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Scanning and Choosing Nano emulsion Components: A Technical Memo

KAVITA SAHU*, ANKITA DAMAHE ,HARI PRASAD SONWANI
MEGHA SAHU , MANISH SAHU , PRAGATI KANNAUJIYA
APOLLO COLLEGE OF PHARMACY,ANJORA DURG 491001(C.G),INDIA

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ABSTRACT
Nanoemulsion are defined as isotropic, thermodynamically stable transparent or translucent systems of oil and water which stabilize by surfactant with a droplet size usually in the range of 5 to 200 nm. Nanoemulsions can be developed by spontaneous emulsification method to enhance the solubility and bioavailability of poorly water soluble drugs. Nanoemulsion is a translucent system compared to ordinary emulsion or sometimes microemulsion. The isotropic nanoemulsionsystem is a very fragile one. Slightest change in conditions can cause destabilization, thereasons are nature of oil phase and addition of polymers to thicken the nanoemulsion gel. The use of nanoemulsions to enhance the solubility of drugs for topical applicationhas been demonstrated and confirmed through several studies. . Formation of nanoemulsion system required a high amount of energy.This energy can be provided either by mechanical equipment or the chemical potential inherent within the component. Nanoemulsion are advantages for intravenous administration, due to the strict requirement of this route of administration, particularly the necessity for the formulation droplet size lower than 1 micrometer. Parenteral (or Injectable) administration of nanoemulsion is employed for a variety of purposes, namely nutrition eg. Fats, Carbohydrates, Vitamins etc.

Keyword: Nanoemulsion ,emulsion ,Surfactant ,Drug delivery ,Droplet size, Microemulsion

I. Introduction

Nanoemulsion are defined as isotropic, thermodynamically stable transparent or translucent systems of oil and water which stabilize by surfactant with a droplet size usually in the range of 5 to 200 nm**.**Nanoemulsions can be developed by spontaneous emulsification method to enhance the solubility and bioavailability of poorly water soluble drugs. These are non-toxic non-irritant hence can be easily applied to skin and mucous membranes.[9]Nanoemulsion is a translucent system compared to ordinary emulsion or sometimes microemulsion. The isotropic nanoemulsionsystem is a very fragile one. Slightest change in conditions can cause destabilization, thereasons are nature of oil phase and addition of polymers to thicken the nanoemulsiongel[10].

Classification of Nanoemulsions
On the basis of composition of oil and water portions nanoemulsion are classified into three types:
a) Oil in water (O/W) nanoemulsions in this type the oil droplets are dispersed in continuous aqueous phase
b) Water in oil (W/O) nanoemulsions here the water droplets are dispersed in continuous phase which are oil.
c) Bi-continuous nanoemulsions in this type the microdomains of oil and water are inter-dispersed within the system.[5]

Stabilization of interface is done by an appropriate combination of surfactants and/or co-surfactants (Figure 1). The O/W nanoemulsions further classified into three types based on the type of surfactants used which are as follows-

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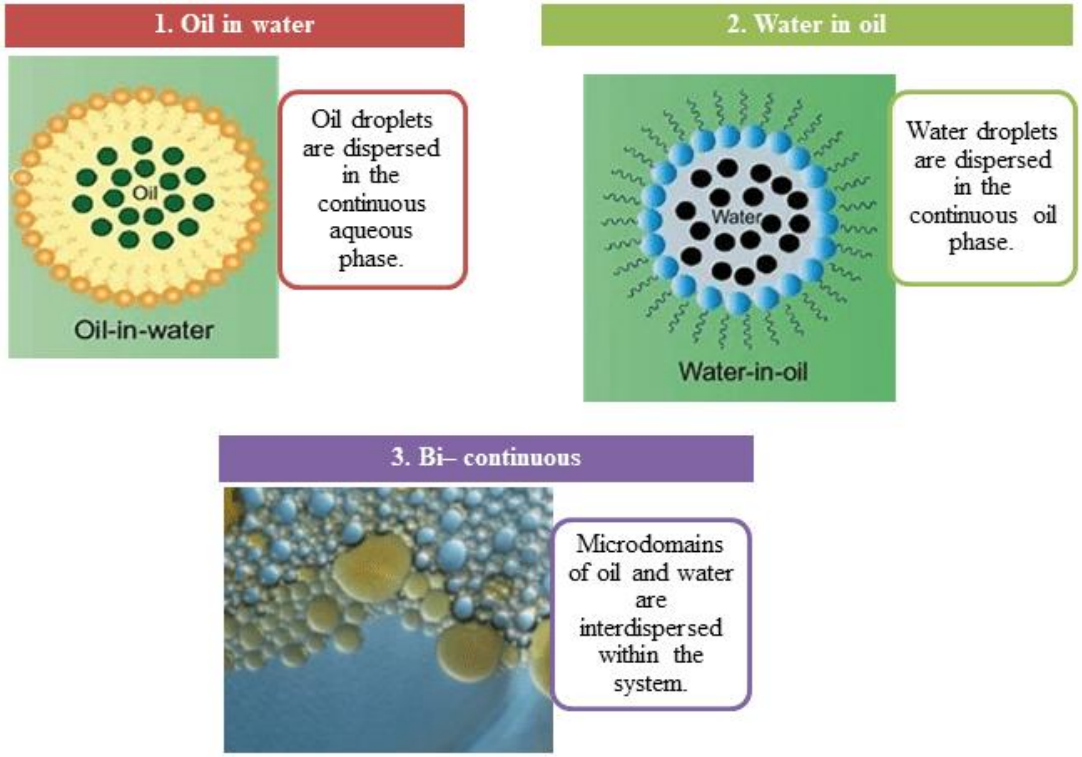

• Neutral O/W nanoemulsions, in this type the neutral surfactant are used
• Cationic O/W nanoemulsion, Here cationic surfactants are used
• Anionic O/W nanoemulsions, the anionic surfactants are used

Inayat Pathan etal developed a nanoemulsion for the transdermal drug delivery of meloxicam. The area of nanoemulsion was identified by constructing pseudo ternary phase diagram. Nanoemulsion evaluated by Transmission electron microscopy, In-vitro permeation study, Droplet size distribution, Stability studies, Refractive index The results concluded, that prepared nanoemulsions are promising vehicles for transdermal delivery of meloxicam to treat pain or inflammation in treatment of rheumatoid arthritis. Nanoemulsions droplet size was found to be in ranged from 60.6 nm -195.5 nm [5]

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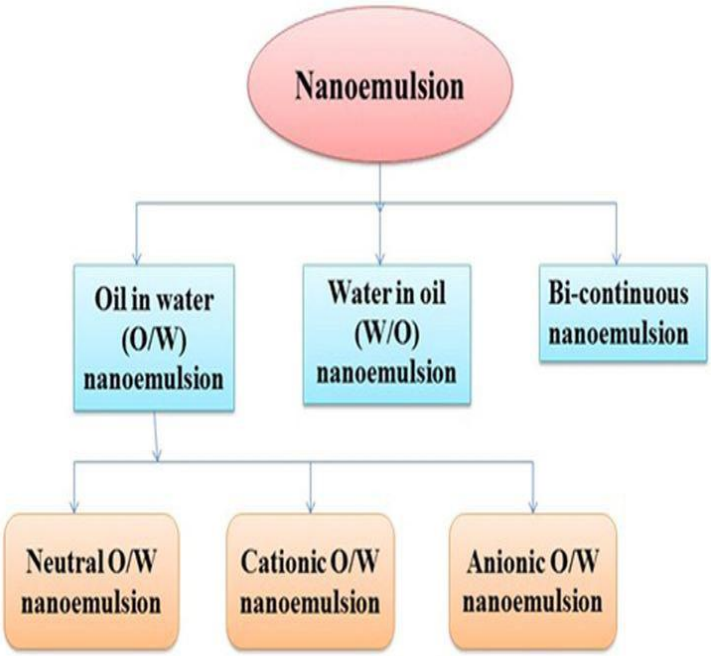

The use of nanoemulsions to enhance the solubility of drugs for topical applicationhas been demonstrated and confirmed through several studies. An example is prednicarbate,a next-generation corticosteroid with a good benefit/risk ratio, but with a reducedwater solubility. Nanoemulsions containing prednicarbate promote an improvement inpenetration and in the drug delivery capacity of this corticosteroid, being advantageousfor the treatment of atopic dermatitis[18]

Advantage of nanoemulsion
1. Increase the rate of absorption.
2. Eliminates variability in absorption.
3. Helps in solublizing lipophilic drug.
4. Provides aqueous dosage form for water insoluble drugs.
5. Increases bioavailability.
6. Various routes like tropical, oral and intravenous can be used to deliver the product.
7. Rapid and efficient penetration of the drug moiety.
8. Helpful in taste masking

9. Provides protection from hydrolysis and oxidation as drug in oil phase in O/W Nanoemulsion is not exposed to attack by water and air.
10. Liquid dosage form increases patient compliance.
11. Less amount of energy requirement.
12. Nanoemulsions are thermodynamically stable system and the stability allows self emulsification of the system whose properties are not dependent on the process followed.
13. Same Nanoemulsions can carry both lipophilic and hydrophilic drugs.
14. The use of Nanoemulsion as delivery systems can improve the efficacy of a drug, allowing the total dose to be reduced and thus minimizing side effects. [4]

Disadvantages of Nanoemulsions
1. It requires large concentration of surfactant and cosurfactant for stabilizing the nanodroplets
2. It generally shows a limited solubilizing capacity for high-melting substances
3.There is lacuna for understanding the interfacial chemistry which is involved in production of nanoemulsions

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4.For use in pharmaceutical applications the nature of surfactant must be nontoxic
5.To requires the use of high concentrations of emulsifiers [5]

Limitation of nanoemulsion

Although this formulation provide great advantages as adelivery system for the consumers but sometimes the reducedsize of droplets are responsible for the limited use ofnanoemulsion formulation. Some limitations of nanoemulsionare as follows -

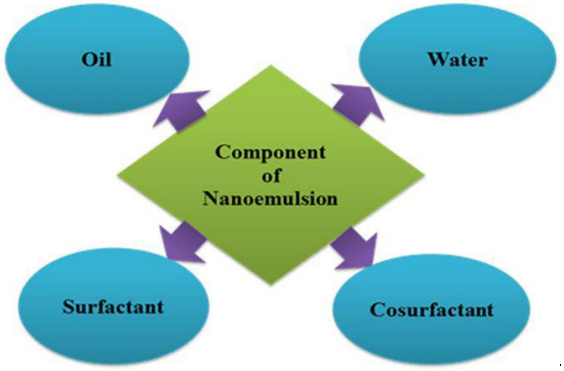
* The manufacturing of nanoemulsion formulation is anexpensive process because size reduction of droplets isvery difficult as it required a special kind of instrumentsand process methods. For example, homogenizer(instrument required for the nanoemulsion formulation)arrangement is an expensive process. Again microfludizationand ultrasonication (manufacturing process)require high amount of financial support

*Stability of nanoemulsion is quite unacceptable andcreates a big problem during the storage of formulationfor the longer time period. Ostwald ripening is the mainfactor associated with unacceptability of nanoemulsionformulations. This is due to the high rate of curvatureof small droplet show greater solubility as compared tolarge drop with a low radius of curvature.

* Less availability of surfactant and cosurfactant requiredfor the manufacturing of nanoemulsion is another factorwhich marks as a limitation to nanoemulsion manufacturing[3]

[4]The major components of micro emulsion system are:

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



1] Oil phase : After water the Oil phase is second most important vehicle because of its properties to solubilize lipophilic drug molecules and improve absorption through lipid layer which are present in body. Oil is very useful for lipophilic active drug delivery because of its unique property of penetrating cell wall (Figure 3). Oil phase influence the swelling of tail group region of the surfactant. As compared to long chainalkane such penetration is to greater extent in case of short chain alkanes

TABLE 1: LIST OF OILS USED IN NANOEMULSIONS

Name	Chemical Name	Manufacture
Captex 355	Glyceryl Tricaorylate/Caprate	Abitec
Captex 200	Propylene Dicaprylate/Dicaprate Glycol	Abitec
Captex 8000	Glyceryl Tricaprylate (Tricaprylin)	Abitec
Witepsol	90:10 % w/w c12 Glyceride tri: diesters	Sasol pharmaceutical excipient
Myritol 318	c8/c10 triglycerides	Russia
Isopropyl myristate	Myristic acid isopropyl ester	Fluka

2]Surfactant: To facilate the dispersion of all components surfactant must be able to reduce the interfacial tension nearest to zero. In preparation of W/O nanoemulsion Surfactants with HLB values3-6 are useful where for the preparation of O/W nanoemulsion surfactants with higher HLB values8-18 are useful. Surfactants which having the HLB value more than 20 are acts as cosurfactant for reduction of concentrations of the surfactants to an acceptable limit and micro emulsion formation.

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TABLE 2: LIST OF SURFACTANT USED IN NANOEMULSIONS

SR.No.	**Solubilizing agents, surfactants, emulsify**ing agents adsorption enhancers
1	Caproyl 90
2	Gelucire 44/14, 50/13
3	Cremophor RH 40
4	Imwitor 191, 308(1), 380, 742, 780 K, 928, 988
5	Labrafil M 1944 CS, M 2125 CS
6	Lauroglycol 90
7	PEG MW > 4000
8	PlurolOleique CC 497
9	Poloxamer 124 and 188
10	Tween 80

3] Cosurfactant: To reduce the interfacial tension between oil and water to a level to enable a spontaneous formation of a nanoemulsion high concentrations of single-chain surfactants are required. Due to presence of fluidizing groups like unsaturated bonds cosurfactant raises the fluidity of the interface, then demolishes liquid crystalline or gel structure and alters the HLB value in such way to cause spontaneous formation of nanoemulsion .

TABLE 3.LIST OF CO-SURFACTANT USED IN NANOEMULSION

Sr. No.	**Co Surfactant**
1	TranscutolP
2	Glycerin, Ethylene glycol
3	Propylene glycol
4	Ethanol
5	Propanol

Method of Preparation of Nanoemulsion

Several methods have been suggested for the preparation of nanoemulsion. The basic objectives of the nanoemulsion preparation to achieve the droplet size range of 100-600 nm and another is to provide the stability condition. Formation of nanoemulsion system required a high amount of energy.This energy can be provided either by mechanical equipment or the chemical potential inherent within the component . Here some methods are discussed which are freely used for the nanoemulsionpreparation[3].

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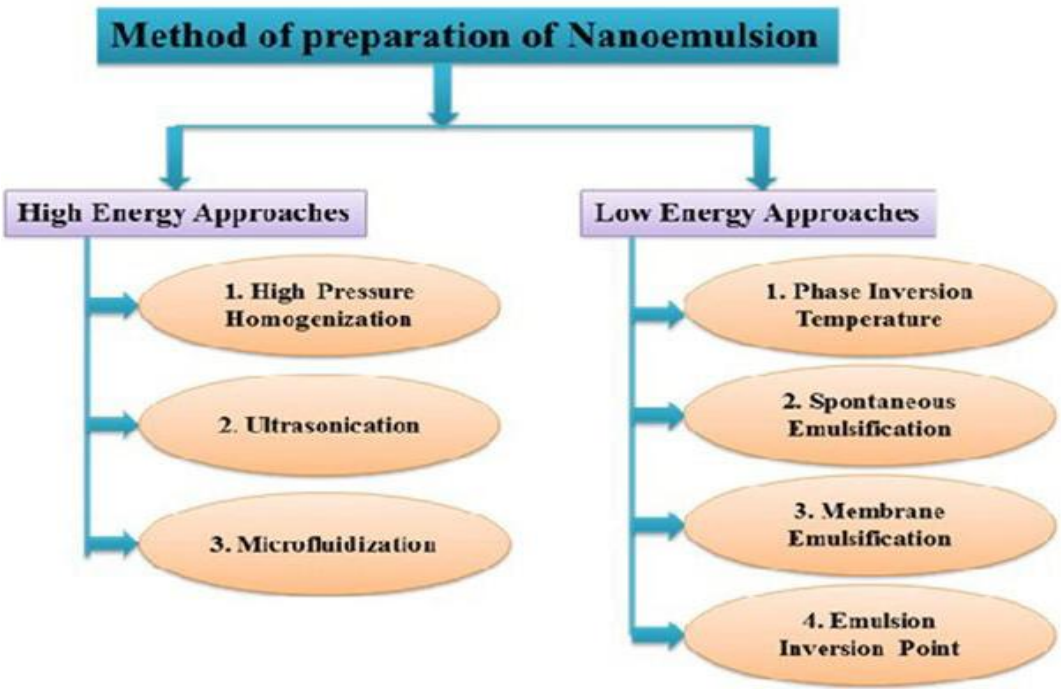

High Energy Approach

Based on selected composition, i.e. surfactant compound, functional compound, and on the quantity of energy supplied the nanoemulsions are formed by high-energy methods

1. High Pressure Homogenization: High pressure homogenizer is required for the preparation of nanoemulsion. This method produces a nanoemulsions of low particle size which is of 10-100nm. The oil and water mixture is force through a small inlet orifice at very high pressure such as 500 to 5000psi to achieve a dispersion of it, which subjects the product to hydraulic shear and intense turbulence which resulting in extremely fine particles of emulsions. The particles which are formed by then exhibit a liquid, lipophilic core which is separated from the surrounding aqueous phase by a monomolecular layer of phospholipids. The following process variables should be investigated for obtaining the optimized formulation:

• **Effect of Homogenization Pressure:** If pressure is high then low particle size is obtained. It must be from 1450.4 to 2175.6 psi

• **No. of Homogenization Cycles:** If homogenization cycles are smaller the smaller is the particle size obtained. Around 3, 4 or 10 cycles are carried out[5]

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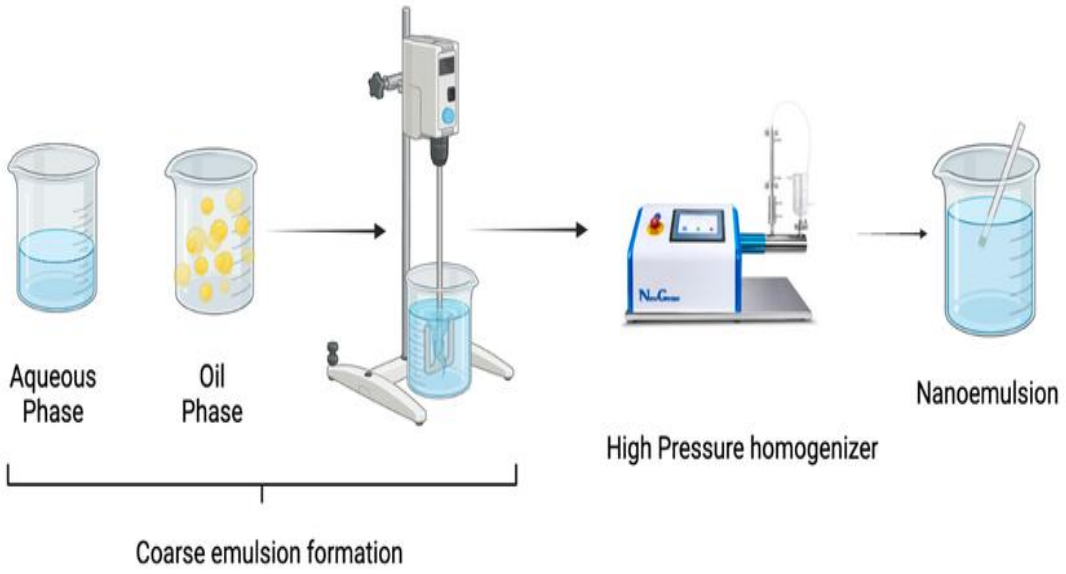
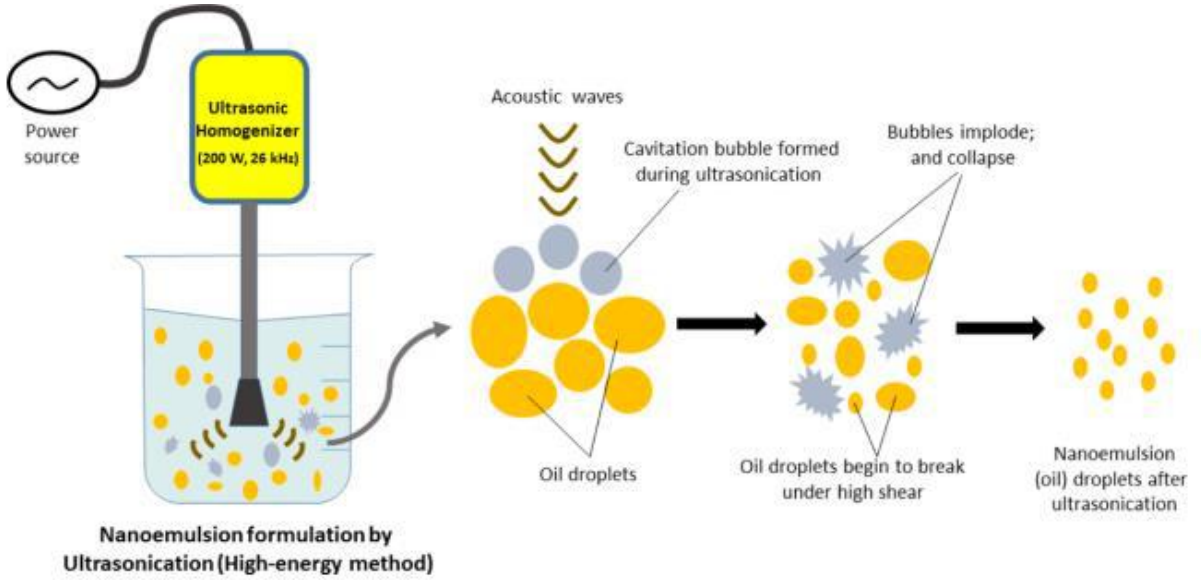


3.. Sonication method

Sonication method is another best way to prepare nanoemulsion. In this method the droplet size of conventionalemulsion or even microemulsion are reduced with the help of sonication mechanism. This method is not suitable for large batches only small batches of nanoemulsion can be prepared by this method[3].



2. **Microfluidization:** Microfluidization is a mixing technique, which makes use of a device called microfluidizer. This device uses a high-pressure positive displacement pump (500 to 20000psi), which forces the product through the interaction chamber, which consists of small channels called 'microchannels'. The product flows through the microchannels on to an impingement area resulting in very fine particles of sub- micron range. The two solutions (aqueous phase and oily phase) are combined together and processed in an inline homogenizer to yield a coarse emulsion. The coarse emulsion is into a microfluidizer where it is further processed to obtain a stable nanoemulsion. The coarse emulsion is passed through the interaction chamber microfluidizer repeatedly until desired particle size is obtained. The bulk emulsion is then filtered through a filter under nitrogen to remove large droplets resulting in a uniform nanoemulsion [6]

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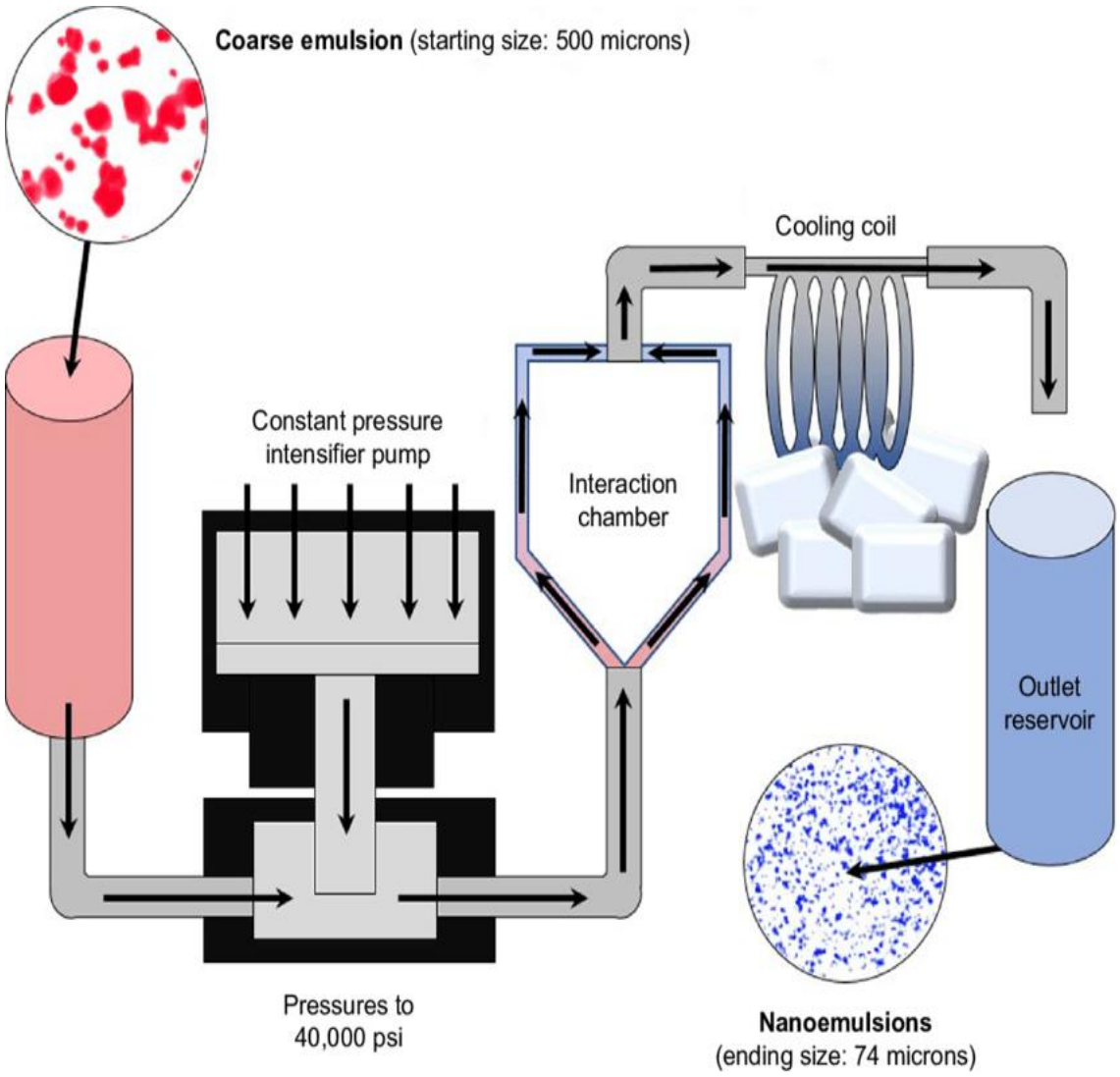

Low Energy Approach

Nanoemulsions are obtained as a result of phase transition in case of low energy approaches which produced during the emulsification process. This carried out, usually, changing the composition or at constant composition and at constant temperature or changing the temperature.

1.Phase Inversion Temperature: In case of this method, due to the chemical energy resulting of phase transitions produced by emulsification pathway, the fine dispersion is obtained. By varying the composition of the emulsion and keeping temperature constant or vice versa the phase transition is produced [28] in an emulsion phase inversion can be of two types which are as follows:

- **Transitional Inversion:** This is induced by changing factors which affect the HLB of the system. For e.g. temperature and/or electrolyte concentration.
- **Catastrophic Inversion:** which induced by changing the HLB number of the surfactant at constant temperature using surfactant Mixtures[5].

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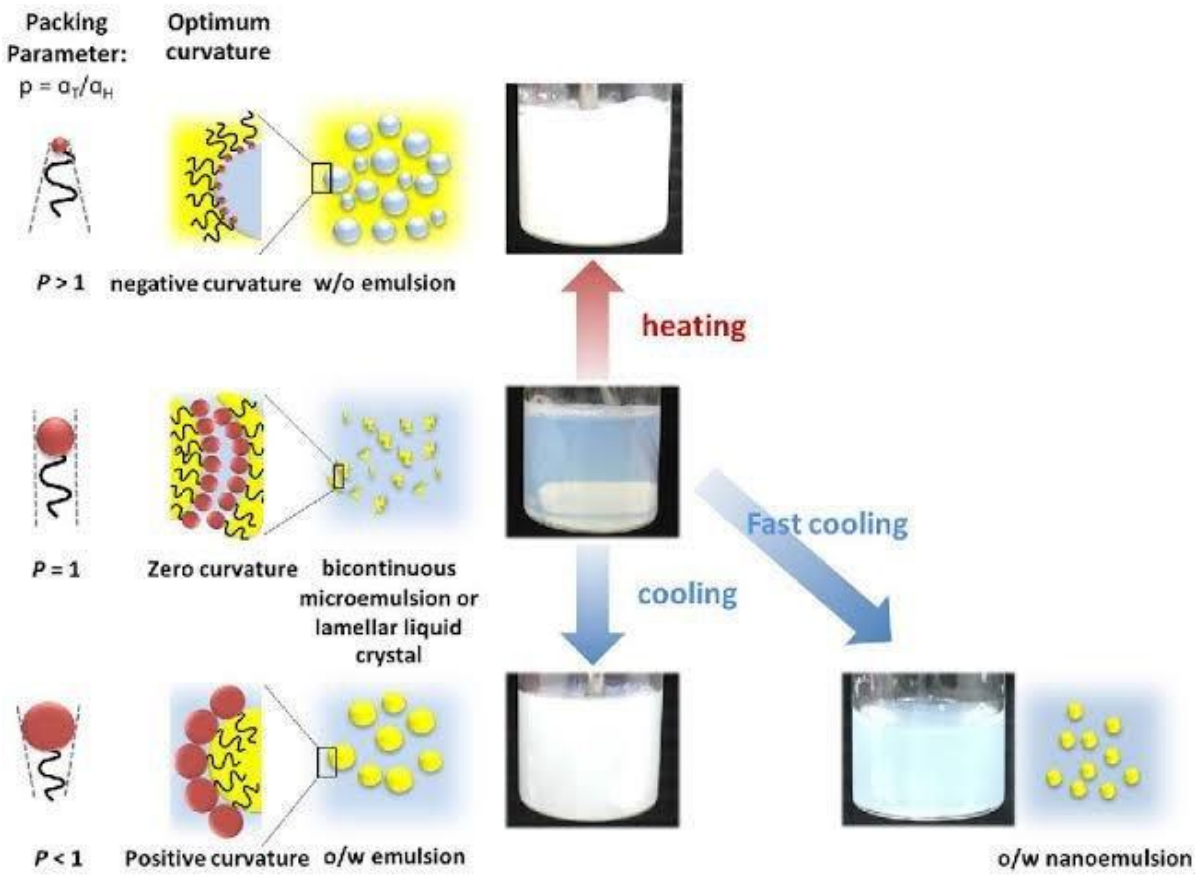
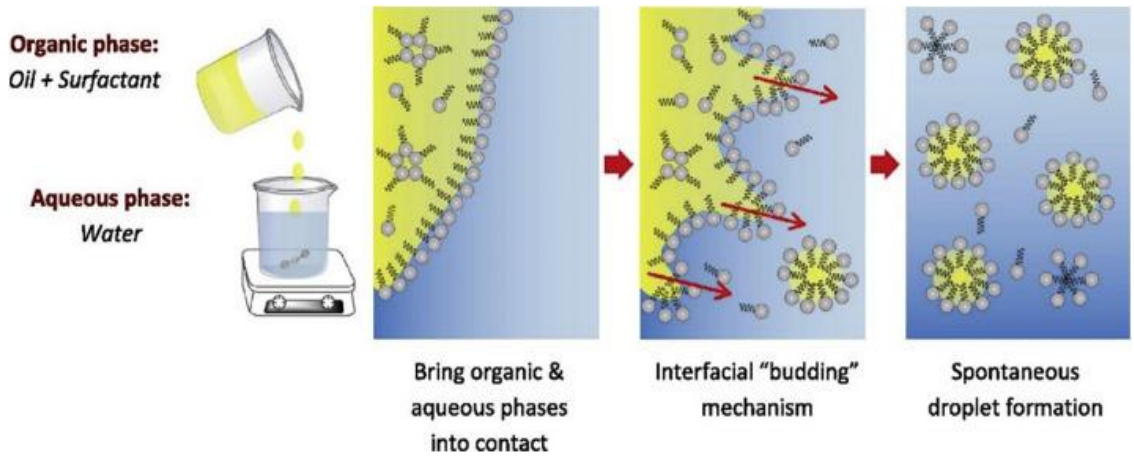


2.Spontaneous emulsification: This technique involved preparation of nanoemulsion in 3 stages. The first stage included formation of an organic solution, comprising of oil and lipophilic surfactant in water miscible solvent and hydrophilic surfactant and then the O/W emulsion is formed by injecting this organic phase into the aqueous sphase under magnetic stirring. The organic solvent was then removed in the third stage by evaporation. Sugumar *et al*. formulated stable eucalyptus oil nanoemulsion by adopting spontaneous emulsification and the mean droplet size was found to be in the range of 50-100 nm[19]



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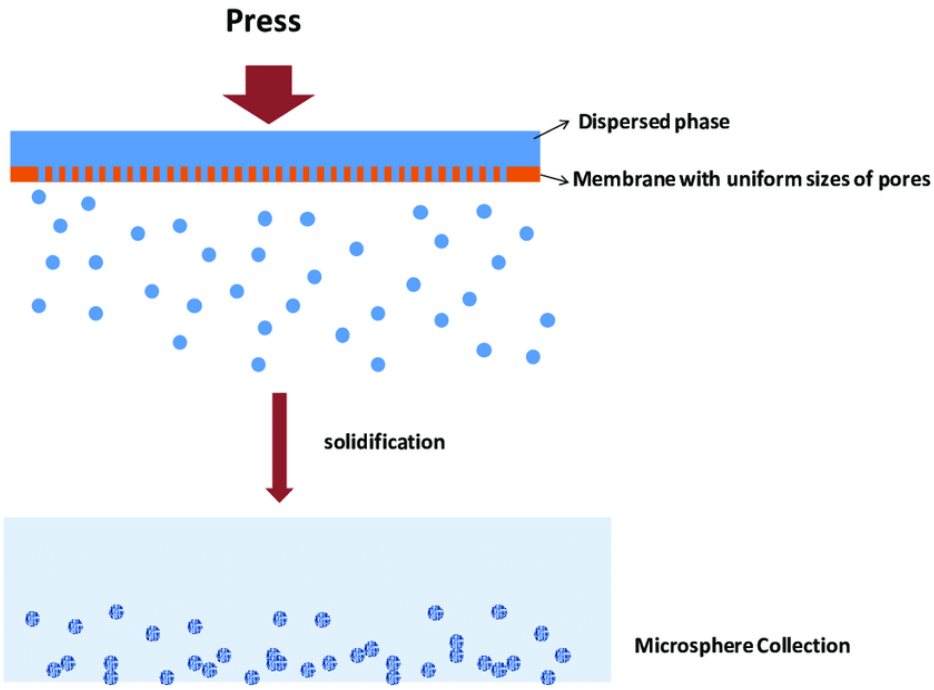
3.Membrane Emulsification: Membrane emulsification is a low energy nanoemulsion method. Requirement of surfactant is very less for this method and this produce emulsion with a narrow size distribution range. Formation of a dispersed phase through a membrane into a continuous phase is involves in this method. Disadvantage of this method is it has low flux of the dispersed phase through the membrane, during scale-up this being an issue.



4.Emulsion Inversion Point: Vartation of composition of the system at a constant temperature is carried out in this method.
Structures are formed due to a progressive dilution with oil or water in order to create the kinetically stable nanoemulsions[5]

Factors affecting the Formulation of Nanoemulsion:

- Appropriate composition is required to avoid Oswald ripening the dispersed phase should be highly insoluble in the dispersed medium.
- The surfactant is an essential part of the Nanoemulsion. They should not form lyotropic liquid crystalline “microemulsion” phases. Systems containing short chain alkanes, alcohols, water, and surfactants form the phases which are generally used with the co surfactant.
- The presence of excess surfactants enables new surface area of nanoscale to be rapidly coated during emulsification there by inhibiting induced coalescence.
- Extreme share must be applied to rupture microscale droplets to nanoscale by providing the stress level to reach above the Laplace pressure of the droplets with a pressure of 10- 100 atm. Out of various methods ultrasonication is widely used in laboratory [4]

Characterization of nanoparticles

Nano-emulsions are not thermodynamically stable, and,because of that, their characteristics will depend on preparation method. Here some parameters are discussed which should be analyzed at the time of preparation of nanoemulsion.

(i) Phase behaviour study: This study is a characterization and optimization of ingredients (surfactant, oil phase and aqueous phase). Generally the study is necessary in case of nanoemulsion formulation prepared by phase inversion temperature method and self emulsification method in order to determine the phase of nanoemulsion and dispersibility.
Study is done by placing the different ingredients of nanoemulsion by varying the concentration in glass ampules and thoroughly homogenized at a certain temperature for a time until equilibrium. Anisotropic phase can be identified by polarized light.

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(ii) Particle Size Analysis: Formulated nanoemulsion should be analyzed for their hydrodynamic particle size and particle size distribution. Generally in case of nanoemulsion dynamic light scattering (DLS) method are used for the measurement of particles and further particle size distribution[3].

(iii) Surface charge measurement: Surface zeta potential of nanoemulsion droplets should be measured with the help of mini electrode to predict the surface properties of nanoemulsion.

(**iv) Transmission Electron Microscopy (TEM):** This method is used to observe the morphology in the nanoemulsion.

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(v) Drug contain: This method is used to determine the amount of drug contained in the formulation. Various methods (especially Western Blot method) are used in this order.

(vi) Viscosity: Viscosity should be measured to ensure the better delivery of the formulation.[3].

Applications of Nanoemulsions:

Nanoemulsions have proved to be a better alternative due to there various properties which resulted in their increases usage in different applications.[10]

1.Parenteral Delivery: Nanoemulsion are advantages for intravenous administration, due to the strict requirement of this route of administration, particularly the necessity for the formulation droplet size lower than 1 micrometer. Parenteral (or Injectable) administration of nanoemulsion is employed for a variety of purposes, namely nutrition eg. Fats, Carbohydrates, Vitamins etc. [4]

2.Magnetic nanoemulsions and Cancer treatment

Hyperthermia is proven to reduce the effects of cancer by killing the cancerous cells, with minimum injury to normal cells. Hence researchers are trying to induce local hyperthermia at the site of cancer by the use of these magnetic nanoemulsions of oil in water with biodegradable properties . Emulsions for this purpose are synthesized by direct emulsification from biodegradable surfactants. The magnetic properties were due to phosphate coated magnetite that is stabilized as aqueous colloid at optimum pH . When the body administered with this nanoemulsion system is exposed to alternative current of suitable frequency, hyperthermia is observed in places where the emulsion system is present.[10]

3.Nanoemulsion vaccine

Nanoemulsions adjuvant vaccine is known to be composed of surfactant (Cremophor),cosurfactant(propylene glycol), and MRSA (Methicillin-Resistant *Staphylococcus aureus*) recombination protein antigen. This nanoemulsion vaccine showed good protein stability, protein structure integrity and protein specificity. It also improved the immune responses of immunoglobulin such as IgA, IgG1, IgG2a, and IgG2b, in the C57 mice nasal immunization and in the serum after Balb/c mice intramuscular immunization. It also improved cytokine cell immune response such as interleukin-17A and interferon-γ, increased the survival ratio and decreased bacterial growth.[10]

II. CONCLUSION

NE formulations offer several advantages for the delivery of drugs, biologicals, or diagnostic agents. Traditionally, NEs have been used in clinics for more than four decades as total parenteral nutrition fluidsNanoemulsions are thermodynamically stable, clear, isotropic liquid mixtures of oil, water, surfactant and co-surfactant. Nanoemulsions are the most useful dosage form which protect labile drug, control drug release, increase drug solubility of poorly water soluble drug, increase bioavailability and reduce patient variability. Now a day nanoemulsion is able to formulate for variety of route of administration. Nanoemulsion formulation may be considered as effective, safe and patient compliance formulation for the delivery of pharmaceuticals. By controlling factors such as type and concentration of surfactant and cosurfactant, type of oil phase, methods used, process variables and addition of additives Stability of formulation may be enhanced.

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