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Nanoemulsion In Pharmaceuticals

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ABSTRACT

Nanoemulsions appeared as a novel drug delivery system which allows controlled or sustained release of drug and biological active ingredients. Nanoemulsion is a dispersion consisting of oil, surfactant and an aqueous phase, which is an isotropically clear and thermo-dynamically or kinetically stable liquid solution, usually with droplet diameter within the range of 1-100 nm. This review gives the idea about the nanoemulsions system and provides brief information about the method of preparation and evaluation of nanoemulsion as well as various pharmaceutical applications of nanoemulsions in drug delivery including parenteral and pulmonary drug delivery, cosmetics, cancer therapy, vaccine delivery, formulations for improved oral delivery of poorly soluble drug and in cell culture technology.

Keywords*:* Nanoemulsion, Method of preparation, Pharmaceutical applications

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INTRODUCTION

Nanotechnology is an important field of modern research dealing with design, synthesis and manipulation of particles ranging from 1-100 nm. Nanotechnology is emerging and is rapidly growing due to its applications in science and technology.[1]Nanoemulsions are the colloidal dispersions composed of an oil phase, aqueous phase, surfactant and co surfactant at appropriate ratios.[2] (figure: 1). They are kinetically stable liquid-in-liquid dispersions with droplet sizes on the order of 100 nm.[3] The Nanoemulsions are also referred as submicron emulsion(SME), ultrafine emulsions, mini emulsion .It is a appeared as a novel drug delivery system which allows sustained or controlled release of drug, biological active ingredient.[4] These particles are solid spheres and their surface is amorphous and lipophilic with a negative charge and can be used to enhance the site specificity. They enhance the therapeutic efficacy of the drug and minimize adverse effect and toxic reactions of the drug.[5]

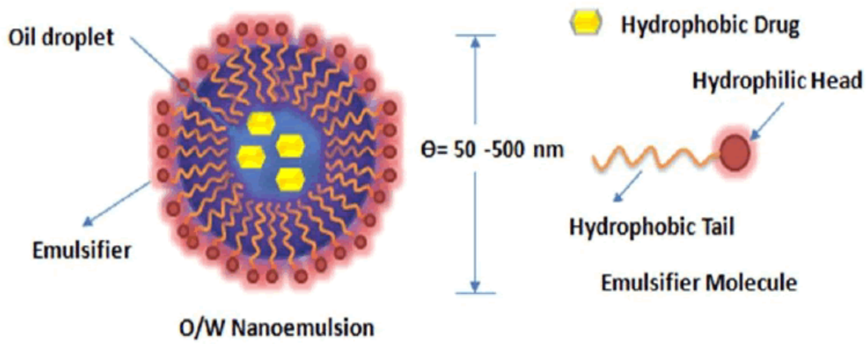

Figure 1: Nanoemulsion Droplet

The major advantages of nanoemulsions as drug delivery systems include increased drug loading, enhanced drug solubility and bioavilability, reduced patient variability, controlled drug release, and protection from enzymatic degradation. The nanoemulsions of natural products are used for several purposes. Three types of Nanoemulsions are most likely to be formed depending on the composition.[6]

- Oil in water Nanoemulsions where oil droplets are dispersed in the continuous aqueous phase.
- Water in oil Nanoemulsions where water droplets are dispersed in the continuous oil phase.
- Bi- continuous Nanoemulsions where in microdomains of oil and water are interdispersed within the system.

In all three types of Nanoemulsions, the interface is stabilized by an appropriate combination of surfactants and co-surfactant.[7]

Advantages of Nanoemulsion [8]

- Increases the rate of absorption
- Helps to solubilize lipophilic drug
- Provides aqueous dosage form for water insoluble drugs
- Increases bioavailability of active drug
- Helpful in taste masking
- Liquid dosage form increases patient compliance
- Less amount of energy requirement
- Improved physical stability
- Non- toxic and non- irritant in nature

Disadvantages Of Nanoemulsion [9]

- Use of a large concentration of surfactant and co- surfactant for stabilizing the nanoparticles
- Limited solubilizing capacity for high- melting substances
- Stability of nanoemulsions is affected by temperature and pH variation
- The surfactant must be nontoxic for using pharmaceutical applications

Components of Nanoemulsion[10]

Main three components of Nanoemulsions (figure : 2)are as follows:

- Oil
- Surfactant/Co-surfactant
- Aqueous phase
- Additives

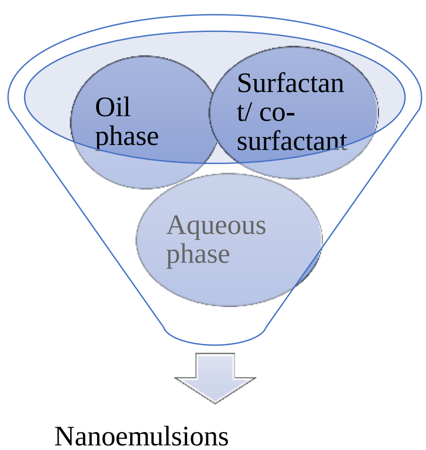

Figure 2: Components of nanoemulsions

Oils

Oils may be used to solubilize the lipophilic drugs and increases the drug transport. Choice of oil component can modulate the topical drug delivery from O/W and W/O Nanoemulsions [11].

Surfactant (Surface active agents)

Surfactant molecules consist of two parts, polar and nonpolar region. They are classified according to the nature of polar group within the molecule into: anionic, cationic, non- ionic & zwitter ionic surfactant. Surfactant contribute significantly in the formulation of nanoemulsions by lowering the interfacial tension between two immiscible liquids and make them miscible [12].

Cosurfactant

A single surfactant alone may not be able to reduce the oil/water interfacial tension for preparing nanoemulsions, hence arises the need of cosurfactants. They reduce the interfacial tension by increasing the fluidity of the interface [13].

Aqueous phase

The stability of nanoemulsion and size of the droplets may be affected by the aqueous phase. The pH and presence of electrolytes in aqueous phase should be given the careful consideration.

Additives

Additives used to make the nanoemulsions last for longer periods.

Factors to be considered in the formation of nanoemulsion

- The dispersed phase molecules must be insoluble in the continuous phase
- A flexible interface must be formed
- The surfactant should be soluble in continuous phase
- Components should be added in a controlled manner

Table 1: Formulation ingredients of nanoemulsion

Components	**Examples**
Oil	Castor oil, Corn oil, coconut oil, Linseed oil, Olive oil
Surfactants	Polysorbate 20,Polysorbate 80, PEG, Sorbitan monooleate
Co-surfactants	Ethanol, Glycerine, Polyene glycol
Emulgent	Natural lecithin from plant and animal source, Phospholipids
Tonicity Modifier	Glycerol, Sorbitol, Xylitol
Additives	Lower alcohol(Ethanol), Propylene glycol, Sugars such as glucose, sucrose, fructose
Antioxidants	Ascorbic acid, Tocopherol

Methods of Preparation Of Nanoemulsions

Various methods are used for the preparation of nanoemulsions including the high-energy and low-energy emulsification methods and the combined methods are also used (figure:2). Among the high-energy methods, the commonly used are high pressure homogenization, high-energy stirring and ultrasonic emulsification. Among the low- energy emulsification methods, the attention is focused on the phase inversion temperature method, the emulsion inversion point method and the spontaneous emulsification method. Using a combined method, which includes the high-energy and low energy emulsification, it is possible to prepare the reverse nanoemulsions in highly viscous systems.[14]

High pressure homogenization method

This method is performed by applying a high pressure over the system having oil phase, aqueous phase and surfactant or co-surfactant. The pressure is applied with the help of homogenizer and the two liquids along with surfactant, co-surfactants are made to pass through a small orifice at high pressure (500- 5000 psi) to produce nanoemulsions (figure: 3). Some problems associated with homogenizer are poor productivity, component deterioration due to generation of much heat.[15]

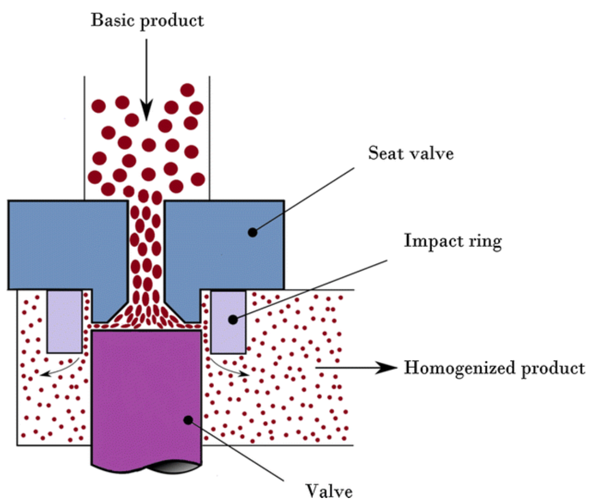

Figure 3: High pressure homogenizer

Phase inversion method

Fine dispersion is obtained by chemical energy resulting of phase transitions occur through emulsification method. Phase transition is brought about either by alteration in temperature at constant composition or keeping the temperature constant and altering the composition(figure: 4). A quick change in temperature (increase or decreasing HLB temperature by 25-30^{0}C) prevents coalescence and produce stable nanoemulsions [16].

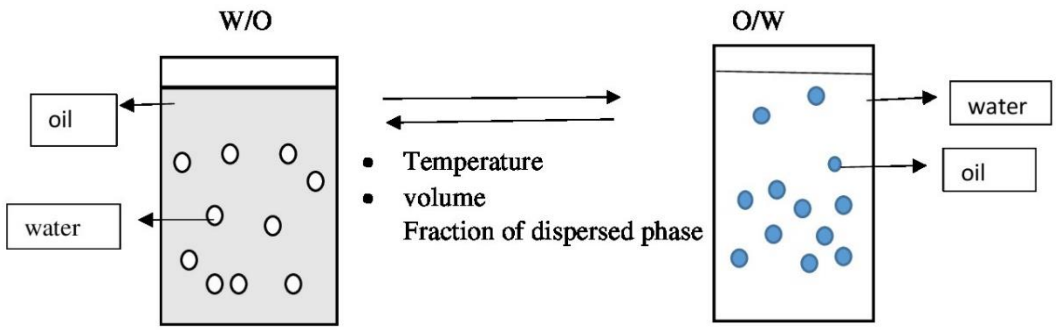

Figure 4: Phase inversion method

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Sonication Method

In this method the droplet size of conventional emulsion are reduced with the use of sonication method (figure: 5). Only small batches of nanoemulsions can be prepared by this mechanism.[17]

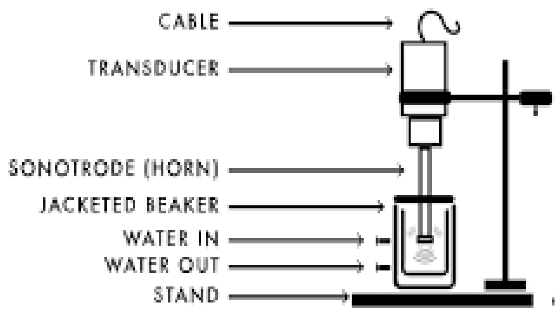

Figure 5: Sonication method

Microfluidization method

Microfluidizer is used in Microfluidization technology. This device uses a high pressure positive displacement pump (500- 20000 psi) to produce fine nanoemulsions. Coarse emulsion is made to pass repeatedly through the interaction chamber microfluidiser (figure: 6) till desired size of droplets is obtained.[18]

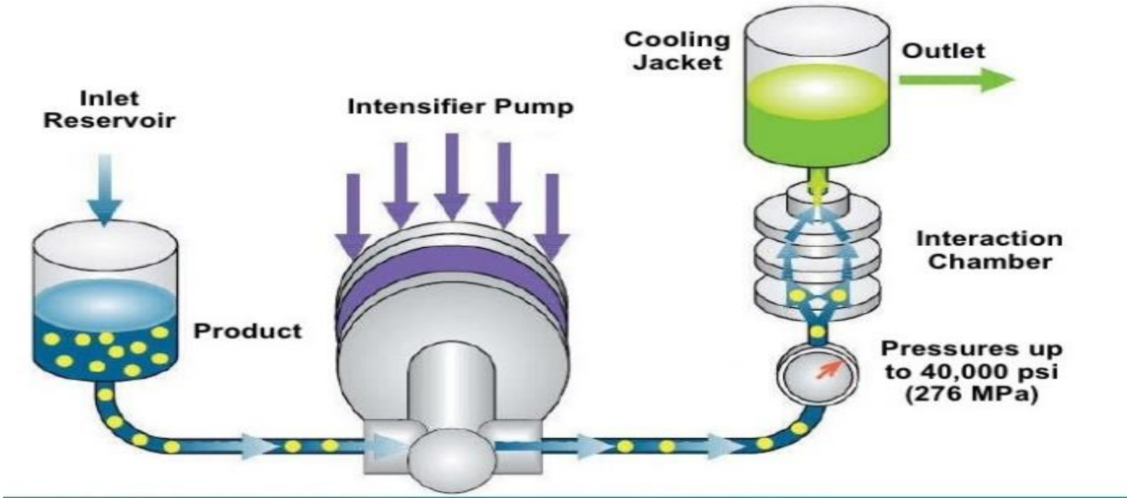

Figure 6: Microfluidise

Solvent displacement method

In this method nanoemulsions can be prepared at room temperature by pouring the organic phase containing oil dissolved in a solvent like acetone or ethanol into aqueous phase having surfactants (figure: 7). A high ratio of solvent to oil is needed to prepare small sized droplets. This method requires additional effort for removal of the solvent.[19]

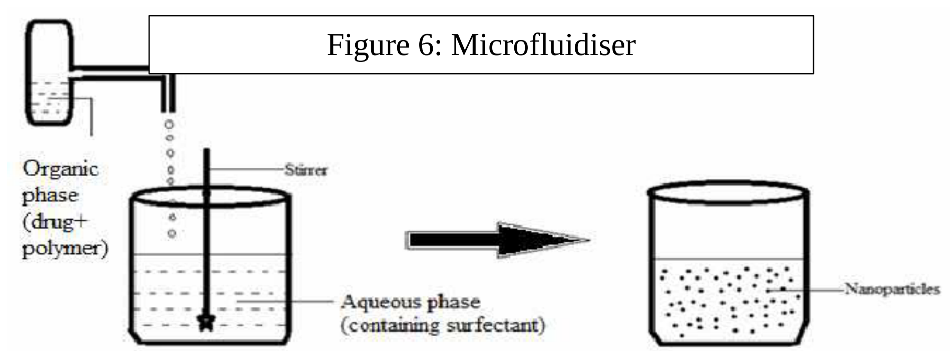

Figure 7: Solvent displacement method

Spontaneous emulsification method

Nanoemulsions can be produced by this method at room temperature without the use of any special device. Water is added stepwise into the solution of oil and surfactant at constant temperature and stirred gently to produce O/W nanoemulsions. The spontaneous emulsification method depends mainly on: interfacial tension, interfacial and bulk viscosity, phase transition region and surfactant structure and its concentration.[20]

Production with high amplitude ultrasound

This method is a viable alternative to high pressure homogenization. Intense shear forces necessary for the nanoemulsification are generated by the ultrasonic cavitation (figure: 8). This method is used in the small scale production of nanoemulsions.[21]

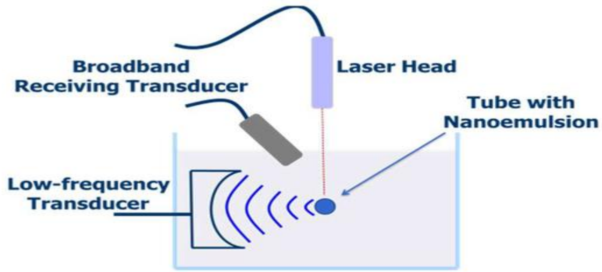

Figure 8: High amplitude ultrasound method

Evaluation Parameters Of Nanoemulsion[22]

Droplet size analysis:

Droplet size analysis of nanoemulsion is measured by a diffusion method using a light-scattering, particle size analyser counter, LS 230. It is also measured by correlation spectroscopy that analyzes the fluctuation in scattering of light due to Brownian motion. Droplet size analysis of nanoemulsion can also be performed by transmission electron microscopy (TEM).

Viscosity determination:

The viscosity of nanoemulsion is measured by using Brookfield-type rotary viscometer at different shear rates at different temperatures.

Dilution test:

Dilution of a nanoemulsion either with oil or with water can reveal this type. The test is based on the fact that more of the continuous phase can be added into a nanoemulsion without causing the problem of its stability. Thus, an o/w nanoemulsion can be diluted with water and a w/o nanoemulsioncan be diluted with oil.

Drug content:

Pre-weighed nanoemulsion is extracted by dissolving in a suitable solvent, extract is analyzed by spectrophotometer or HPLC against standard solution of drug.

Refractive index:

Refractive index of nanoemulsion is measured by Abbes refractometer.

pH: The pH of nanoemulsion can be measured by pH meter.

Zeta potential:

Zeta potential is measured by an instrument known as Zeta PALS. It is used to measure the charge on the surface of droplet in nanoemulsions .[23]

Applications of Nanoemulsions in Drug Delivery

Nanoemulsions have been applied in various aspects of drug delivery such as parenteral drug delivery, pulmonary delivery of drugs, formulations for improved oral delivery of poorly soluble drug, ocular and otic drug delivery, intranasal drug delivery (figure: 9). It is also applied in the field of cosmetics and transdermal delivery of drug, cancer therapy, vaccine delivery and cell culture technology.

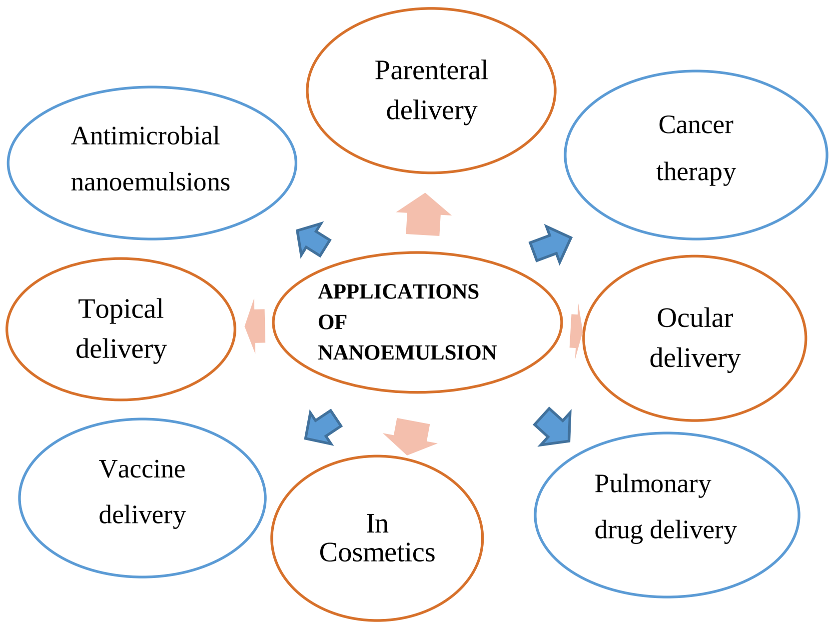

Figure 9: Different applications of nanoemulsions

Parenteral Delivery: This is the most common and effective route of drug administration for the drug with low bioavailability and narrow therapeutic index. Nanoemulsions are more advantages for i v administration, due to the strict requirement of this route of administration, particularly the necessity for the formulation droplet size lower than 1 micrometer. Parenteral administration of nanoemulsions is used for a variety of purposes like fats, carbohydrates, vitamins etc. Nanoemulsions have a longer residence time in the body. Diazepam, Propofol, Prostaglandin E1 are the some parenteral nanoemulsion formulation have been documented. Both O/w and W/O Nanoemulsions can be used for parenteral delivery.[24]

Nanoemulsion formulations for improved oral delivery of poorly soluble drugs: Nanoemulsions formulations was developed to increase oral bioavailability of hydrophobic drugs. Nanoemulsions offer the several benefits for oral administration including increased absorption, improved clinical potency and decreased drug toxicity. Nanoemulsions have been reported to ideal delivery of drugs such as steroids, hormones, diuretic and antibiotics.[25]

Topical delivery:

The nanoemulsions can achieve a level of topical antimicrobial activity that has only been achieved by systemic antibiotics. The nanoemulsions has board spectrum activity against bacteria and fungi. The use of nanoemulsions in transdermal drug delivery represents an important area of research in drug delivery, which enhances the therapeutic efficacy and bioavailability of the drugs. It also have many advantages including high storage stability, low preparation cost, thermodynamic stability and good production feasibility.[26]

Ocular delivery:

For the treatment of eye diseases, drugs are essentially administered topically. O/W Nanoemulsions have been investigated for ocular administration, to dissolve the poorly soluble drugs, to increase absorption and to attain prolong release profile. Nanoemulsions increases the contact time of the drug in the eyes, this may increases the bioavailability and reduces the need for frequent administration leading to improved patient compliance.[27]

In cosmestics:

Nanoemulsions are used in cosmetics because there is no inherent creaming, sedimentation flocculation, that are observed with macroemulsion. Due to the lipophilic interior, nanoemulsions are suitable for the transport of lipophilic drug than liposomes and it support the skin penetration of active ingredients and thus increases their concentration in the skin. Another advantage of nanoemulsion is the small-sized droplet with its high surface area permits the effective delivery of the active ingredients to the skin. The incorporation of potentially irritating surfactants can be avoided by using high energy equipment during manufacturing. PEG- free nanoemulsions for cometics have also been developed and which exhibits good stability.[28]

Antimicrobial Nanoemulsions:

Antimicrobial nanoemulsions are O/W droplets and their size ranges from 200-600 nm. They are made by oil and water and are stabilized by surfactant and alcohol. The antimicrobial nanoemulsins has a broad spectrum of activity against bacteria like E.coli, Salmonella; viruses like HIV, Herpes simplex,etc. When nanoparticles fuses with the pathogens, they release part of the energy trapped within the emulsion and which destabilize the pathogen lipid membrane, resulting in cell lysis and death.[29]

Nanoemulsions in vaccine delivery:

Nanoemulsions used to vaccinate against Human immunodeficiency virus (HIV). There is recent evidence that HIV can infect the mucosal immune system. Therefore, developing mucosal immunity through the use of nanoemulsions may become very important in the future fight against HIV.[30]

Nanoemulsions in cell culture technology:

Cell culture are used to produce biological compounds like an antibodies or recombinant proteins. For optimization of cell growth, the culture medium can be supplemented with a large number of molecules. It has been very difficult to provide the media with oil-soluble substances that are available to the cells, nanoemulsions are a new method for the delivery of oil-soluble substances to human cell cultures.[31]

Nanoemulsions in cancer therapy and targeted drug delivery:

Another interesting application for the nanoemulsion formulations is the controlled and targeted drug delivery. Because of their submicron size, they can easily be targeted to the tumor area. The development of magnetic nanoemulsions is the innovative approach for cancer therapy. This methodology can be used for the treatment of cancer in the form of photodynamic therapy. [32]

Pulmonary drug delivery:

The lung is an attractive target for drug delivery due to noninvasive administration via inhalation aerosols, avoidance of first-pass metabolism, direct delivery to the site of action for the treatment of respiratory diseases, and the availability of a huge surface area for local drug. Nanocarrier systems in pulmonary drug delivery offer the uniform distribution of drug dose in the nose, improved solubility of drugs, improved patient compliance and decreases incidence of side effects.[33]

CONCLUSION

Nanoemulsions provides several advantages for the delivery of drugs and improves the delivery of active pharmaceutical ingredients. Nanoemulsions also provides control drug release, increase drug solubility, increase bioavailability and reduce patient variability. They are applicable for almost all routes of delivery. Thus nanoemulsions of natural products hold promise in revolutionising the future of pharmaceuticals, cosmetics, food technology, agricultural and biotechnological fields.

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