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CURRENT REVIEW ON NANO EMULSION

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ABSTRACT

Nanoemulsion is said to be transparent, clear and thermodynamically stable isotropic mixtures of oil, co-surfactant, water, and surfactant. Usually the average droplet size is between 100 and 500 nm. One of the unique characteristic of the nanoemulsion technology is the relatively high percentage of the total particle volume occupied by the internal hydrophobic oil core of the droplets. Nanoemulsion efficiency can be enhanced by the type and nature of the surfactant and co-surfactant which are used in formulation of nanoemulsion. This review provides brief information about the method of preparation, evaluation, structure, advantages, disadvantages and limitations of nanoemulsion

INTRODUCTION:

Nanoemulsions are colloidal preparation consists of an aqueous phase, oil phase, co-surfactant, surfactant at appropriate ratios. Nanoemulsions can be defined as oil-in-water (o/w) emulsions with a droplet size ranging from 50 -1000 nm. Usually the average droplet size is between 100 and 500 nm, since, the first nanoemulsion was prepared in 1940s. Nanoemulsions are clear and transparent. These nanoemulsion are of three types such as oil-in-water (O/W), water-in-oil (W/O), and bi-continuous. Surfactants which are used in the preparation of the Nanoemulsion surfactants approved for human consumption and for the common food substances these are "Generally Recognized as Safe" (GRAS) by the FDA. Nanoemulsions can be easily produced in large quantities by mixing a water-immiscible oil phase into the aqueous phase under the high shear stress, or the mechanical extrusion process that is widely available in the world-wide. Synonyms of the nanoemulsion are miniemulsion, ultrafine emulsions and submicron emulsions.

The pharmaceutical products are developed based on the nanotechnology are known as 'NANOPHARMACEUTICALS' the emulsifier also plays a role in stabilizing nanoemulsion through repulsive electrostatic interactions and stearic hindrance. The emulsifier used is generally a surfactant, but proteins and lipids have also been effective in the preparation of nanoemulsion. Over the past decade or more, the research focus has been on preparing nanoemulsion through various methods, broadly classified into two primary categories: high-energy method and low-energy method. High energy methods such as high pressure homogenization and ultrasonication consume significant energy (B108–1010 W kg_1) to make small droplets. On other hand, low energy methods exploit specific system properties to make the small droplets without consuming significant energy (B103 W kg_1). Phase inversion temperature (PIT) & emulsion inversion points (EIP) are two examples of low energy approaches for the formation of nanoemulsions.

TYPES OF NANOEMULSION:

Depending on the composition, nanoemulsions are of three types. They are:

1. Oil in water nanoemulsions: In this type oil is dispersed phase, and water is continuous aqueous phase.

2. Water in oil nanoemulsions: In this type water is dispersed phase, and, the continuous phase is oil.

3. Bi-continuous nanoemulsions: In these type oil phase and water phase are inter dispersed within the system.

Advantages; [9-17]

1. Nanoemlsion can eliminates variability in absorption
2. Absorption rate can be increased
3. Nanoemulsion can be used for solublizing of lipophilic drug
4. Provides aqueous dosage form for water insoluble drugs.
5. Bioavailability can be increased
6. Various routes like topical, oral and intravenous can be used to deliver the product.
7. Rapid and efficient penetration of the drug molecule.
8. Helps in taste masking
9. Patient compliance can be increased
10. Nanoemulsions can carry both lipophilic and hydrophilic compounds.
11. Use of Nanoemulsion as delivery systems can improve the efficacy of a drug, allowing the total dose to be reduced and thus minimizing the side effects.
12. Nanoemulsions are non-toxic and non-irritant so can be easily applied to skin and mucous membranes
13. It is do not damage healthy human and animal cells, so nanoemulsions are suitable for human and veterinary therapeutic purposes.
14. They have potential to deliver peptides that are prone to enzymatic hydrolysis in GIT.
15. Nanoemulsions have higher surface area and higher free energy than macro emulsions that make them an effective transport system.
16. Problems of inherent creaming, flocculation, coalescence, and sedimentation are not seen in nanoemulsions, which are commonly associated with macroemulsions.
17. The structures of the nanoemulsions are much smaller than the visible wavelength, so most nanoemulsions appear optically transparent, even at large loading.
18. Nanoemulsions may be used as a substitute for liposomes
19. Nanoemulsion can be used for controlled drug release & drug targeting

Disadvantages of Nanoemulsion; [18-19]

1. Large quantity of surfactant and co-surfactant can be used for stabilizing the nanodroplets.
2. There is a limited solubilizing capacity for high-melting substances.
3. The surfactant must be nontoxic for using pharmaceutical applications.
4. Stability of nanoemulsion can be influenced by environmental parameters such as temperature and pH.
5. There is a perception in the personal care and cosmetic industry that nanoemulsions are expensive to produce. Expensive equipment are required as well as the use of high concentrations of emulsifiers.
6. Lack of understanding of the mechanism of production of submicron droplets and the role of surfactants and co-surfactants.
7. Lack of demonstration of the benefits that can be obtained from using nanoemulsions when compared with the classical macroemulsions systems.
8. Lack of understanding of the interfacial chemistry that is involved in production of nanoemulsions
9. Nanoemulsions are damaged due to Oswald ripening
10. Changing in pH may cause stability problems

Limitations of Nanoemulsions

- The formulation of nanoemulsions is an expensive process due to size reduction of droplets is very difficult as it required special kind of instruments & process methods. For example:

  Homogenizer arrengement is an expensive process.
- Oswald ripening could damage the nanoemulsions.

- ❖ Changing of pH may cause stability problems

Components of nanoemulsion: [20-21]

While coming to components of Nanoemulsion, it mainly consists of

1. Oil
2. Surfactant/co-surfactant
3. Aqueous phase
4. Preservatives
5. Ph adjusting agents

METHODS OF PREPARATION OF NANOEMULSION:

1. High Pressure Homogenization: [22]

Nanoemlsion prepared by this method requires the use of the high pressure homogenizer. This high pressure homogenization technique can produce nanoemulsion of low particle size i.e. 10-100nm. Oily and aqueous phase dispersion can be achieved by forcing the mixture of oil and aqueous phase into a small inlet orifice at a high pressure of (500 to 5000 psi); here the product to subject to intense turbulence and the hydraulic shear these results in production of extremely fine particles of the emulsions. The particles which are formed can exhibit a liquid, lipophilic core separated from the surrounding aqueous phase by a monomolecular layer of the phospholipids.

To obtain the stable formulation following process variables are necessary

a) Effect of Homogenization Pressure:

The pressure in the high pressure homogenization should ranges from 100 -150 bars. If the pressure is increased then the particle size can be decreased.

b) No. of Homogenization cycles:

Homogenization cycles can be increased the particle size should be reduced, this results in reducing the particle size. Generally 3, 4, or 10 cycles can be carried out. The number of homogenization cycles is analyzed by polydispersity index of drug after the each cycle

Advantages:

1. Easy in Scale-up and there is a little variation from batch-to-batch
2. Narrow size distribution of the nanoparticulate drug.
3. There is a Flexible in handling the drug quality.
4. Thermolabile substances can be effectively used

Disadvantages:

1. High energy there is a consumption of high energy
2. There a is increasing in temperature during processing

2. Microfluidization:

In these microfludization technique there is use of a device which is called as microfluidizer. These microfludizer devices uses a high-pressure positive displacement pump (500 to 20000psi), Microfluidization is a patented mixing technology. In this technique the product forces through the interaction chamber which consists of small channels called as “micro channels”. In this the product flows into the microchannels on to an impingement area which results in the production of very fine particles of submicron range. The two phases i.e., (aqueous phase and oily phase) both are combined together and then processed in an inline homogenizer to yield a coarse emulsion. Then the coarse emulsion can be introduced into a microfluidizer where it is further processed to obtain a stable nanoemulsion. Then the coarse emulsion is passed repeatedly into the interaction chamber of the microfluidizer until the desired particle size has to be obtained. Then the bulk emulsion is to be filtered by using a filter paper (whattsmann filterpaper) under the nitrogen this nitrogen is used to remove the large droplets resulting in a uniform nanoemulsion. These two techniques that are High pressure homogenization and Microfluidization can be used for the fabrication of Nanoemulsion at laboratory and industrial scale, whereas ultrasonic emulsification is mainly used in laboratory scale

3. Ultrasonication: [23]

Nanoemulsions can be prepared by using the ultrasonic sound frequency for the reduction of the particle size. Another approach is the use of a constant amplitude sonotrode at system pressures in excess of the ambient value. It is well known that increasing the external pressure increases the cavitations threshold within an ultrasonic field and thus fewer bubbles form. However, the external pressure is increased also increases in the collapse pressure of cavitations bubbles. This means that the collapse of the bubbles when the cavitation occurs becomes stronger and

more violent than when the pressure is at atmospheric conditions. As cavitation is the most important mechanism of power dissipation in a low frequency ultrasonic system, these changes in navigational intensity can be related directly to changes in the power density. The system also uses a water jacket to control the temperature to optimum level.

4. Phase Inversion Temperature Technique (PIT): [24, 25]

Nanoemulsion can also been prepared by using phase inversion temperature method. Nanoemulsion formulation is studied by using phase inversion temperature method have shown a relationship between the minimum droplet size of emulsion and complete solubilization of the oil in a microemulsion bicontinuous phase independently of whether the initial phase equilibrium is single or multiphase. Nanoemulsions droplet size is small that's why the formulatin possess stability against the sedimentation or creaming with Ostwald ripening forming the main mechanism of nanoemulsion breakdown. Phase inversion in emulsions can be of two types: of them one is transitional inversion induced by changing in factors which can affect the hydrophilic-lipophilic-balance (HLB) of the system, e.g. temperature and/or electrolyte concentration, and catastrophic inversion, which can also be induced by changing in the HLB number of the surfactant at constant temperature by using surfactant mixtures. Phase inversion temperature (PIT) method employs temperature-dependent solubility of nonionic surfactants, such as polyethoxylated surfactants, to modify their affinities for water and oil as a function of the temperature. It has been observed that polyethoxylated surfactants tend to become lipophilic on heating showing to dehydration of polyoxyethylene groups. This phenomenon forms a basis of nanoemulsion fabrication using the PIT method. In the PIT method, oil, water and nonionic surfactants are mixed together at room temperature. This mixture typically comprises o/w microemulsions co-existing with excess oil, and the surfactant monolayer exhibits positive curvature. When this macroemulsion is heated gradually, the polyethoxylated surfactant becomes lipophilic and at higher temperatures, the surfactant gets completely solubilized in the oily phase and the initial o/w emulsion undergoes phase inversion to w/o emulsion. The surfactant monolayer has negative curvature at this stage. This method involves heating of the components and it may be difficult to incorporate thermolabile drugs, such as tretinoin and peptides, without affecting their stability. Although it may be possible to reduce the PIT of the dispersion using a mixture of components (surfactants) with suitable characteristics, in order to minimize the degradation of thermolabile drugs.

5. Spontaneous Emulsification: [26]

Nanoemulsion can be prepared by using spontaneous emulsification method, these spontaneous emulsification methods involves three main steps: first one is Preparation of homogeneous organic solution which composed of oil and lipophilic surfactant in water miscible solvent and hydrophilic surfactant. Then the organic phase is to be injected into the aqueous phase under the magnetic stirrer which can give o/w emulsion. The water-miscible solvent is to be removed by evaporation process under the reduced pressure. Nanoemulsions which can be prepared from the spontaneous nanoemulsification process are not thermodynamically stable, but kinetically stable and long-term colloidal stability.

6. Solvent Evaporation Technique: [27]

Nanoemulsion can also be formulated by using the solvent evaporation method. This solvent evaporation technique involves preparing a solution of drug followed by its emulsification in another liquid that is non-solvent for the drug. Evaporation of the solvent leads to the precipitation of a drug. Crystal growth and particle aggregation can be controlled by creating high shear forces which can be done by using high-speed stirrer.

7. Hydrogel Method : [28]

Nanoemulsion can also be prepared by using hydrogel method. These hydro gel methods are similar to the solvent evaporation method. There is only one difference between the two methods (solvent evaporation method &hydrogel method) is that the drug solvent is to be miscible with the drug anti-solvent. Use of higher shear force can prevent the crystal growth and the Ostwald ripening

Fig 1: Structure of nanoemulsion:

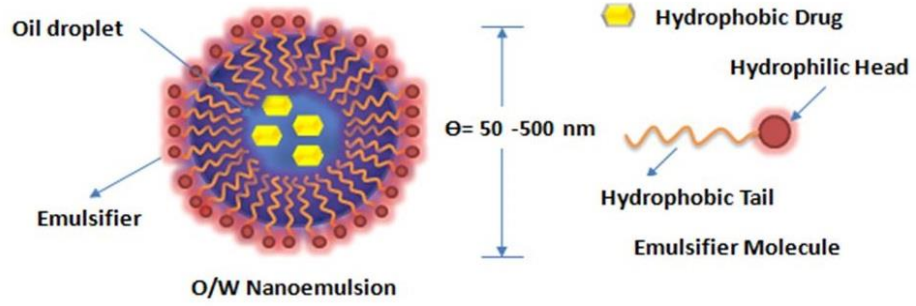

Fig 2: Emulsification process using a High pressure homogenizer

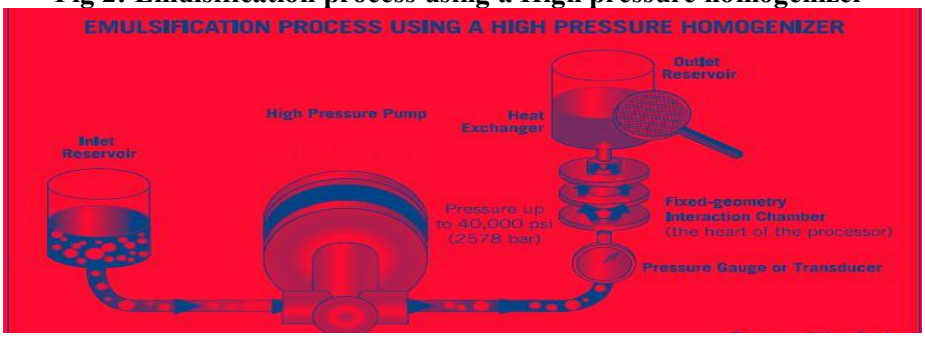

Fig 3: Ultrasonication

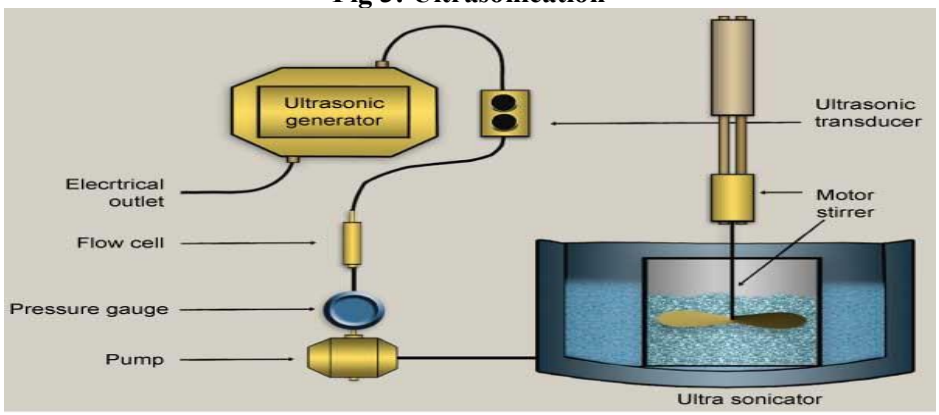

Fig 4: Viscosity measurement of nanoemulsion

CHARACTERIZATION OF NANOEMULSION: [29-31]

1. Viscosity measurement:

In the preparation of nanoemulsion whether the water content is increased it will lower the viscosity of the nanoemulsion. While surfactant or co-surfactant amount is decreased in the formulation it will increase the interfacial tension between the water and oil these results in increasing the viscosity of formulation. Viscosity can be measured by using brookfold viscometer, and other viscometers.

2. Droplet size Analysis:

Size of the droplet can be analyzed by using the instrument i.e. Helium-Neon laser and it is having a particular wavelength of 632.8 nm

3. Surface charge:

Surface charge can be determined by the using equipment i.e. **Zetasizer Nano Z.** Zeta potential is used to identify the surface charge of particles. Thus it gives information about the repulsive forces between the particles and the droplets. Zeta potential valve of a formulation should have **a value about 30mV** thus the formulation is considered as a stable formulation.

4. Refractive index:

The refractive index of a nanoemulsion can be determined by subjecting the Nanoemulsion formulation to Abbes type refractrometer (Nirmal International) at 25±0.5°C.

5. Transmission Electron Microscopy (TEM):

Nanoemulsion structure and morphology can be carried out by using a transmission electron microscopy (TEM). Combination of bright field imaging at increasing magnification and of diffraction modes can be used to identify the form and size of the nanoemulsion droplets.

II. THERMODYNAMIC STABILITY STUDIES:

Nanoemulsion has been subjected to thermodynamic studies. These thermodynamic studies are as follows:

a. Heating Cooling Cycle:

In this test the prepared Nanoemulsion are subjected to 6 cycles between lower temperature (refrigerator 4°C) and higher temperature 45°C. The prepared nanoemulsion which passes the heating cooling cycle then the prepared nanoemulsion is then subjected to centrifugation test.

b. Centrifugation:

In this test the prepared Nanoemulsion are centrifuged at 3500 rpm, and observe if any phase separation is takes place or not, if the prepared nanoemulsion shows separation of phases it will fail the test. If the nanoemulsion didn't show any separation of phases then it is forwarded to freeze thaw cycle test.

c. Freeze Thaw Cycle:

In this test the prepared nanoemulsion are subjected to 3 freeze thaw cycles between the temperature ranges from 21°C and +25°C kept under the standard laboratory conditions.

APPLICATIONS:

Nanoemulsions can be utilized for the production of pharmaceutical dosage forms. Infusion solutions; especially oral liquids, solutions, ocular drops and nasal drops which can be manufactured in the form of Nanoemulsion. Nanoemulsion is available in the market in the form of pastes, lotions

1) Parenteral Delivery:

Both O/W and W/O nanoemulsions can be used for parenteral delivery. Nanoemulsions have great advantages when compared to the macroemulsions. Nanoemulsion droplet size is less when compared to macroemulsions that's why nanoemulsion is most widely used as a parenteral dosage forms (or Injectable). Fats, Carbohydrates, Vitamins can be injected into the human body in the form of nanoemulsion. Nanoemulsions are clear in appearance and they have long residence time in human body

2) Oral Delivery:

Nanoemulsion formulations can offer many advantages when compared to conventional oral formulation for oral administration including increased the rate of drug absorption, improved clinical potency and decreased drug toxicity. Thus, Nanoemulsion proves to be an ideal dosage form in delivering of drugs such as steroids, hormones, diuretic and antibiotics

3) Topical Delivery:

Topical administration of drugs can have advantages over other methods for several reasons; one of the advantage is the avoidance of hepatic first pass metabolism of the drug and related toxicity effects.

Fig 5: Droplet size analysis of nanoemulsion

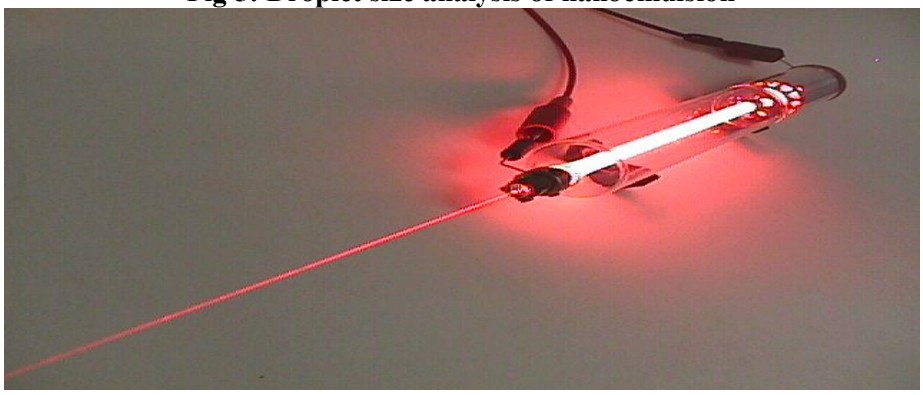

Fig 6: Surface charge determination

Fig 7: Refractive index determination

Another is the direct delivery and targetability of the drug to affected area of the skin or eyes. The nanoemulsion can achieve a high level of topical antimicrobial activity that has only been previously achieved by systemic antibiotics. The nanoemulsion has broad spectrum activity against bacteria (e.g. E.coli, 3) S. aureus) fungi (e.g. Candida, Dermatophytes) [32, 33]

4) Nasal route: [34-38]

The nasal route has received great attention due to number of advantages over parenteral and oral administration especially by bypassing the liver. Nanoemulsions increase absorption by solubilizing the drug in the inner phase of an emulsion and prolonging contact time between emulsion droplets and nasal mucosa. Examples: Lipid soluble renin inhibitor was incorporated into an O/W emulsion, insulin and testosterone can also be delivered by this route

5) Use of nanoemulsion in cosmetics:

Using of Nanoemulsions in cosmetics is increasing in now-a-days recently nanoemulsion acts as a potential vehicle for the controlled delivery of cosmetics and for optimized dispersion of active ingredients into the skin. Nanoemulsion gain increasing interest in cosmetics due to their own bioactive effects. Nanoemulsions are acceptable in cosmetics because there is no inherent creaming, sedimentation, flocculation or

coalescence of the formulation. These effects are observed with macro emulsions

6) Transdermal drug delivery:

Nanoemulsion can also be used in transdermal drug delivery system, due to its less particle size

7) In Biotechnology:

Many enzymatic and bio-catalytic reactions are conducted in pure organic or aqua-organic media. Biphasic media are also used for these types of reactions. The use of pure a polar media causes the denaturation of biocatalysts. The use of water-proof media is relatively advantageous.

8) Nanoemulsions in Cancer Therapy: [39, 40]

Nanoemulsions can be used as vehicle in cancer chemotherapy for prolonging the rate of drug release after intramuscular and intratumoral injection (W/O systems). It also enhances the transdermal drug delivery due to increase in the transport of anti-cancer drugs via lymphatic permeation through the skin and it is also non-irritant system

9) Nanoemulsions in pulmonary drug delivery:

The lungs are the most important organ for targeting drug delivery due to noninvasive administration via inhalation through aerosols, which can avoids the first-pass metabolism, due to these the drug can be directly delivery at the site of action for the treatment of respiratory diseases, and the availability of a huge surface area for local drug action and systemic absorption of drug. Colloidal carriers (i.e., nanocarrier systems) in pulmonary drug delivery offer more advantages such as the potential to achieve relatively uniform distribution of drug dose among the alveoli, achievement of improved solubility of the drug from its own aqueous solubility.

10) Nanoemulsion in gene delivery vector: [41]

Emulsion systems have been emerged as alternative gene transfer vectors to liposomes. Other emulsion studies for gene delivery (non-pulmonary route) have shown that the binding of emulsion/DNA complex is much stronger than the liposomal carriers. This stable emulsion System can deliver the genes more efficiently than the liposome's.

CONCLUSION:

Overall nanoemulsion formulation may be considered as safe, effective and patient compliance formulation for the delivery of pharmaceuticals. One of the unique characteristics of the Nano emulsion technology is to be relatively high percentage of the total particle volume occupied by the internal hydrophobic oil core of the droplets. This provides high solubilization of lipophilic compound as compared to liposomes. Although NEs are chiefly seen as vehicles for administering aqueous insoluble drugs, they have more recently received increasing attention as colloidal carriers for targeted delivery of various anticancer drugs, photo sensitizer's neutron capture therapy agents, or diagnostic agents. Because of their submicron size, they can be easily targeted to the tumor area. This review mainly focused on the structure, limitations, advantages, and disadvantages, method of preparation and evaluation of nano emulsion.

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