperatures.

• **Spontaneous Emulsification:** This straightforward technique employs an oil-water-lipophilic-and-hydrophilic-surfactant volatile organic solvent composition. Through magnetic stirring, this mixture is made to mix evenly. The water-miscible solvent is then evaporated under vacuum to produce the nano-emulsion.[39]

• **Solvent Evaporation process:** Using a suitable surfactant, this process involves first combining the medication with the organic solvent to create the O/W emulsion. After obtaining microspheres loaded with the medicine, organic solvent should be evaporated under vacuum, heat, or ambient conditions. Centrifugation or filtration should then be performed.[40]

• **The hydrogel technique** is comparable to solvent evaporation method. To create a drug-solvent nanoemulsion that is miscible with the drug anti-solvent, high shear forces are utilised.

DIFFERENT PARAMETER/CHARACTERISTICS OF EMULSIONS:

Parameters	**Emulsion[1-5]**	**Microemulsion 6-15**	**Nano emulsion[35-42]**
Appearance	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
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	oil in water nano emulsion in which oil is dispersed in the continuous aqueous phase, water in oil nanoemulsion 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	Thermodynamic theory	Surface tension theory Interfacial theory

	Repulsion theory Viscosity modification theory Oriented-Wedge Theory Interfacial film theory	Solubilisation 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	

EVALUATION OF SUSPENSION:

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. PH meter is useful to determine PH 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/red and 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 these multicomponent systems is by means of pseudo ternary 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 buffer saline 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 in receptor 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 (centimetres per

	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.

Applications of Nanoemulsion:

1. Nanoemulsions are used in cosmetics[1].
2. Nanoemulsions that are antimicrobial.
3. Preventative measures in bioterrorism attacks.
4. Mucosal vaccines made of nanoemulsions.
5. Non-Toxic Disinfectant Cleaner Using Nanoemulsion.
6. The technology of nanoemulsions in cell culture.
7. Nanoemulsion preparations for better oral absorption of insoluble drugs[21].
8. Drug delivery methods that self-nanoemulsify [8].
9. Nanoemulsions as a transdermal delivery system Diclofenac cream, a possible therapy for osteoarthritis, is one example of a condition that can be treated using nanoemulsion [25, 10.]
10. Solid self-nanoemulsifying delivery systems as a base technology for poorly soluble drug formulation.
11. Targeted medication delivery and cancer treatment using nanoemulsion.

CONCLUSION:

For the administration of pharmaceuticals, biologicals, or diagnostic agents, nanoemulsion formulations provide a number of benefits. They can manage drug release, preserve labile pharmaceuticals, improve pharmaceutical solubility, boost bioavailability, and lessen patient variability. For more than 40 years, clinics have been using Nanoemulsions as fluids for whole parenteral feeding. In contrast to their traditional use as delivery systems for aqueous insoluble medications, nanoemulsions are now receiving more and more attention as colloidal carriers for the precise administration of different anticancer

medications, photosensitizers, neutron capture treatment agents, or diagnostic agents. They are easily able to target the tumour location due to their submicron size. Additionally, the targeting moiety has created new opportunities for the precise delivery of compounds such as photosensitizers, medicines, genes, and other molecules to the tumour site. It is anticipated that additional in the near future, research and development activities will be conducted for the clinical realisation of these focused delivery vehicles.

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