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Nanoemulsions: A Review on Various Pharmaceutical Application

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Abstract: Nanoemulsions are submicron sized emulsion that is under extensive investigation as drug carriers for improving the delivery of therapeutic agents. These are by far the most advanced nanoparticle systems for the systemic delivery of active pharmaceutical for controlled drug delivery and targeting. These are the thermodynamically stable isotropic system in which two immiscible liquid (water and oil) are mixed to form a single phase by means of an appropriate surfactants or it mixes with a droplet diameter approximately in the range of 0.5-100 um. Nanoemulsion droplet size falls typically in the range of 20-200 nm and shows a narrow size distribution. Nanoemulsion show great promise for the future of cosmetics, diagnostics, drug therapies and biotechnologies. Thus the aim of this review is focused on nanoemulison advantage and disadvantage, various methods of preparation, characterization techniques and the various applications of sub micron size emulsion in different areas such as various route of administration, in chemotherapy, in cosmetic, etc.

Key words: Nanoemulsion · Submicron size droplet · Self emulsifying agent · Drug delivery system

INTRODUCTION

Nanoemulsion is a heterogeneous system and it consist of two immisible phase, one phase is oil phase other is aqueous phase, while the droplet is of sub micron size range of 5-200nm. It is thermodynamically stable, optically clear and transparent [1]. Now-a-day's nanoemulsions are frequently used for various purpose like delivery of vaccine, DNA encoded drug, antibiotics, cosmetic and topical preparations and can be administrated via various routes like oral, pulmonary, ocular and transdermal etc [2, 3].

Depending on its composition there are three types of nanoemulsions: o/w (oil in water), w/o (water in oil), multiple emulsion {o/w/o (oil in water in oil), w/o/w (water in oil in water)}. The major difference between emulsion and nanoemulsion are [4]: While Nanoemulsions are thermodynamically and kinetically stable, emulsions are unstable. Emulsions are cloudy while nanoemulsions are clear and translucent. Emulsion require the large energy input while nanoemulsions are formed either with (sometime spontaneously) or without high energy input [4]. Emulsions have smaller surface area to volume, less free energy than Nanoemulsion. Emulsions requires high amount of surfactant as compared to nanoemulsion, for e.g. 20-25% surfactant is added in the preparation of emulsion but 5-10 % surfactant is added in Nanoemulsion [5]. Ostwald ripening is the main mechanism of nanoemulsion breakdown [6].

Nanoemulsions are formulated using oil such as glyceryltricaorylatecaprate, surfactants/ cosurfactants and aqueous phase. Surfactants such as tween 80, PEG (>4000), poloxamer, Brij-35 etc are used [7]. Surfactants added in formulation approved are 'Generally Recognized as Safe' (GRAS) by the FDA [3].

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ADVANTAGE AND DISADVANTAGE [8, 4]

S. no.	Advantages	Disadvantages
1.	Nanoemulsions are thermodynamically and kinetically stable therefore flocculation, aggregation, creaming and coalescence do not occur.	Large concentration of surfactants /cosurfactants is required for stabilization.
2.	It is non toxic and non-irritant.	Its stability is affected by temperature and pH.
3.	Nanoemulsion is administered by various routes, such as oral, topical, parentral and transdermal etc.	Instability can be caused due to Oswald ripening effect.
4	Nanoemulsions can deliver both hydrophilic and lipophilic drugs.	
5.	Droplet size are nano, so surface area is higher thus increases the rate of absorption and reduces variability, thus enhances bioavailability of drug.	
6.	Nanoemulsions are suitable for human and veterinary uses because they do not damage human or animal cell.	
7	It protects the drug from hydrolysis and oxidation due to encapsulation in oil-droplet. It also provides taste masking.	
8.	Nanoemulsion also enhances permeation of drug through skin.	

Method of Preparation of Nanoemulsion

Ultrasonic Agitation of a Premixed Emulsion: Premixed emulsion is formulated to fix composition of the emulsion and then it was agitated at ultrasonic frequency of (20 kHz of layer) causing the droplet to break into nano droplets. The emulsion is recirulated through region of high shear to produce uniform droplet size distribution. In this method the water jacket is used to control and maintain the temperature and the ultrasonic frequency reduces the particle size (fine droplet) [8-10].

Microfluidization: Rapidly flowing stream of a premixed emulsion (decrease the droplet size 10μm) are passed through stainless steel micro channels (100μ) to create strong dimensional flow using a high pressure positive displacement pump (500-20,000psi). This results in very fine droplets of sub-micron size range. The premixed emulsion is circulated through the microfludizer repeatedly until required droplet size is achieved [1,3,10].

Phase Inversion: In this method the fine dispersions are produced as the phase inversion occurs which is caused by varying the composition and keeping the temperature constant or vice versa [10].

High Pressure Homogenizer

Aqueous phase + oleaginous phase
(Heated and pH adjustment) (Heated and filtration)
⇓
Add emulsifying agent
⇓
Rapid cooling
⇓
High pressure homogenizer (500-20000psi)
⇓
Formation of droplet very small size (nano size) [4, 10, 11]

Characterization Technique of Nanoemulsion: Nano-emulsions characteristics will depend on particle size, viscosity, density, phase inversion, turbidity, refractive index, skin permeation studies and these characteristics are measured by the various technique discuss below[1].

Thermal Conductivity Technique: In this technique, named 3ω-wire method wasdeveloped to measured nanoemulsion by the thermal conductometer. In this method, the temperature of the metal wire is measured in the time domain [12]. O/W Nanoemulsion where the external phase is water are highly conducting [4].

Dynamic Light Scattering Spectrophotometer: Dynamic light scattering measurements are done at 90° using a neon laser of wavelength 632nm. The particle size and particle size distribution is determined by dynamic light scattering spectrophotometer [13,4].

Zeta Potential: Zeta potential measures the surface charge of nanoemulsion with the help of a mini electrode [14].

Transmission Electron Microscopy (TEM): It is a very simple method to determine the size, number, weight and structure (morphology characteristic). O/w nanoemulsion is stain with uranyl acetate and placed on a grid, coated with monolayer polymer, then water is evaporated and observation is done using TEM [3, 8,15].

Drug Content: Western Blot method is used to measured amount of drug present [7,16].

Viscosity Measurement: Viscosity of nanoemulsion should be measured by using the rotary viscometer at different rate and temperature. Nanoemulsions have very low viscosity [4,17, 18].

Phase Analysis Technique: It is done for nanoemulsion generally prepared by phase inversion method and self emulsification method to measures the dispersibility of nanoemulsion [3,19].

Applications of Nanoemulsion

Use in Cosmetic: Nanoemulsion is widely used in the cosmetic because the active constituents are easily absorbed to give effective action due to the small size of the droplet and reduce the water loss from the skin. Nanoemulsions are used as moisturizer and creams. Attractive delivery vehicle in the cosmetics as nanoemulsion droplet size is very small, creaming and flocculation is not observed leading to a more elegant and stable product [1, 3, 20, 21].

Use as Anti Microbial Agent: Antimicrobial nanoemulsions are O/W droplet which has a broad-spectrum activity against bacteria, enveloped viruses (e.g. HIV), fungi and spores. Nanoemulsions are droplets fused with lipid containing organisms and release part of the energy trapped within the emulsion. Pathogen lipid membrane is destabilized by active ingredient and the energy released by the emulsion, leading to microbial cell lysis [22, 23].

Nanoemulsions in Cancer Therapy: Nanoemulsions are 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 transport of anti-cancer drugs via lymphatic system [24, 25].

Prophylactic in Bio-Terrorism Attack: Nanoemulsions are used as a prophylactic medication and are used against bio-attack pathogens such as anthrax and ebola. In broad-spectrum, used as a chemical decontamination agent for anthrax, gangrene etc and can even be used on contaminated wounds to salvage limbs [1, 26].

Nanoemulsion as Mucosal Vaccines: Nanoemulsions can be used forneedle free immunization by delivering recombinant protein and inactivated organism to a mucosal surface as nanoemulsion cause the protein surface to be adjuvanted and thus facilitates uptake by antigen-presenting cells [3, 26].

Nanoemulsion in Cell Culture Technology: Nanoemulsions are used in cell culture technology because they increase uptake of oil soluble component in cell culture and improve growth of culture cell [26].

Oral Drug Delivery System: A nanoemulsion can be used to improve oral bioavailability of poorly to soluble drug because it has a very small particle size and can incorporate hydrophobic drug in oil droplets [3, 26].

Transdermal Drug Delivery System: Nanoemulsion can be used for transdermal drug delivery due to increase permeation through the skin and are also it is non-irritant [26, 27].

PATENTED NANOEMULSION [1, 3, 26,]

Patent Name	Assignee	Patent no.
Method of preventing and treating microbial infection	NanoBio corporation(US)	6,506,803
Nanoemulsion based on phosphoric acid fatty acid ester and its uses in the cosmetics, dermatological, pharmaceutical and ophthalmological field.	L'Oreal (Paris, FR).	6,274,50
Nanoemulsion based on ethylene oxide block copolymer and its uses in the cosmetic, dermatological and ophthalmological fields.	L'Oreal (Paris, FR).	6,464,990
Nanoemulsion of 5-aminolevulinic acid.	ASAT AG (Applied Science and Technology).	6,559,183

CONCLUSION

Nanoemulsion can act as a colloidal carrier for various lipophilic drug diagnostic agents etc. The skin penetrative properties and low irritancy make it a suitable carrier for the transdermal delivery of the drugs. In the upcoming future further research work and development will be carried out for Clinical application of nanoemulsion.

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