EMULSION, MICRO EMULSION AND NANO EMULSION: A REVIEW

Abstract

Hydrophobic pharmacological compounds are well-suited for administration through lipid dosage forms. One of the most widely used systems for many years has been emulsion. The use of emulsions in pharmaceuticals has expanded, particularly with the introduction of micro- and nano-emulsions. This essay aims to provide a summary of comparative elements such as definitions, theories, kinds, preparation techniques, benefits, drawbacks, and analysis techniques for emulsion, micro-emulsion, and nano-emulsion.

Keywords: emulsion, Pharmaceuticals, administration.

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I. INTRODUCTION

Dispersions are emulsions consisting of 2 immiscible liquid phases combined with a surfactant and mechanical shear. Surfactants are amphiphilic molecules. They are responsible for reducing one kind of naturally occurring attractive force called surface tension. Hydrophilic-lipophilic balance (HLB) value or critical packing parameter (CPP) can be used to select a surfactant that will help with the development of the intended emulsion. High HLB values (8–18) of surfactants are employed to create O/W emulsion. Conversely, those with low HLB values (3–8) aid in the formation of W/O emulsion. The critical packing parameter (CPP) of a surfactant molecule is the ratio of its hydrophilic to hydrophobic regions.

A micro-emulsion is an isotropic, transparent a liquid combination with thermodynamic stability. Water, oil, co-surfactant, and surfactant are utilized in its preparation. In contrast to a traditional emulsion, it contains particles as tiny as the nanometer. But nano-emulsions are spontaneous dispersions of nanoscale particles that are extremely similar to micro-emulsions and are obtained by mechanical force.

II. EMULSION

Emulsions are dispersed systems that are thermodynamically unstable and made up of two or more immiscible liquid phases, where one is distributed as globules in the other liquid phase. An emulsifying agent is present to stabilize the system. Emulsification is the process by which an emulsion forms. The dispersed phase globules typically have a diameter of between 0.1 and 10 μm, while they can have diameters limited to 0.01 μm or big as 100 μm.

1. Advantages of Emulsion

- By creating an emulsion, such as castor oil emulsion or cod liver oil emulsion, medications with a disagreeable taste and odor able to rendered more appealing for administration orally.
- Oil-soluble medications are easily diluted in a less costly medium, such water. Emulsions can therefore be made more affordable.
- Compared to solid dose forms, medication absorption is improved in emulsion form.
- In X-ray examinations, radio opaque emulsions are utilized as diagnostic materials.
- Concentrated emulsions, such as Cold cream and vanishing cream, are used as semisolid carriers in transdermal drug delivery systems.
- Patients can receive sterile, stable intravenous emulsions comprising fats, carbohydrates, vitamins, and supplements.
- Drug release from an emulsion can occur at a specified rate and time. In certain emulsions, it can extend the release of the medication.

2. Disadvantages of Emulsion

- The shelf life of emulsions is brief.
- Because the dosage form is liquid, caution should be used during packaging.
- Emulsions may experience phase inversion, flocculation, cracking (breaking), and creaming while being stored.

III. CLASSIFICATION OF EMULSIONS

Emulsion may be classified as simple emulsion and special emulsion. Simple emulsions can be categorized according to the characteristics of both the dispersion medium and the dispersed phase. It is two types such as Oil-in-water (O/W type) and Water-in-oil (W/O type). The dispersed phase in an O/W type emulsion is water, and the dispersion medium is oil. The dispersion medium in W/O type will be oil, and the dispersed phase will be water.

There are several emulsions under special emulsions such as multiple emulsion, microemulsions, and nanoemulsions. Again multiple emulsions are categorized as Water-in-oil-in-water (W/O/W) – type an Oil-in-water-in-oil (O/W/O) – type emulsion.

IV. IDENTIFICATION TESTS FOR EMULSION TYPE

To identify the type of emulsion, various techniques are frequently employed (Table 1).

Table 1: Techniques for Identifying the Type of Emulsion

Test	Observation	Comments
Dilution test	Diluting an emulsion requires an external phase.	Useful for liquid emulsions only.
Dye test	Solid dye soluble in water only hues O/W emulsion and opposite. Microscopic observation is generally useful.	May not work if there are ionic emulsifiers.
Conductivity test	Because ionic species are present in water, O/W emulsions conduct electric current.	Fails in nonionic W/O emulsions.
Fluorescence test	W/O emulsions glow continuously, while oils fluoresce when exposed to UV light. O/W emulsions show a dot pattern.	Not always applicable
$CoCl_2$/ filter paper test	When (O/W) emulsion is put to filter paper that has been treated with $CoCl_2$ and dried (blue), the paper turns pink.	If the emulsion is unstable or breaks when electrolyte is present, it might fail.
Creaming test	The emulsion type is accurately decided upon by the direction of creaming. Since water has a greater density than oil, W/O emulsions typically cream downward. Typically, O/W emulsions cream upward.	

V. THEORIES OF EMULSIFICATION

The most well-known theories are explained below.

1. **Surface tension theory:** The use of surfactants reduces the tension across the two immiscible liquids' surfaces, which lessens the repulsive force separating the liquids from each liquid's for attracting its own molecules, in accordance with the surface tension hypothesis of emulsification. Therefore, surfactants facilitate the disintegration of big globules into smaller globules and inhibit the fusion of tiny globules into larger globules.

2. **Oriented wedge theory:** As stated by oriented wedge theory, the surfactant envelops the droplets of the emulsion's internal phase in monomolecular layers. The notion is predicated where surfactants organize themselves within and around a solvent in accordance with how soluble they are in that specific liquid. This idea states that the emulsifying agents' polar ends turn towards the polar liquid while their oil-like, or non-polar, ends turn towards the oil.

3. **Interfacial film theory:** According to the interfacial film theory, the emulsifier surrounds the internal phase droplets as a thin layer of film adsorbed on their surface, creating an interface in which water and oil meet. The film keeps the dispersed phase from coming into touch with one another and consolidating; the more flexible and durable the film, the more stable the emulsion.

VI. METHODS OF PREPARATION OF EMULSION

Emulsions preparations can be done by experimental method/By HLB method, small scale/conventional method and large scale/industrial scale method. Preparation of emulsions by small scale includes dry gum method, wet gum method, and bottle method. Generally all the emulsions for oral purpose are prepared with gum acacia. To prepare a thick acacia emulsions, using mortar and pestle, a thick primary emulsion must be made first.

In large scale industrial method is based on principle of addition of internal phase and external phase in different ways.

VII. MICRO-EMULSION

A dispersion of water, oil, and surfactant is called a micro-emulsion. It is a thermodynamically stable, isotropic structure featuring a distributed domain diameter that can range from 10 to 50 nm, on average. Other names for microemulsions include micellar solution, swollen micelle, and transparent emulsion. T. P. Hoar and J. H. Shulman coined the term "microemulsion" in 1953.

1. Advantages of Microemulsion

- Its ability to form spontaneously makes it incredibly simple to prepare and scale up.
- It increases bioavailability of drug.
- It is a longer-term system that is more thermodynamically stable than a conventional system.

- Creating a drug delivery system with controlled and sustained releases may be the better option.
- The optimal system minimizes metabolism through first pass.

2. Disadvantages of Microemulsion

- The cost of using more surfactant and co-surfactant increases with additional use.
- Mucosal toxicity may result from surfactant concentrations that are too high.

VIII. TYPES OF MICROEMULSIONS

Winsor states that there are four different kinds of microemulsion phases that can be found in equilibrium; these phases are also known as Winsor phases. It's them Winsor I, or oil-in-water microemulsion, Water-in-oil microemulsion, called Winsor II, Bicontinuous microemulsion, also known as Winsor III and Winsor IV, a single-phase homogeneous mixture.

1. **Winsor I (two phase system):** A film of surfactants, or possibly cosurfactants, surrounds the oil droplets in oil-in-water microemulsions, forming the continuous internal phase dispersed throughout the water. Compared to w/o microemulsions, this kind of microemulsion often has a bigger interaction volume.

2. **Winsor II (two phase system):** Water droplets encircled by a continuous oil phase are found in microemulsions of the water-in-oil variety. These are known as "reversemicelles," because the fatty acid tails of the surfactant are facing the oil phase while the surfactant's polar headgroups are facing the water droplets. The aqueous biological system has the potential to destabilize a w/o microemulsion administered orally or parenterally.

3. **Winsor III (three phase system):** The amount of oil and water in a bicontinuous microemulsion system is comparable; in this instance, the two phases are continuous. A "sponge-phase"-like channel of mixed oil and water is asymmetrical. This bicontinuous state may be crossed by microemulsion shifts from W/O to O/W. Bicontinuous microemulsion that can exhibit plasticity and non-Newtonian flow. These characteristics make them particularly helpful for intravenous or topical drug delivery.

4. **Winsor IV (single phase system):** The oil, water, and surfactants are homogeneously mixed in a single phase homogeneous mixture, also known as winsor IV.

IX. THEORIES OF MICROEMULSION FORMATION

1. **Interfacial theory:** Another name for it is dual film theory or mixed film theory. Micro emulsion droplets are produced where oil and water meet when together, surfactant and co-surfactant to form a complex film.

2. **Solubilisation theory:** According to this theory, a swollen micellar system takes the shape of a microemulsion. Normal micelle formation causes oil to become soluble,

whereas reverse micelle formation causes water to become soluble. In general, phase diagrams are helpful in understanding this theoretical premise.

3. **Thermodynamic theory:** Micro emulsions spontaneously form when there is no longer any interfacial tension between two immiscible phases. The negative free energy that is created in this process contributes to the emulsion's thermodynamic stability.

X. PREPARATION METHODS

1. **Phase titration method:** The required amount of medicine is dispersed in the right amount oil to produce a microemulsion, that is necessary for the active pharmaceutical ingredient to become soluble. After the mixture had been homogenized and the surfactant quantity had been precisely weighed, small amounts of co-surfactant blends were added and stirred in. Using a magnetic stirrer, the blends were well combined. Then, drop by drop, double distilled water is included, and the concoction is continuously stirred for the designated amount of time.

2. **Phase inversion temperature method (PIT):** PIT refers to the transformation from an O/W to a W/O system. This is because the spontaneous curvature of non-ionic surfactants can be changed by raising the temperature that reduces the system's surface tension and creates finely dispersed oil droplets.

XI. COMPONENTS OF MICRO EMULSION SYSTEM

Microemulsions are developed and formulated using a variety of ingredients. A microemulsion's primary components are the oil phase, aqueous phase, surfactant, co-surfactant, and co-solvent.

1. **Oil phase:** One of the most crucial ingredients in a microemulsion is oil because it may both raise the amount of lipophilic medication carried by lymphatic system and solubilize the necessary dosage of the lipophilic drug. Vegetable oil, mineral oil, toulene, and cyclohexane are a few examples of this phase.

2. **Aqueous phase:** Preservatives and hydrophilic active ingredients are typically found in the aqueous phase. Buffer solutions are occasionally employed as an aqueous phase.

3. **Surfactant:** A substance that lowers the surface or interface tension and shows some superficial or interfacial activity is referred to as a surfactant. Due to a variety of forces surfactant molecules aggregate. For instance, because it is thermodynamically advantageous, surfactants gather at the oil/water interface when combined with oil and water. Surfactant molecules can arrange themselves in different configurations. The different types of surfactants—cationic, anionic, non-ionic, and Zwitterionic—that support the ongoing development of the microemulsion system. The examples of surfactants include Polysorbate/Tween 20,40,60,80; Sorbitan Monolaurate (Span), Triton X-100 etc.

4. **Co-surfactants:** It is discovered that in order to reduce the O/W interfacial tension to a level at which a spontaneous microemulsion formation is feasible, high concentrations of single-chain surfactants are required. On the other hand, if co-surfactants are added, then

various interfacial film curvatures able to form to produce a consistent composition of micro emulsion at the lowest possible surfactant concentration. Examples of co-surfactants are ethanol, propanol, Isopropanol, butanol, pentanol, Cinnamic alcohol, Cinnamic aldehyde etc.

5. **Co-solvent:** Co-solvents are organic solvents that aid in the dissolution of lipid-soluble medications and surfactants at relatively high concentrations. Mostly alcohols are preferable.

XII. NANO-EMULSIONS (NE)

Known as NE, sub-micron emulsions (SMEs), or mini-emulsions, these transparent or translucent dispersions of oil and water that are thermodynamically stable are kept in place by an interfacial film of surfactant and cosurfactant molecules with globule sizes of less than 100 nm. Appropriate surfactant and/or cosurfactant combinations stabilize the nanoemulsion interface. Three distinct kinds of NE, like oil in water (O/W), are formed depending on the composition: Water in oil (W/O) NE: These consist of continuous aqueous phase with dispersed oil droplets: NE with water droplets strewn throughout the continuous oil phase and those that are bi-continuous—that is, in which the system has small pockets of both water and oil.

1. Advantages Of Nanoemulsions (Ne)

- NEs are an efficient transport system because they have a significantly greater surface area and free energy than macro emulsions.
- NEs do not exhibit the macroemulsion-related issues of inherent creaming, flocculation, coalescence, and sedimentation.
- NEs are safe and non-irritating.
- NEs can be ingested enterically because they are made with surfactants that are GRAS (approved for human consumption).
- These can be used therapeutically for both humans and animals.

2. Disadvantages Of Ne

- Use of high surfactant and cosurfactant concentrations, which are required to stabilize the nanodroplets.
- Restricted capacity to dissolve high melting point materials.
- The environment has an impact on NE's stability.

XIII. PREPARATION METHODS

Several methods have been suggested for the preparation of nanoemulsion. Some methods discussed below.

1. **High-Pressure Homogenization:** An apparatus for high-pressure homogenization is needed to produce nanoscale particles with specialized design is employed. Phase separation occurs between the oil and water at very high pressures (500–5000 psi) when they push through a tiny inlet aperture. As a result, hydraulic shear and strong turbulence

produce incredibly small particles. But this technique needs more energy and heat. As homogenization cycles and pressure rise, particle size decreases.

2. **Micro fluidization:** This technique makes use of a micro fluidizer, which is a specially made apparatus. It generates high pressure, ranging from 500 to 20000 psi. The water and oil phases should first be combined to create a coarse emulsion. This apparatus is comprised of a microchannel-sized interaction chamber that drive coarse emulsion into an impingement area to create nanoscale fine particles. Filtration is then used to produce uniform particles.

3. **Spontaneous Emulsification:** This is a straightforward method that uses an organic volatile solvent made up of water, oil, and surfactants that are both hydrophilic and lipophilic. By magnetic stirring, this composition is made to mix uniformly. After that, use a vacuum to evaporate the water-miscible solvent to create a NE.

XIV. COMPARATIVE STUDY OF EMULSION, MICROEMULSION AND NANOEMULSION

The comparative study of emulsion, microemulsion and nanoemulsion is given in table 2.

Table 2: Comparative Study of Emulsion, Microemulsion and Nanoemulsion

Parameters	Emulsion	Micro emulsion	Nano emulsion
Appearance	Turbid	Clear	Clear
Particle size	0.1 to 100 µm	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 unstable,thermodynamically stable
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	O/W type and W/O type	Winsor I, Winsor II, Winsor III,and Winsor IV.	Oil in water NE, Water in oil NE and Bi-continuous NE.

Table 3 displays the characterization parameters for different emulsions.

Table 3: Emulsion, Microemulsion, and Nanoemulsion Comparative Analysis, along with Characterization Parameters

Parameters	Discussion
Limpidity Test	The percent transmittance that is directly proportional to limpidity can be determined using spectrophotometry. A permissible amount of visible impurities is called limpidity.
Globule size	To distinguish between an emulsion, micro emulsion, and nano emulsion, the globule size is a crucial factor. It can be found using the photomicroscope method or the light scattering method.
Viscosity	Since storage conditions have an immediate impact on viscosity, rheological properties are crucial for stability. The digital viscometer made by Brookfield can determine it.
pH	A pH meter is helpful in figuring out the pH of emulsions.
Specific gravity	Utilizing a pcynometer, the specific gravity of emulsions are determined.
Zeta potential measurement	Electrically charged particles affect flocculation rate and bioavailability. Whether a drug is neutral, positive, or negative depends on its excipients and internal charges. Zetasizer is used to determine zeta potential.
Phase Behaviour Studies	Phase diagrams can be used to determine the efficiency of various surfactant systems, and phase behavior studies are crucial for this research. By adjusting the concentration of one or both components, the ratios of the oil phase, water phase, and surfactant/co-surfactant mixture are maintained, resulting in a useful structural organization of the final emulsion.
In Vitro Skin Permeation Study	Remove the abdominal skins from male Wistar rats that are 6–8 weeks old and weigh 230 ± 20 g. Shave each sacrificed rat's hair and carefully remove its skin from the abdominal area. After cleaning and checking for integrity, the removed rat skins are stored in phosphate buffer saline pH 6.8 (PBS) at 4°C for 24 hours, or until the permeation experiments are conducted. To perform permeation experiments, use Franz diffusion cells fitted with excised rat skins with the epidermal surface facing outward. With a 20 mm diameter orifice, the effective diffusion area is approximately 3.14 cm^2. Pour specified milliliters of PBS into the receptor compartment. For the duration of the experiment, the solution in the receptor chamber will be continuously stirred at 600 rpm while the diffusion cell is maintained at

	37 ± 1°C using a recirculating water bath. Carefully transfer the designated quantity of formulation into a donor chamber. For spectrophotometric analysis, remove the sample (aliquot of 2 mL) from the receptor compartment at 1, 2, 4, 6, and 8 hours. Quickly replace the sample with an equivalent volume of fresh PBS. Plot the average cumulative amount of drug permeated per unit surface area of the skin against time by calculating the average value of three readings of the in-vitro permeation data. Find the coefficient of permeability.
Stability Tests	*Centrifugation stress testing:* Accelerated stability testing is preferred because stability studies are a time-consuming process. The phase separation, phase in version, aggregation, creaming, and cracking of the formulations are assessed by centrifuging a micro emulsion for 30 minutes at 5000 and 10,000 rpm. For emulsions that have already undergone heat testing, use the same process. *Freeze-Thaw Cycles (FTC):* Keep samples for 24 hours at 25°C, then for another 24 hours at -5°C.To access any change in stability, repeat three times. *Determination of thermal stability:* 20 milliliters of drug-loaded emulsions should be kept at three different temperatures (4°, 25°, and 40°C, and 1°C in BOD) for a month in a 25 milliliter transparent borosil volumetric container. Samples should be removed on a regular basis for visual inspection in order to spot any physical changes, such as turbidity, coalessence, and clarity loss. Examine the samples to determine whether there has been an aqueous phase loss, which is crucial for the stability of the emulsion. *Long Term Stability:* Emulsion samples should be kept at room temperature for six months in order to do this. Then, visually inspect the samples and measure the percent transmittance, pH, specific gravity, and rheological assessment at one-, three-, and six-month intervals. Observe the specific steps outlined in the ICH guidelines.

XV. ABBREVIATIONS USED

nm: Nanometre; mm: Micrometre; 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 Council on Harmonisation; BOD: Biological Oxygen Demand.

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