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Self-nano emulsifying drug delivery system

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ABSTRACT

An advanced mode of drug delivery system has been developed to overcome the major drawbacks associated with conventional drug delivery systems. This review gives a detailed idea about a nano emulsion system. Nano emulsions are nano-sized emulsions, which are manufactured for improving the delivery of active pharmaceutical ingredients. These are the thermodynamically stable isotropic system in which two immiscible liquids are mixed to form a single phase by means of an emulsifying agent, i.e., surfactant and co-surfactant. The droplet size of nano emulsion falls typically in the range 20–200 nm. The main difference between emulsion and nano emulsion lies in the size and shape of particles dispersed in the continuous phase. In this review, the attention is focused to give a basic idea about its formulation, method of preparation, characterization techniques, evaluation parameters, and various applications of nano emulsion

Keywords=Nano emulsion Drugdelivery Emulgents High-pressure homogenization

I. INTRODUCTION

Nano emulsions can be defined as boiling-water (o/w) emulsions with mean droplet diameters ranging from 50 to 1000 nm. Usually, the average droplet size is between 100 and 500 nm, terms submicron emulsion (SME) and mini-emulsion are used as synonyms. Since, the preparation of the first nano emulsion in 1940s, it can be of three types such as oil-in-water (O/W), water-in-oil (W/O), and continuous. The transformation between these three types can be achieved by varying the components of the emulsions. Each type of the nano emulsions serves as a template for preparing polymer latex particles, nano porous polymeric solids etc. Apart from this, the nano emulsions with pharmaceutically accepted ingredients are utilized in the development of drug formulations for oral drug delivery. The Nano emulsions are also referred as manumissions, ultrafine emulsions and submicron emulsions. Phase behaviour studies have shown that the size of the droplets is governed by the surfactant phase structure (continuous microemulsion or lamellar) at the inversion point induced by either temperature or composition. Studies on Nano emulsion formation by the phase inversion temperature method have shown a relationship between minimum droplet size and complete solubilization of the oil in a microemulsion continuous phase independently of whether the initial phase equilibrium is single or multiphase. Due to their small droplet size, nano emulsions possess stability against sedimentation or creaming with Ostwald ripening forming the main mechanism of Nano emulsion breakdown. The main application of Nano emulsions is the preparation of nanoparticles using a polymerizable monomer as the disperse phase (the so-called minimising polymerization method) where Nano emulsion droplets act as nanoreactors. Another interesting application which is experiencing an active development is the use of Nano emulsions as formulations, namely, for controlled drug delivery and targeting. The main application of nano emulsions is the preparation of nanoparticles using a polymerizable monomer as the disperse phase where nano emulsion droplets act as nanoreactors

Advantages of nano emulsion

(a) It may be used as substitute for liposomes and vesicles (1,2).
(b) It improves the bioavailability of drug (3).
(c) It is non-toxic and non-irritant in nature.
(d) It has improved physical stability.
(e) Nano emulsions have small-sized droplets having greater surface area providing greater absorption
(f) It can be formulated in variety of formulations such as foams, creams, liquids, and sprays.
(g) It provides better uptake of oil-soluble supplements in cell culture technology.
(h) It helps to solubilize lipophilic drug.

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(I) Helpful in taste masking.
(j) Less amount of energy is required.

FORMULATION ASPECT OF NANO EMULSION(4,5,6,7).

Formulation of nano emulsion includes active drug, additives and emulsifier which are as shown in table 1.

Table 1: Formulation Table of Nano emulsion

Components	Examples
oils	Castor oil, Corn oil, Coconut oil, Evening primrose oil, linseed oil, Mineral oil, olive oil, peanut oil
Emulsifiers	Natural lecithin's from plant or animal source, phospholipids, castor oil Derivatives, polysorbates, stearyl amine.
additives	Lower alcohol (ethanol), propylene glycol, 1, 3-butylenes glycol, sugars such as butylene's glycol, sugars such as glucose, sucrose, fructose, and maltose.
antioxidants	Ascorbic acid, α-tocopherol
surfactant	Polysorbate20, Polysorbate80, Polyoxin 60, castor oil, Surbiton monooleate, PEG300, Caprylic glyceride.
Co-surfactant	Ethanol, glycerine, PEG300, PEG400, Polyene glycol, Poloxamer.
Tonicity modifiers	Glycerol, Sorbitol and xylitol.
Ph adjusting agent	Sodium hydroxide or hydrogen chloride
preservatives	Methyl Paraben, Propyl Paraben, Benzalkonium Chloride (0.01%w/v)

Method of preparation of nano emulsion:
There are two primary methods to prepare a nano emulsion(8):
1. Persuasion and;
2. Brute force
1. By Persuasion:
(1) Phase Transition from Near-Optimum State via Change in Single Variable: This method involves change in one formulation variable such as salinity or temperature for a system near optimal (HLD (hydrophilic lipophilic deviation) near 0), such as applying a higher temperature to a microemulsion. (2) Phase Transition from Near-Optimum State via Change in Multiple Variables: This method involves change in more than one formulation variable, such as applying higher temperature and inclusion of additional salt in a microemulsion.
(3) Catastrophic Inversion: This method involves causing a low internal phase emulsion to invert such that the internal phase becomes the external phase.
(4) Phase Transition Stabilized by Liquid Crystal Formation: This method involves stabilization of nanodroplets by liquid crystal formation from a state near HLD=0.
2. By Brute Force: This method may involve the use of a high-speed mixer, a high-pressure homogenizer, a high frequency ultra-sonic device, a small pore membrane, etc. Formation of O/W and W/O nano emulsions by dispersion or high-energy emulsification methods is apparently fairly common, while nano emulsion formation by

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condensation or "low-energy" emulsification methods, take advantage of the physicochemical properties of these systems based on the phase transition that takes place during the emulsification process.

It can be carried out by operating in particular areas of the phase diagram with a very low interfacial tension, which are areas of liquid crystals and microemulsions; at the end of the emulsification process, nano emulsions formed. Properties of nano emulsions, such as small droplet size, relatively high kinetic stability and optical transparency seem to depend not only on composition variables but also on preparation variables such as emulsifying path, degree of mixing energy input and emulsification time.

Techniques of preparation of nano emulsion

Nano emulsions have very small particle size range; they can be most effectively produced using high-pressure equipment. The most commonly used methods for producing nano emulsions are 'High-pressure homogenization' and 'Micro fluidization' used at both laboratory and industrial scale.

Other methods like 'Ultra sonification' and 'In-situ emulsification' are also suitable for preparation of nano emulsion.

1. **High-Pressure Homogenization**: The preparation of nano emulsions requires high-pressure homogenization. This technique makes use of high-pressure homogenizer/piston homogenizer to produce nano emulsions of extremely low particle size (up to 1nm). The dispersion of two liquids (oily phase and aqueous phase) is achieved by forcing their mixture through a small inlet orifice at very high pressure (500 to 5000 psi), which subjects the product to intense turbulence and hydraulic shear resulting in extremely fine particles of emulsion. The particles which are formed exhibit a liquid, lipophilic core separated from the surrounding aqueous phase by a monomolecular layer of phospholipids. This technique has great efficiency, the only disadvantage being high energy consumption and increase in temperature of emulsion during processing. In Fig. 1, high pressure homogenization shows the formation of nano emulsion (9,10,11)

To obtain the optimized formulation following process variables should be investigated:

- Effect of Homogenization Pressure: It is optimized the process parameter ranging from 100 to 150 bars. The higher is the size the lower is the particle size obtained e.g., RMRP 22.
- No. of Homogenization cycles: The higher the homogenization cycles the smaller is the particle size obtained. The cycles are carried out in 3, 4 or 10 cycles. The number of cycles is analysed by polydispersity index of drug after each cycle.

Advantages:

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

2. **Micro fluidization**: Micro fluidization 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 nano emulsion. 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 nano emulsion.
3. **Spontaneous Emulsification**: It involves three main steps (12):

Preparation of homogeneous organic solution composed of oil and lipophilic surfactant in water miscible solvent and hydrophilic surfactant.

- The organic phase was injected in the aqueous phase under magnetic stirring the o/w emulsion was formed.
- The water-miscible solvent was removed by evaporation under reduced pressure.
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4. **Low Energy Emulsification**: This Technique is used for the preparation of o/w nano emulsion. Take advantage of the physicochemical properties of these systems

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based on the phase transition that takes place during the emulsification process (13,14)

5. **Solvent Evaporation Technique**: This technique involves preparing a solution of drug followed by its emulsification in another liquid that is nonsolvent for the drug. Evaporation of the solvent leads to precipitation of the drug. Crystal growth and particle aggregation can be controlled by creating high shear forces using a high-speed stirrer (15)
6. **Hydrogel Method**: It is similar to solvent evaporation method (15). The only difference between the two methods is that the drug solvent is miscible with the drug anti-solvent. Higher shear force prevents crystal growth and Ostwald ripening. Other method used for Nano emulsion preparation is the phase inversion temperature technique

Characterization and Evaluation of Nano emulsion:

Different characterization parameters for nano emulsion include transmission electron microscopy, nano emulsion droplet size analysis, viscosity determination, refractive index, in vitro skin (4), permeation studies, skin irritation test, in vivo efficacy study, thermodynamic stability studies, and surface characteristics. The surface charge of the nano emulsion droplets has a marked effect on the stability of the emulsion system and the droplet in vivo disposition and nano emulsion droplets were in the size range of 25-40 nm with some particle aggregates in the size range of 100-150 nm (4).

Nano emulsion 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 analyser 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 droplets size distribution, like 0.5 ml emulsion was introduced in the measure compartment (125 ml of water). The results were presented as the volume distribution.

Many other techniques that have been developed to measure droplet size of nano emulsions, two are of interest in this article in which laser light scattering (LLS) and energy filtering transmission electron microscopy (EFTEM). The small droplet size gives them inherent stability against creaming, sedimentation, flocculation and coalescence. It also allows the effective transport of active ingredients to the skin (11,15,16)

Polydispersity Index: The average diameters and polydispersity index of samples were measured by photon correlation spectroscopy. The measurements were performed at 25o C using a He-Ne laser. 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 spindle (15,16).

Refractive Index: The refractive index, n, of a medium is defined as the ration of the speed, c, of a wave such as light or sound in a reference medium to the phase speed, up, of the wave in the medium.

N=C/UP

It was determined using an Abbes type refractometer (Nirmal International) at 25 ± 0.5°C.

pH: The apparent pH of the formulation was measured by pH meter (15,16)

Transmission Electron Microscopy (TEM): Morphology and structure of the nano emulsion were studied using transmission electron microscopy. Combination of bright field imaging at increasing magnification and of diffraction modes was used to reveal the form and size of nano emulsion droplets. Observations was performed as, a drop of the nano emulsion was directly deposited on the holey film grid and observed after drying.

Drug Content: Drug content was determined by reverse phase HPLC method using C18 column (17)

Zeta Potential: Zeta potential is a technique which is used to measure the surface charge properties and further the long-term physical stability of nano emulsions, the instrument which is used to measure the surface charge is known as Zeta PALS. The measurements were carried out with diluted nano emulsion formulations (18) and its values were determined from the electrophoretic mobility of the oil droplets. The minimum zeta potential of ±20mv is desirable

Percentage Transmittance: Percentage transmittance of the prepared nano emulsion formulations was determined spectrophotometrically using UV-VIS Spectrophotometer (19). In Vitro Skin Permeation Studies: In vitro skin permeation studies were performed by using Keshary Chin-diffusion cell. It was performed on abdominal skins and was obtained from male rats weighing 250±10 gm with

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a recirculating water bath and 12 diffusion cells. The skins were placed between the donor and the receiver chambers of vertical diffusion cells. The receiver chambers were filled with freshly water containing 20% ethanol. The receiver chambers were set at 37o C and the solution in the receiver chambers was stirred continuously at 300 rpm. The formulations were placed in the donor chamber. At 2, 4, 6, 8 h, 0.5 ml of the solution in the receiver chamber was removed for GC analysis and replaced immediately with an equal volume of fresh solution (20). Each sample was performed three times. The cumulative corrections were made to obtain the total amounts of drugs permeated at each time interval. The cumulative amounts of drug permeated through rat skins were plotted as a function of time. The permeation rates of drug at a steady-state through rat skins were calculated from the slope of linear portion of the cumulative amount permeated through the rat skins per unit area versus time plot.

Thermodynamic Stability Studies: During the thermodynamic stability of drug loaded Nano emulsions following stress tests as reported (21)

- **Heating Cooling Cycle**: Nano emulsion formulations were subjected to six cycles between refrigerator temperature (4°C) and 45°C. Stable formulations were then subjected to centrifugation test.
- **Centrifugation**: Nano emulsion formulations were centrifuged at 3500 rpm and those that did not show any phase separation were taken for the freeze thaw stress test.
- **Freeze Thaw Cycle**: In this the formulation were subjected to three freeze thaw cycles between 21°C and +25°C kept under standard laboratory conditions. These studies were performed for the period of 3 months. Three batches of formulations were kept at accelerated temperature of 30°C, 40°C, 50°C and 60°celsious at ambient humidity. The samples were withdrawn at regular intervals of 0, 1, 2 and 3 months and were analysed for drug content by stability-indicating HPLC method.

Applications of Nano emulsion:

1. Use of nano emulsions in cosmetics (22).
2. Antimicrobial Nano emulsions.
3. Prophylactic in Bio-Terrorism Attack.
4. Nano emulsions as Mucosal Vaccines.
5. Nano emulsion as Non-Toxic Disinfectant Cleaner.
6. Nano emulsions in Cell Culture Technology.
7. Nano emulsion formulations for improved oral delivery of poorly soluble drug (23)
8. Self-nanoemulsifying drug delivery systems (24, 25, 26).
9. Nano emulsions as a vehicle for transdermal delivery (27, 28).
10. Nano emulsion in the treatment of various other disease conditions like diclofenac cream, a potential treatment for osteoarthritis.
11. Solid self-nanoemulsifying delivery systems as a platform technology for formulation of poorly soluble drugs.
12. Nano emulsion in cancer therapy and in targeted drug delivery.

Table 2 provides a thorough review on the advancement on nano emulsion.

TABLE 2: LITERATURE REVIEW ON NANOEMULSION

Sr no	drug	carrier	method	use
1.	Prednicarbate	Phyto sphingosine	High Pressure Homogenization	Atopic Dermatitis
2.	Risperidone	PEG400	Brain targeting through nasal administration	Antipsychotic
3.	Celecoxib	Diethylene glycol	Spontaneous emulsification	Arthritis and osteoarthritis
4.	Praziquante	Poloxamer	Spontaneous emulsification	Increase schistosomicidal effectiveness

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5.	Benzathine	penicillin G Poloxamer	Spontaneous emulsification	Potential dosage form to encapsulate more soluble drugs
6.	Ampicillin	PEG 400	Solid Dispersion	Delivery of protein drug inside the oil phase
7.	Polyanionic	Poloxamer 188	High Pressure Homogenization	Cancer disease, inflammation
8.	Primaquine	Poloxamer 188	High Pressure Homogenization	Treat latent stage malaria
9.	Ramipril	Capryl caproyl macrogol-8-glyceride	Spontaneous emulsification	Liquid formulation for paediatric and geriatric patients
10.	Aceclofenac	PEG400	Spontaneous emulsification	Improved transdermal delivery
11.	Ramipril	Cabitol	Spontaneous emulsification	Enhance the bioavailability
12.	Citronella Oil	Glycerol	High Pressure Homogenization	Mosquito repellent
13.	Celecoxib	Propylene mono caprylic ester	Low Energy emulsification	Evaluation of stability
14.	Saquinavir	pufa	----------	Enhance bioavailability and brain disposition
15.	Domperidone	Polysorbate 20, Oleic acid	Pseudoternary phase diagrams	Enhance percutaneous absorption through Transdermal delivery
16.	Lipidic	Intravenous injection	1.G1 into the mammary tissue 2.G2 into the peritumoral 3.G3 into the tumoral tissue	Decreases toxicity without decreasing the anticancer action

II. CONCLUSION:

Nano emulsion formulations offer several advantages for the delivery of drugs, biologicals, or diagnostic agents and able to protect labile drug, control drug release, increase drug solubility, increase bioavailability and reduce patient variability. Traditionally, Nano emulsions have been used in clinics for more than four decades as total parenteral nutrition fluids. Nano emulsions 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, photosensitizers, neutron capture therapy agents, or diagnostic agents. Because of their submicron size, they can be easily targeted to the tumour area.

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