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NANOEMULSION AS NOVAL DOSAGES FORM-A REVIEW

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ABSTRACT

Nanoemulsions are emulsions of the submicron size that are under study as drug carriers to enhance therapeutic agent delivery. These are the thermodynamically stable isotropic schemes in which two immiscible liquids are combined with appropriate surfactants and cosurfactants to form a single phase. Normally, nanoemulsion droplet sizes fall in the range of 20-200nm and display a small distribution of size. The focus of this review is to provide brief information on the formulation aspect, the preparation method, the characterization techniques, the evaluation parameters and the different application of nanoemulsions,several techniques are to be used for the preparation of nanoemulsions like microfluidization, high-pressure homogenization, low energy emulsification and solvent evaporation method and parameter that are to be used for its characterization like, viscosity determination, drug content, refractive index, pH, Transmission electron microscopy, droplet size analysis, zeta potential.

KEYWORDS: Nanoemulsion, Self emulsification, Phase separation, High pressure homogenization.

1. INTRODUCTION

Nanoemulsions are droplet size emulsions in the range of 20-200 nm and are kinetically stabilized dispersions formulated using a surfactant by combining, and stabilizing two immiscible phases. Due to the small droplet size leading to high surface area per unit volume, greater stability, optically transparent appearance, versatile fluidity, and improved bioavailability of lipophilic materials, they exhibit useful properties. Interdisciplinary nanoemulsion applications in consumer goods, i.e. pharmaceuticals, pesticides, cosmetics, food, paint and environmental applications, have recently attracted interest in its research.

Miniemulsions, ultra-fine emulsions, and submicron emulsions are often referred to as nanoemulsions Phase behaviour studies have shown that the size of the droplets is determined by the structure of the surfactant phase (bicontinuous microemulsion or lamellar) at the point of inversion due to either temperature or composition. Studies on the formation of nanoemulsion by the method of phase inversion temperature have shown a relationship between the minimum droplet size and the complete solubilization of the bicontinuous phase microemulsion oil, irrespective of whether the initial phase balance is single or multiphase.

Nanoemulsions have resilience against sedimentation or creaming due to their small droplet size, with Ostwald ripening being the main mechanism of nanoemulsion breakdown.The primary application of nanoemulsions is the preparation of nanoparticles as a disperse step (called miniemulsion polymerization method) using a polymerizable monomer in which nanoemulsion droplets act as nanoreactors. The use of nanoemulsions as formulations, namely for controlled drug delivery and targeting, is another interesting application that is experiencing active growth. The main use of nanoemulsions is in the dispersed preparation of nanoparticles using a polymerizable monomer, with nanoemulsion droplets acting as nanoreactors.

Nanoemulsion, which is categorized as colloidal multiphase dispersion, is distinguished by its stability and clarification in general. Small particles or droplets, ranging in size from 5 nm to 200 nm, and very low oil/water interfacial tension characterise the dispersed process. Nanoemulsions are transparent since the droplet size is less than 25 percent of the wavelength of visible light. Nanoemulsion, usually without high-energy input, is readily and often spontaneously formed. In certain situations, in addition to the surfactant, the oil process, and the water level, a cosurfactant or cosolvent is used.[1]

1.2 TYPES OF NANOEMULSION

Depending on the composition there are three types of nanoemulsions:

1. Oil in water nanoemulsions wherein oil droplets are dispersed in the continuous aqueous phase.
2. Water in oil nanoemulsions wherein water droplets are dispersed in the continuous oil phase
3. Bi-continuous nanoemulsions where in microdomains of oil and water are interspersed within the system.[2]

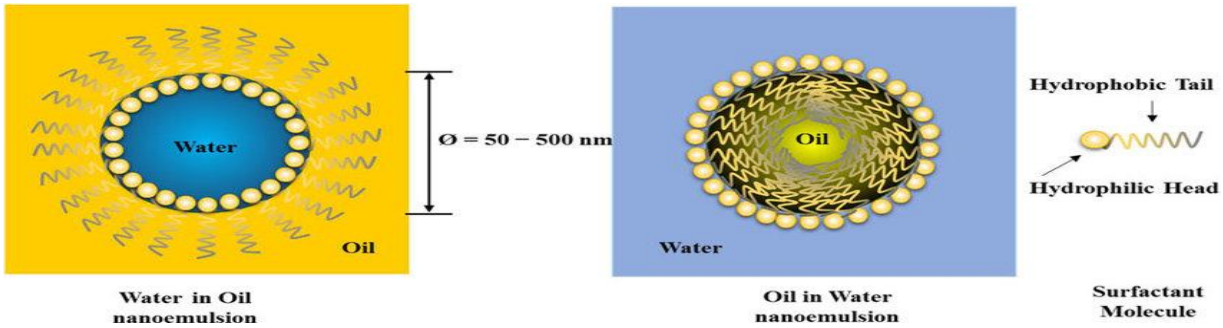

Figure 1: Schematic diagram of the water-in-oil (W/O) and the oil-in-water (O/W) nano-emulsion consisting of surfactant micelles.

1.3 Merits of nanoemulsion

a) It may be used as a substitute for liposomes and vesicles.
b) It improves the bioavailability of the drug.
c) It helps to solubilize lipophilic drugs.
d) It is the preferred dosage form to incorporate GIT irritation causing active drugs.
e) It is the preferred dosage form to incorporate first-pass metabolism mediated degradation prone drugs.
f) Increase the rate of absorption.[3]
g) Nanoemulsions are thermodynamically stable systems and the stability allows self-emulsification of the system.[4]

1.4. Demerits of nanoemulsion

a) The large concentration of surfactants /cosurfactants is required for stabilization.
b) Its stability is affected by temperature and pH.
c) Stability can be caused due to Oswald ripening effect**.**

1.5 Nanoemulsions are generally fabricated from oil phase (organic phase), aqueous phase, surfactant, and possibly a co-surfactant.[5]

Organic phase: The formulation of the organic phase involves a variety of non-polar components, such as triacylglycerols, diacylglycerols, monoacylglycerols, free fatty acids, flavor oils, essential oils, mineral oils, fat substitutes, waxes, oil-soluble vitamins, and lipophilic nutraceuticals (carotenoids, coenzyme Q). The formation, stability, and properties of nanoemulsions are influenced by bulk physicochemical characteristics (polarity, water-solubility, interfacial stress, refractive index, viscosity, density, phase behavior, and chemical stability) of the oil phase.

Aqueous phase: The aqueous phase of nanoemulsions is primarily water, but various other chemical components, such as acids, bases, minerals, proteins, carbohydrates, and co-solvents, can be present in the aqueous phase. Nanoemulsion formation, stability, and physicochemical properties are directly affected by the composition, since the components affect the aqueous phase polarity, interfacial tension, refractive index, rheology, density, phase behavior, pH, and ionic strength.[6]

Particle size is one of the nanoemulsion's most important characteristics. The droplet sizes of nanoemulsions are 20 nm to 500 nm. However, in literature, there are no different size ranges to distinguish between nano-emulsions and traditional emulsions. Stability, optical, properties, and nanoemulsion rheology are primarily influenced by gout size. The primary objective of nanoemulsion research is to achieve particle size with a high degree of uniformity (monodispersed system). The Polydispersity Index is an indicator for the size distribution (PDI). If the PDI is 0.200 or smaller.[7]

Phase separation: Surfactants increase emulsion stability as they form a protective layer that prevents aggregation. Surfactants decrease interfacial tension and friction between oil and water molecules occurs in Laplace. One or more functional classes of surfactant molecules are highly attracted to the medium in bulk as well as to the medium.[8]

Table 1: Surfactants considered under three categories.[9]

Protein emulsifiers	soybean protein isolate, whey protein isolate, β-lactoglobulin	
Polysaccharide emulsifiers	Gum arabic (Acacia Senegal), modified starches, modified celluloses, some kinds of pectin	
Small Molecule surfactants (Both hydrophilic (head group) and hydrophobic parts)	**Anionic surfactant**	Anions of alkali metal, salts of fatty acids, anions of long-chain sulfonates, sulfates, and phosphates
	Cationic surfactant	amine salts or ammonium and pyridinium compounds
	Non-ionic surfactant	polyoxyethylene compounds sugar esters, amine oxides, and fatty alkanolamides
	Zwitterionic surfactants	positive and negative charges, Tween 80 (Polysorbate 80) is (derived from polyethoxylated sorbitan, and oleic acid)

2. Techniques of preparation of nanoemulsion

Nanoemulsions have a very small particle size range; they can be most effectively produced using high pressure equipment. 'High pressure homogenization' and 'Microfluidization' are the most widely used methods for generating nanoemulsions on a laboratory and industrial scale, respectively. For the preparation of nanoemulsions, other methods such as "ultrasonification" and "in-situ emulsification" may be used.

2.1. High-Pressure Homogenization

High-pressure homogenization is required for the preparation of nanoemulsions. This technique uses a high-pressure homogenizer/piston homogenizer to generate very small particle size nanoemulsions (up to 1nm). The dispersal of two liquids is forced by a small, very high-pressure inlet opening (500-5000 psi), which exposes the material to intense turbulence and hydraulic shear, resulting in extremely fine emulsion particles. (the oily phase and the aqueous phase). The shaped particles reveal a liquid, lipophilic center separated by a monomolecular layer of phospholipids from the surrounding aqueous phase. This technique has great efficiency, the only disadvantage being high energy consumption and an increase in temperature of the emulsion during processing.[1]

In order to obtain an optimised formulation, the following process variables should be investigated

- **Effect of Homogenization Pressure:** A process parameter ranging from 100 to 150 bars is optimized. The greater the size, the smaller the particle size obtained, e.g., RMRP 22.
- **No. of Homogenization cycles:** The larger the homogenization periods, the smaller the acquired particle size is. Cycles are carried out in cycles of 3, 4, or 10. After each cycle, the number of cycles is analyzed by the drug's polydispersity index.

Advantages

- Ease of scale-up and little batch-to-batch variation.
- The narrow size distribution of the nanoparticulate drug.
- Flexibility in handling the drug quality.
- Effectively used for thermolabile substances.[10]

2.2. Microfluidization: Microfluidization is a mixing technique, which makes use of a device called a microfluidizer. The substance is forced through the interaction chamber, which is made up of small channels known as "microchannels," by a high-pressure positive displacement pump (500 to 20000 psi). The product passes through the microchannels and impinges on an impingement area, resulting in very fine sub-micron particles To make a coarse emulsion, the two solutions (aqueous phase and oily phase) are mixed and homogenised in an inline homogenizer. The coarse emulsion is processed further in a microfluidizer to produce a stable nanoemulsion.The coarse emulsion is repeatedly passed through the interaction chamber microfluidizer until the particle size desired is achieved. The bulk emulsion is then filtered through a nitrogen-filled filter to extract large droplets, giving a uniform nanoemulsion.[11]

2.3. Spontaneous Emulsification: It involves three main steps

- Preparation of homogeneous organic solution in water-miscible solvent and hydrophilic surfactant consisting of oil and lipophilic surfactant.
- In the aqueous phase, the organic phase was injected with the o/w emulsion produced under magnetic stirring.
- The water-miscible solvent was removed by evaporation under reduced pressure

2.4. Low Energy Emulsification: This Technique is used for the preparation of o/w nanoemulsion. Take advantage of the physicochemical properties of these systems based on the phase transition that takes place during the emulsification process.[12]

2.5. Solvent Evaporation Technique: This technique involves preparing a solution of the drug followed by its emulsification in another liquid that is non-solvent for the drug. Evaporation of the solution causes the substance to precipitate. Crystal growth and particle aggregation can be controlled by creating high shear forces using a high-speed stirrer.[13]

2.6. Hydrogel Method: It is similar to the solvent evaporation method. The drug solvent is miscible with the drug anti-solvent, which is the only distinction between the two processes. Crystal growth and Ostwald ripening are prevented by increased shear force. Another method used for Nanoemulsion preparation is the phase inversion temperature technique.[14]

3. Characterization and evaluation of nanoemulsion

3.1. Nanoemulsion Droplet Size Analysis: Droplet size distribution is one of the important physicochemical characteristics of a nano-emulsion, was measured by a diffusion method using a light-scattering particle size analyzer Coulter LS 230. It measures the size distribution using the diffusion of laser light by particles. Polarization intensity differential scattering (PIDS) is the assembly consists of an incandescent light source and polarizing filters, a PIDS sample cell, and an additional seven photodiode detectors. It is used to measure the droplet's size distribution, like 0.5 ml emulsion was introduced in the measuring compartment (125 ml of water). The results were presented as the volume distribution. Many other techniques have been developed to measuring the droplet size of nanoemulsions, two are of interest in this article in which laser light scattering (LLS) and energy filtering transmission electron microscopy (EFTEM). Because of their small droplet size, they are naturally resistant to creaming, sedimentation, flocculation, and

coalescence. It also facilitates the delivery of active ingredients to the skin.

3.2. Polydispersity Index: Photon correlation spectroscopy was used to determine the average diameters and polydispersity index of the samples. A He–Ne laser was used to conduct the measurements at 25°C.

3.3. Viscosity Determination: The viscosity of the formulations was determined as such without dilution using a Brookfield DV III ultra V6.0 RV cone and plate rheometer using a spindle.[15]

3.4. Refractive Index: The refractive index, n, of a medium is defined as the ratio f the speed, c, of a wave such as light or sound in a reference medium to the phase speed, vp, of the wave in the medium. n=c/vp It was determined using an Abbes type refractrometer (Nirmal International) at 25 ± 0.5°C.

3.4. pH: The apparent pH of the formulation was measured by a pH meter.[16]

3.5. Transmission Electron Microscopy (TEM): Transmission electron microscopy was used to examine the nanoemulsion's morphology and structure. A Combination of bright field imaging at increasing magnification and diffraction modes was used to reveal the form and size of nanoemulsion droplets. The experiments were carried out by putting a drop of nanoemulsion directly on the holey film grid and observing it dry.

3.6. Drug Content: Drug content can be determined by the reverse phase HPLC method using the C18 column.[17]

3.7. Zeta Potential: Zeta potential is a technique for measuring the surface charge properties of nanoemulsions as well as their long-term physical stability. The instrument used to calculate the surface charge is called ZetaPALS. The measurements were made with diluted nanoemulsion formulations 16 and the electrophoretic mobility of the oil droplets was used to calculate the values.The minimum zeta potential of ±20mv is desirable.[18]

3.8. Percentage transmittance: Percentage transmittance of the prepared nanoemulsion formulations was determined spectrophotometrically using a UV-vis spectrophotometer.

4. Applications of Nanoemulsion

a) Nanoemulsions are used in cosmetics, antimicrobial and antifungal.[19]
b) Nanoemulsion is used as Mucosal Vaccines.
c) Nanoemulsions in Cell Culture Technology.
d) Nanoemulsion formulations are used for improved oral delivery of a poorly soluble drugs.
e) Nanoemulsions as a vehicle for transdermal delivery.
f) Nanoemulsion in the treatment of various other disease conditions like diclofenac cream, a potential treatment for osteoarthritis.
g) Solid self-nano emulsifying delivery systems as a platform technology for the formulation of poorly soluble drugs.[20]
h) Nanoemulsion in cancer therapy and in targeted drug delivery.[21]

5. CONCLUSION

Nanoemulsion formulations offer several advantages for the delivery of drugs, biologics, or diagnostics and are capable of protecting labile drugs, controlling drug release, increasing drug solubility, increasing bioavailability, and reducing patient variability. Nanoemulsions have traditionally been used in clinics as total parenteral nutritional fluids for more than four decades. Nanoemulsions have recently gained prominence as colloidal carriers for the targeted delivery of anticancer drugs, photosensitizers, neutron capture therapy agents, and diagnostic agents, and are mainly used as vehicles for aqueous insoluble drug administration. They can be easily targeted to the tumor region due to their submicron scale. Furthermore, the targeting moiety has opened up new possibilities for transmitting drugs, genes, photosensitizers, and other molecules to tumors. Shortly, further research and development work for the clinical application of these targeted delivery vehicles is planned.

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