



NANOEMULSION: AN INNOVATIVE DRUG DELIVERY- A REVIEW

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ABSTRACT

Nanoemulsion is kinetically stable and isotropic system of two immiscible liquids in sub micron size range. Nanoemulsions are composed of oil droplets dispersed in an aqueous medium and stabilized by surfactant molecules. Advantages of nanoemulsions include increased drug loading and enhanced bioavailability. The methods used for the production of nanoemulsions include HPH, microfluidization; ultrasonication and spontaneous emulsification. Nanoemulsions have widespread applications in different fields such as pharmaceuticals, food technology and cosmetics. This article mainly focuses on its application. In pharmaceutical observation, nanoemulsion is one of the chief dosage forms in delivering active ingredients to the objective area which has engrossed a great attention in recent years for its application in various fields. In the pharmaceutical field, nanoemulsions have been used as a drug delivery system through various systemic routes such as oral, topical and parenteral. Nanoemulsions are submicron sized emulsions which are used under high investigation as drug carriers for improving the delivery of therapeutic agents. The small droplets size 10-200 nm, high solubilization capacity, high interfacial area, low viscosity, transparent or translucent appearance, and high kinetic stability, make nanoemulsions used for various applications.

KEYWORDS: Nanoemulsion, surfactant, emulsification, food technology and cosmetics.

INTRODUCTION

Nanoemulsions/Sub-micron emulsions (SMEs)/Mini-emulsions/Ultrafine emulsions are thermodynamically stable transparent (translucent) dispersions of oil and water stabilized by an interfacial film of surfactant and cosurfactant molecules having a droplet size of less than 100 nm. Nanoemulsion, which is categorized as multiphase colloidal dispersion, is generally characterized by its stability and clarity. The dispersed phase typically comprises small particles or droplets, with a size range of 5 nm-200 nm, and has very low oil/water interfacial tension. Because the droplet size is less than 25% of the wavelength of visible light, Nanoemulsions are transparent. Nanoemulsion is formed readily and sometimes spontaneously, generally without high-energy input. In many cases a cosurfactant or cosolvent is used in addition to the surfactant, the oil phase and the water phase.^[1,2] Now a day's nanoemulsion are frequently used for various purpose like delivery of vaccine, DNA encoded drug, antibiotics, cosmetic and topical preparations and can be administered via various routes like oral, pulmonary, ocular and transdermal etc.^[3,4] It has been demonstrated that with the help of nanoemulsion as a delivery system retention time of a drug in the body can be increased, so low amount of drug is required for the therapeutic action. Past studies shows the utilization of nanoemulsion

technology for the enhancement of bioavailability of lipophilic drug.^[5]

Types of Nanoemulsions

Depending on the composition, there are three types of nanoemulsions.

1. Oil in water nano emulsions where in oil droplets are dispersed in the continuous aqueous phase.
2. Water in oil nano emulsions where in water droplets are dispersed in the continuous oil phase.
3. Bi- continuous nanoemulsions where in micro domains of oil and water are inter dispersed within the system.^[6]

Components of Nanoemulsion: Main three components of Nanoemulsions are as follows

1. Oil
2. Surfactant/Cosurfactant
3. Aqueous phase^[7]

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

Cosurfactant

S.no.	Solubilizing, surfactants, emulsifying agents adsorption enhancers
1	Capryol 90
2	Gelucire 44/14, 50/13
3	Cremophor RH 40
4	Imwitor 191, 308(1), 380, 742, 780K, 928, 988
5	Labrafil M 1944 CS, M 2125 CS
6	Lauroglycol 90
7	PEG MW>4000
8	Plurol oleique CC 497
9	Poloxamer 124 and 188
10	Softigen 701, 767
11	Tagat TO
12	Tween 8

Advantages of Nanoemulsions over other dosage forms

1. Eliminates variability in absorption
2. Increases the rate of absorption.
3. Helps in solubilizing lipophilic drug.
4. Provides aqueous dosage form for water insoluble drugs.
5. Increases bioavailability.
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. Provides protection from hydrolysis and oxidation as drug in oil phase in o/w emulsion
10. Less amount of energy required
11. Liquid dosage form increases patient compliance
12. Nanoemulsions are thermodynamically stable systems and the stability allows self-emulsification of the system whose properties are not dependent on the process followed.
13. Nanoemulsions carry both lipophilic and hydrophilic compounds.
14. Use of Nanoemulsion as delivery systems improves the efficacy of a drug, allowing the total dose to be reduced and thus minimizing side effects.^[8]

Disadvantages of Nanoemulsion Based Systems

1. Use of a large concentration of surfactant and cosurfactants necessary for stabilizing the Nanodroplets.
2. Limited solubilizing capacity for high melt-ing substances.
3. The surfactant must be nontoxic for pharmaceutical applications.
4. Nanoemulsion stability is influenced by environmental parameters such as temperature and pH. These parameters change upon Nanoemulsion delivery to patients.^[9]

Theory of the Formation of Nanoemulsion: In Nanoemulsion which is categorized as multiphase colloidal dispersion which is generally characterized by its stability and clarity. There is an application of high shear generally obtained by micro fluid or ultrasonic approach generally used to reduce the droplet size to nanoscale. There is a marginal difference between the terms Nanoemulsion and microemulsion also known as micellar phase or mesophase. The microemulsion generally forms through thermodynamic self assembly whereas nanoemulsion requires external shear for rupturing the droplets. In retrospect, the historical choice of the word “microemulsion” to describe the nanoscale is unfortunate since they are structurally between 1 to 100 nm as for Nanoemulsion. Micro emulsions are not the emulsions of micro scale droplets. They are formed by self assembled equilibrium phase in which the surface tension does not play a significant role. The Nanoemulsions underline the basic principle in its formulation. They generally comprise of two immiscible phase with an interfacial tension between them reduced by addition of surfactant.^[10]

Factors affecting the Formulation of Nanoemulsion

1. Appropriate composition is required to avoid Oswald ripening the dispersed phase should be highly insoluble in the dispersed medium.
2. 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.
3. The presence of excess surfactants enables new surface area of nanoscale to be rapidly coated during emulsification there by inhibiting induced coalescence.
4. Extreme shear 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.^[11]

Methods of Preparation of Nanoemulsion

Numerous methods have been optional to practise nanoemulsion. Development of nanoemulsion system

needs an elevated amount of energy. This energy can be obtained either by mechanical equipment or by the chemical potential inherent within the component. Some methods used for the preparation of nanoemulsion are.

1. Sonication Method: In this technique, the droplet size of usual emulsion is compact with the help of sonication mechanism. Only fewer amounts of batches of nanoemulsion can be produced by this method.^[12]

2. High Pressure Homogenizer: This method is based on by applying a large pressure over the system consisting an oil phase, aqueous phase and surfactant or co-surfactant. The high pressure is applied with the help of homogenizer. Some problems allied with homogenizer are poor productivity, component deterioration due to production of much heat. From this method, only oil in water (o/w) liquid nanoemulsion of less than 20% oil phase can be formed and cream nanoemulsion of high viscosity or hardness having a mean droplet diameter less than 200 nm cannot be prepared.^[13]

3. Phase Inversion Method: Fine dispersion can be obtained by chemical energy resulting in phase transitions through emulsification method. The sufficient phase transitions are produced by changing the composition at constant temperature or by changing the temperature at constant composition. The phase inversion temperature (PIT) method was introduced based on the principle of changes of solubility of polyoxyethylene type surfactant with temperature. This surfactant becomes lipid soluble with increase in temperature because of dehydration of polymer chain. At low temperatures the surfactant monolayer has a great positive spontaneous curvature forming oil swollen micellar solution phase.^[14]

4. Production with high amplitude ultrasound

This method is an alternative for high pressure homogenization. High shear forces are necessary for the nanoemulsification are produced by ultrasonic cavitations which produces violently and asymmetrically imploding vacuum bubbles and reduce the particle size to the nanometer scale. This method is successfully used in small scale production of nanoemulsions.^[15]

5. Solvent Displacement Method

In this method, oily phase is dissolved in water miscible organic solvents such as acetone, ethanol. The organic phase is mixed into an aqueous phase containing surfactant to produce nanoemulsion by rapid diffusion of organic solvent. Organic solvent is removed from nanoemulsion by vacuum evaporation.^[16]

6. Microfluidization: Microfluidization technology makes use of a device called 'MICRO FLUIDIZER'. This device consist of high pressure positive displacement pump (500-200 PSI) which forces the product through the interaction chamber, consisting of small channels called micro channels. The product

moves through the micro channels on to an impingement area which results in very fine particles of submicron range. The two solutions (aqueous phase and oily phase) are mix together and processed in an inline homogenizer to get a coarse emulsion. The coarse emulsion is into a micro fluidizer where it is further processed to get a stable nanoemulsion.^[17]

Characterization of Nanoemulsion

1. 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 nanoemulsion. Emulsifiers not only act as a mechanical barrier but also through formation of surface charges. Zeta potential can produce repulsive electrical forces among approaching oil droplets and this hinders coalescence. The more negative zeta potential, greater the net charge of droplets and more stable the emulsion is. Zeta potential values lower than -30 mV generally indicate a high degree of physical stability. Malvern Zetasizer is based on dynamic light scattering and measures Zeta potential.

2. Polydispersity: Polydispersity is the ratio of standard deviation to mean droplet size, so it indicates the uniformity of droplet size within the formulation. The higher the polydispersity, the lower the uniformity of the droplet size in the formulation. Malvern Zetasizer is based on dynamic light scattering and measures polydispersity.^[18]

3. Particle Size Analysis: Generally in case of nanoemulsion dynamic light scattering (DLS) method is used for the measurement of particle size and their distribution.^[19]

4. Percent Drug Loading: Pre-weighed nanoemulsion is extracted by dissolving in 25ml suitable solvent, extract is than analyzed spectrophotometrically/ H.P.L.C. against the standard solution of drug. Drug content determine by reverse phase HPLC method using different columns of appropriate porosity.^[20]

5. Transmission Electron Microscopy (TEM): Morphology and structure of the nanoemulsion can be studied using transmission electron microscopy (TEM).

6. In-vitro drug release: The *in vitro* release studies of nanoemulsion containing drug can be investigated through semi permeable membrane used in a dissolution apparatus. A glass cylindrical tube (2.5 cm in diameter and 6 cm in length) is attached instead of the basket and should tightly cover with the semi permeable membrane. Drug loaded nanoemulsion is placed in the cylindrical tube at the semi permeable membrane surface. The cylindrical tube should dip in 100 ml buffer maintaining the pH to allow the establishment of the sink conditions and to sustain permanent solubilization. The release study can be carried out for 24 hrs. at 32°C. The stirring shaft should rotate at speed of 100 r.p.m. At predetermined time intervals (1, 2, 4, 6, 8, 12, 20, 24

hrs.) aliquots of one millilitre of the release medium is withdrawn and diluted then filtered for analysis and replaced with equal volume of the buffer solution to maintain a constant volume. The absorbance of the collected samples can be measured by UV spectrometer.^[21]

Applications of Nanoemulsions

1. Parenteral Delivery

Nanoemulsion has advantages in 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 e.g. Fats, Carbohydrates, Vitamins etc. Nanoemulsion formulations have distinct advantages over macroemulsion systems when delivered parenterally because of the fine particle Nanoemulsion is cleared more slowly than the coarse particle emulsion and, therefore, have a longer residence time in the body. Both O/W and W/O Nanoemulsion can be used for parenteral delivery.

2. Oral Delivery

Nanoemulsion formulations offer many advantages over conventional oral formulation for oral administration including increased absorption, improved clinical potency and decreased drug toxicity. Thus, Nanoemulsion proves to be ideal in delivering of drugs such as steroids, hormones, diuretic and antibiotics. Pharmaceutical drugs of peptides and proteins are highly potent and specific in their physiological functions.^[22] Primaquine when incorporated into oral lipid nanoemulsion showed effective antimalarial activity against *Plasmodium berghei* infection in mice at a 25% lower dose level as compared to conventional oral dose. Lipid nanoemulsion of primaquine improved oral bioavailability by the liver with drug concentration higher by at least by 45% as compared with the pure drug.

3. Topical Delivery

Topical administration of drugs can have advantages over other methods for several reasons, one of which is the avoidance of hepatic first pass metabolism of the drug and related toxicity effects. 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*, *S. aureus*) fungi (e.g. *Candida*, *Dermatophytes*).^[23]

4. Ocular Delivery

For the treatment of eye diseases, drugs are essentially delivered topically. Nanoemulsions have been investigated for ocular administration, to dissolve poorly

soluble drugs, to increase absorption and to attain prolonged release profile.^[24]

5. In Cosmetic

The aesthetic properties, i.e. low viscosity and transparent visual aspects of nanoemulsion with droplet sizes below 200nm, its high surface area allowing effective transport of the active ingredient to the skin make them especially attractive for their application in cosmetics. Nanoemulsions are acceptable in cosmetics because there is no inherent creaming, sedimentation, flocculation or coalescence that is observed with macroemulsion. The incorporation of potentially irritating surfactants can be avoided by using high energy equipment during manufacturing. Nanogel technology to create miniemulsion from oil-in water concentrate suited to minimizing transepidermal water loss, enhanced skin protection and penetration of active ingredient. It would be useful for sun care products, moisturizing and antiageing creams. It helps to give skin care formulations a good skin feel.^[25]

6. Transdermal

Indomethacin a potent NSAID, the anti-inflammatory effects of true optimized nanoemulsion formulation were compared with marketed gel in carrageenan induced paw edema in rats. The %inhibition value was significant for developed Nanoemulsion, so huge potential for transdermal application of indomethacin. Nanoemulsions for transdermal delivery of celecoxib, formulation which consisted of 2% celecoxib 10% oil phase (Sefsol 218 and Tri-acetin) 50% surfactant mixture (Tween 80 and Transcutol-P) and 40% water. The anti-inflammatory effect and percent inhibition value after 24h administration was found to be high for nanoemulsion formulation (81.2%) as compared to celecoxib gel (43.7%) and nanoemulsion gel (64.5%). The *in vitro* - *in vivo* studies revealed a significant increase in the anti-inflammatory effects of aceclofenac nanoemulsion (82.2%) as compared to nanoemulsion gel formulation (71.4%) and conventional gel (41.8%).

7. Nanoemulsions in Cancer Therapy

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 its non-irritant system.^[24,25]

8. Nanoemulsions in intranasal drug delivery

Intranasal drug delivery system has now been recognized as a reliable route for the administration of drugs next to parenteral and oral routes. Nasal mucosa has emerged as a therapeutically viable channel for the administration of systemic drugs and also appears to be a favourable way to overcome the obstacles for the direct entry of drugs to the target site. This route is also painless, non-invasive and well tolerated. The nasal cavity is one of the most

efficient sites because of its reduced enzymatic activity, high availability of immunoactive sites and its moderately permeable epithelium. There are several problems associated with targeting drugs to brain, especially the hydrophilic ones and those of high molecular weight. This is because of the impervious nature of the endothelium, which divides the systemic circulation and barrier between the blood and brain. The olfactory region of the nasal mucosa provides a direct connection between the nose and brain and by the use of nanoemulsions loaded with drugs, conditions such as Alzheimer's disease, migraine, depression, schizophrenia, Parkinson's diseases, meningitis, etc. can be treated. Preparation of nanoemulsions containing risperidone for its delivery to the brain via nose has been reported. It is inferred that this emulsion is more effective through the nasal rather than intravenous route. Another application of intranasal drug delivery system in therapeutics is their use in development of vaccines. Immunity is achieved by the administration of mucosal antigen. Currently, the first intranasal vaccine has been marketed. Among the possible delivery systems, the use of nano based carriers hold a great promise to protect the biomolecules, promote nanocarrier interaction with mucosae and to direct antigen to the lymphoid tissues. Therefore the use of nanoemulsions in intranasal drug delivery system is set to bring about significant results in targeting of the drugs to the brain in treatment of diseases related to the central nervous system. Bhanushali *et al* developed intranasal nanoemulsion and gel formulations for rizatriptan benzoate for prolonged action. Various mucoadhesive agents were tried out to form thermo-triggered mucoadhesive nanoemulsions.

9. Nanoemulsions in pulmonary drug delivery

The lung is the most important 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 action and systemic absorption of drug. Colloidal carriers (ie, nanocarrier systems) in pulmonary drug delivery offer many 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, a sustained drug release which consequently reduces dosing frequency, improves patient compliance, decreases incidence of side effects, and the potential of drug internalization by cells.

10. Nanoemulsions in gene delivery vector

Emulsion systems have been emerged as an alternative gene transfer vectors to liposomes. Other emulsion studies for gene delivery (non-pulmonary route) have shown that binding of the emulsion/DNA complex is stronger than liposomal carriers. This stable emulsion system delivered genes more efficiently than liposomes. Silva *et al* evaluated factors that influence DNA compaction in cationic lipid nanoemulsions [cationic nanoemulsions containing stearylamine (a cationic lipid that presents a primary amine group when in solution, is able to compact genetic material by electrostatic interactions, and in dispersed systems such as nanoemulsions this lipid anchors on the oil/water interface conferring a positive charge to them). The influence of the stearylamine incorporation phase (water or oil), time of complexation, and different incubation temperatures were studied. Characterization was done by dynamic light scattering (DLS). The results demonstrate that the best DNA compaction process occurs after 120 min of complexation, at low temperature (4 ± 1 °C), and after incorporation of the cationic lipid into the aqueous phase. Although the zeta potential of lipoplexes was lower than the results found for basic nanoemulsions, the granulometry did not change. Moreover, it was demonstrated that lipoplexes are suitable vehicles for gene delivery.^[26]

Marketed product of nanoemulsion^[27]

Drug/bioactive	Brand name	manufacturer	indication
Alprostadil palmitate	Lipile	Mitsubishi pharmaceutical	Vasodilator, platelet inhibitor
Dexamethason	Limethason	Mitsubishi pharmaceutical	Steroid
Propofol	Diprivan, troypofol	Astra zanece, troika	Anaesthetic
Flurbiprofen axtil	Ropion	Kaken pharmaceutical	NSAID
Vitamins A,D,E and K	Vitalipid	Fresenius kabi	Parenteral nutrition
Etomidate	Etomidat-lipuro	B.Braun melsungen	Anaesthetic
cyclosporine	Restasis, gengraf	Allergen, abott	Immunosuppressant
ritonavir	norvir	abbott	antiretroviral

CONCLUSION

The aim of this review is to duly focus on nanoemulsion as drug delivery vehicle. Nanoemulsion formulations offer several advantages for the delivery of drugs, biological, or diagnostic agents and able to protect labile drug, control drug release, increase drug solubility, increase bioavailability and reduce patient variability. Lipophilic molecules are cardinal component and

dissolve the drug, this whole mixture have increasing attention as colloidal carriers (size less than 100 nm). The diverse nanonization strategies provide flexible options to develop tailor-made nano therapeutics for different drugs and administration routes. These techniques can also be used to revive the clinical efficacy of toxic drugs or facilitate the clinical translation of drug candidates that are deemed failures simply because of

lack of solubility. Nanoemulsions have been shown to exhibit robust stability with research focusing on the study of different parameters to lower the rate of Ostwald ripening. As discussed in this article, strategies such as trapped species methods have been developed to make stable nanoemulsions. However, current research has not explored the idea of designing polymers that can be used as emulsifier for the preparation of stable nanoemulsions. Polymers can be tuned from being hydrophobic to hydrophilic which can result in rich properties, including tunable rheology and stability. Due to their small size, molecules sitting at the interface of nanoemulsions experience higher curvature which will greatly influence self-assembly at the interface. Nanoemulsions can also serve as a model system to enhance understanding of colloidal assembly and rheology of complex emulsion systems. They can be readily density matched, selectively dyed for visualization, and made magnetic field responsive. Their liquid interfaces are dynamic, which expands the richness of their soft matter physical properties.

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