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REVIEW ARTICLE

Pharmaceutical Nano emulsion as a Rational Carrier for Drug Delivery

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ABSTRACT:
Nanoemulsions are transparent system mostly covering droplet size in nanometric scale because of their small droplet sizes. Nanoemulsion appears transparent and is kinetically stable. The long term physical stability of nanoemulsion makes them unique and is sometime referred as 'Approaching Thermodynamic stability'. These increases the rate of absorption eliminates variability in absorption and increase bioavailability. These can carry lipophilic and hydrophilic drugs. This review aims on the method of preparation, characterization techniques, advantages and disadvantages and the various route of drug delivery of nanoemulsion.

KEYWORDS: Nanoemulsion, Thermodynamic stability, Rate of absorption, Drug delivery.

INTRODUCTION:[1,2,4,11]
The term "Nanoemulsion" refers to a thermodynamically stable isotropically clear dispersion of two immiscible liquids, such as oil and water stabilized by an interfacial film of surfactant molecules. It is defined as oil-in-water (o/w) emulsion with mean droplet diameters ranging from 50 to 1000 nm. Usually, the average droplet size between 100 and 500 nm, term sub-micron emulsion (SME) and mini-emulsion are used as synonyms. Since the preparation of first nanoemulsion in 1940, it can be 3 types such as oil-in-water (o/w), water-in-oil (w/o), and bi continuous. The transformation between these three types can be achieved by varying the component of the emulsion. Each type of the emulsions serves as a template for the preparing polymer latex particles, nonporous polymeric solids etc. Apart from these the nanoemulsions with pharmaceutically accepted ingredients are utilized in the development of drug formulation for oral drug delivery.

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Nanoemulsion formation by the phase inversion temperature method have shown relationship between minimum droplet size and complete solubilization of the oil in a microemulsion by continuous phase independently of whether the initial phase equilibrium is a single or multiphase due to their small droplet size, nanoemulsion possess stability against sedimentation of creaming with Ostwald ripening forming the main mechanism of nanoemulsion breakdown. The main application of nanoemulsion is the preparation of nanoparticles using a polymerizable monomer as the disperse phase (the so called mini emulsions polymerization method) where nanoemulsion droplets acts as nanoreactors. Another interesting application which is experiencing an achieve development is the use of nanoemulsions as formulations, namely, for controlled drug delivery and targeting. The main applications of nanoemulsions is the preparation of nanoparticles using a polymerizable monomer as the disperse phase where nanoemulsion droplet acts as nonreactors.

Types of Nanoemulsions[6, 5,11]
Depending on the composition, there are three types of Nanoemulsions.
1. Oil in water nanoemulsion 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 nano emulsions where in micro domains of oil and water are inter dispersed within the systems.

The main different between emulsion and Nano emulsion are that even though emulsion is having kinetic stability they are thermodynamically unstable. Emulsions are cloudy but nanoemulsions are clear and translucent. They also differ in their method of preparation.

Advantages[1, 4, 6, 8]

-Nano emulsions are thermodynamically stable system and stability allows self-emulsification system.
-Increases the rate of absorption.
-Increases bioavailability.
-Eliminates variability in absorption.
-Nano emulsions can carry both lipophilic and hydrophilic drugs.
-Various routes like topical,oral and intravenous can be used to deliver the product.
- Helpful in taste masking.
-Provides protection from hydrolysis and oxidation as drug in oil phase in o/w nanoemulsions is not exposed to attack by water and air.
-Nanoemulsions have higher surface area and higher free energy than micro emulsions that makes them an effective transport system.
-Nanoemulsions offer can alternative for the administration of poorly water soluble drugs.
-These leads to improved efficiency and patient compliance.
-It is do not damage healthy human and animal cells,so nanoemulsions are suitable for human and veterinary therapeutic purposes.

Disadvantages[8,3, 9]

-Nanoemulsion stability is influenced by environmental parameters such as temperature and pH.
-Limited solubilizing capacity for high-melting substances.
-The surfactant must be non-toxic for using pharmaceutical application.
-Use of large concentration or surfactant and co-surfactant necessary for stabilizing the nanodroplets.
- Instability caused due to Ostwald ripening effect.
-There is the perception in the personal care and cosmetic industry that nanoemulsions are expensive to produce. Expensive equipment are required as well as the use of high concentration of emulsifiers.
-Lack of understanding of the mechanism of production of submicron droplets and role of surfactant and co-surfactant.

Components of Nanoemulsion[6, 9, 15]

Nanoemulsion contains three main components.
1. Oil
2. Surfactant/Co Surfactant
3. Aqueous phase.

Oil

Solubility of the drug in the oil phase is important criterion for the selection of oils. This is particularly important in the case of oral formulation development, as the ability of the nanoemulsion to maintain the drug in solubilized form is greatly influenced by the solubility of the drug in the oil phase. If the surfactant or co-surfactant is contributing to drug solubilization, there could be a risk of precipitation, as dilution of nanoemulsionin the gastrointestinal tract will lead to lowering of the solvent capacity of the surfactant or co-surfactant

TABLE 1: Different Oils Used In Nanoemulsion

OILS USED IN NANOEMULSION	CHEMICAL NAME	MANUFACTURE
Captex 355	Glyceryl Tricaorylate/ Caprate	Abitec
Captex 200	Propylene Dicaprylate /Glycol	Abitec
Captex 8000	Glyceryl Tricaprylate (Tricaprylin)	Abitec
Witepsol	90:10%w/w c12Glyceride tri: diester	Sasol pharmaceutical excipient
Myritol 318	C8/c10 triglycerides	Russia
Isopropyl myristate	Myristic acid Isopropyl alcohol	Fluka

Surfactant

Surfactants used for stabilizing the systems there are three types surfactant anionic, cationic, and non-ionic. Non-ionic surfactants are relatively less toxic than their ionic counter parts and typically have lower CMCs. Also, o/w nanoemulsion dosage forms for oral or parenteral used based on non-ionic surfactants are likely to offer in vivo stability.Therefore, proper selection of surfactant with proper HLB value. Hydrophilic surfactant and cosurfactant are considered to prefer the interface and to lowers the necessary energy to form the nanoemulsions, consequently improving the stability.

Classification of surfactant

1.Nonionic-Fatty alcohols, Glycerol esters, Fatty acid esters.
2.Anionic-Carboxylate group, Soaps, Sulfonates, Divalent ions.

3.Cationic Amines and Quaternary ammonium compounds.

Cosurfactant

Cosurfactant are added to obtain nanoemulsion systems at low surfactant concentration. Short –to-medium–chain–length alcohols (C3-C8) are commonly added as cosurfactant which is further reduce the interfacial tension and increase the fluidity of interface. They also increase the motility of the hydrocarbon tail and allow greater penetration of the oil into the region. Alcohol may also increase the miscibility of the aqueous and oily phases due to its partitioning between these phases. Therefore,ethanol, isopropylene alcohol, 1-butanol, and propylene glycol were selected as cosurfactants.PEG 400 and carbitol were also selected as they also show increased permeation when incorporated into formulations and are relatively tolerable.

Example: Transcutol p, Glycerin, Propylene glycol, Ethanol, Propanol.

Factors affecting formulation of Nanoemulsion[8,7, 16,19]

1. Appropriate composition of 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, waters, and surfactants form the phases which are generally used with the co-surfactant.
3. The presence of excess surfactant enables new surface area of nano scale to be rapidly coated during emulsification there by inhibiying coalescence.
4. 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 on 10-100atm.

Method of preparation of Nanoemulsions

1. High Pressure Homogenization

This technique makes used of high- pressure homogenizer/piston homogenizer to produce Nanoemulsions of extremly low particle size (up to1nm).Method is performed by applying a high pressure over the system having oil phase, aqueous phase and surfactant or co-surfactant. Homogenizer is used for applying the high pressure. There are some problems associated with homogenizer such as poor productivity, component deterioration and generation of much heat. This method is only applicable for oil-in-water (o/w) liquid nanoemulsion having less than 20% of oil phase and cream nanoemulsion of high viscosity or hardness with a mean droplets diameter lower than 200nm cannot be prepared.

2. Microfluidization

This is patented mixing technology, which makes use of device called microfluidizer. This devices uses a high-pressure positive displacement pump (500-20000 psi), which forces the product into the interaction chamber, consisting of small channels called "microchannels". The product flows through the microchannels on to an impingement area resulting in very fine particle of submicron range. The two solutions (aqueous phase and oily phase) are mixed together and processed in an inline homogenizer to yield a coarse emulsion. The prepared coarse emulsion is introduced into a microfluidizer where it is further processed to obtain a stable nanoemulsion. The coarse emulsion is continuously passed into the interaction chamber of the microfluidizer until the desired particle size is obtained. The prepared emulsion is then filtered under nitrogen to remove large droplet resulting in uniform nanoemulsion.

3. Phase Inversion Temperature Technique

Studies on nanoemulsion formulation by the phase inversion temperature method have shown a relationship between minimum droplet size and complete solubalization of the oil a microemulsion bicontinuous phase independently of whether the initial phase equilibrium is single or multiphase. Due to their small droplet size nanoemulsion possess stability against sedimentation or creaming with Oswald ripening foaming the main mechanism of nanoemulsion breakdown. Phase inversion induced by changing factors which affects the HLB of the system, e.g. temerature and/or which can also be induced by changing the HLB number of the surfactant at constant temperature using surfactant mixtures.

Phase inversion temperature (PTI)method employs temperature dependent solubility of nonionic surfactant, such as polyethoxylated surfactants, to modify their affinities for water oil as a function of the temperature. It has been observed that polyethoxylated surfactants tend to become lipophilic on water into solution or surfactant in oil, with gentle stirring at constant temperature. The spontaneous nanoemulsion has been related to the phase transition during the emulsification process and involves lamellar liquid crystalline phases or D-type bi-continuous microemulsions during the process. Nanoemulsions obtained from the spontaneous nanoemulsification procfrequency for the reduction of these are not thermodynamically stable although they might have high kinetic energy and long term colloidal stability.

4. Ultrasonication[4, 9,15,18]

The preparation of nanoemulsion is reported in various research papers which aim to use the ultrasonic sound frequency for the droplet size. Another approach is the use of a constant amplitude sanotrode at system pressure in excess of the ambient value. It is well known that increasing the external pressure increases the cavitations threshold within an ultrasonic field and thus fewer bubbles form. However, increasing the external pressure also increasing the collapse pressure of cavitations bubbles. This means that the collapse of the bubble when cavitation occurs becomes stronger and more violent that when the pressure is at atmospheric conditions. As cavitation is the most important mechanism of power dissipation in low frequency ultrasonic system, these changes in navigational intensity can be related directly to changes in the power density. The system also uses a water jacket to control the temperature to optimum level.

Characterization of Nanoemulsion[2,4,7,12,20]

Nanoemulsion Droplet Size Analysis

Droplet size distribution is one of the most important physicochemical characteristics of a nano-emulsion, was measured by a diffusion method using a light scattering particle size analyzer Coulter LS-230.It measures the size distribution using the diffusion of laser light by particles. Polarization intensity diffential scattering (PIDS) is the assembly consists of an incandescent light source and polarizing filters, a PIDS sample cell and the additional seven photodiode detectors. It is used to measure the droplet size distribution, like 0.5ml emulsion is introduced in the measure compartment (125ml of water). The results are presented as the volume distribution.

Polydispersity Index

The average diameter and polydispersity index of samples are measured by photon correlation spectroscopy. The measurements are performed at 25^0C using a He-Ne laser.

Dilutability Test

O/W Nanoemulsions are dilutable with water whereas W/O are not and undergo phase inversion into O/W Nanoemulsion.

pH

The apparent pH of the formulation was measured by pH meter.

Refractive index

The refractive index, n, of a medium is defined as the ration f the speed, c, of a wave such as light or sound in a reference medium to the phase speed, vp, of the wave in the medium. n=c/vp; It was determined using an Abbes type refractometer (Nirmal International) at 25± 0.5^0C.

Phase Analysis

To determine the type if nanoemulsion that has formed the phase system (O/W or W/O) of the Nanoemulsions is determined by measuring the electrical conductivity using a conductometer.

Dynamic light Scattering Measurement

The DLS measurements are taken at 90^0 in a dynamic light scattering spectrophotometer which used a Neon laser of wavelength 632nm. The data processing is done in the built in computer with its instruments.

Interfacial Tension

The formation at the properties of Nanoemulsions can be studied by measuring the interfacial tension. Ultra low values of interfacial tension are correlated with phase behaviour, particularly the existence of surfactant phase or middle phase Nanoemulsions in equilibrium with aqueous and oil phases. Spinning-drop apparatus can be used to measure the Ultra-low interfacial tension. Interfacial tensions are derived from the measurement of the shape of a drop of the low density phase, rotating it in cylindrical capillary filled with high-density phase.

Viscosity Measurement

The viscosity of Nanoemulsions of several compositions can be measured at different shear rates at different temperatures using Brookfield type rotary viscometer. The sample room of the instrument must be maintained at 37±0.2^0C by a thermo bath and samples for the measurement are to be immersed in it before testing.

Thermodynamic Stability Studies

During the thermodynamic stability of drug loaded Nanoemulsions following stress test are reported.

Heating Cooling Cycle

Nanoemulsion formulations were subjected to six cycles between refrigerator temperatures (4^0C)
And 45^0C. Stable formulations were then subjected to centrifugation test.

Centrifugation

Nanoemulsion formulations were centrifuge at 3500rpm and those that did not show any phase separation were taken for the freeze thaw stress test.

In-vitro Skin permeation Studies [4,14,22]

In-vitro skin permeation studies are performed by using KesharyChien-diffusion cell. It is performed on abdominal skins and is obtained from male rats weighing 250±10gm with recirculating water bath and 12 diffusion cell. The skins were placed between the donor and receiver chamber of the vertical diffusion cell. The receiver chambers were filled with freshly water containing 20% ethanol. The receiver chambers were set

at 37^0C and the solution in the receiver chambers was stirred continuously at 300rpm. The formulations were placed in the donor chamber. At 2,4,6,8 h, 0.5ml of solution in the receiver chamber was removed from GC analysis and replaced immediately with an equal volume of fresh solution. Each sample was performed three times. The cumulative corrections were made to obtain the total amount of the drug permeated through rat skins were plotted as a function of time. The permeation of the drug at steady-state to through rat skins were calculated from the slope of the linear portion of the cumulative amount permeated through the rat skins per unit area versus time plot.

Application of Nanoemulsions [13, 15, 18, 21]

1. Solubilization of poorly soluble drugs

Solubilization of poorly soluble drugs in the most apparent application for Nanoemulsion.

Eg: Lorazepam is injected intravenously for premedication and sedation before an operation. It is usually administered as a solution in organic solvent such as propylene glycol. The highest concentration that can be achieved in aqueous diluents (5% dextrose in water) is 0.05 mg/ml. A phospholipids stabilised soyabean oil emulsion was able to stably emulsify Lorazepam at 1mg/ml, a 20-fold increased, which could significantly reduce the volume needed for injection.

2. Reduced pain and inflammation

At a direct site of intravenous injection, some drugs can cause local irritation. These drugs as, well as certain co-solvents in aqueous solutions, can also cause phlebitis, an inflammation of vein that can lead to pain or redness. Nanoemulsions eliminate the need for co-solvents, as well as encapsulating drugs that might otherwise be irritants, and in both cases can local irritation upon injection.

3. Reduced toxicity of drugs

Beyond the site of injection, drugs or their delivery vehicles can also cause irritation or toxicity once in the body. Paclitaxel is an important chemotherapeutic agent used in the treatment of breast, ovarian colon and non-small cell lung carcinomas. The commercially available product Taxoll(Bristol –Myers Squibb) is formulated in a 1:1v/v mixture of ethanol and polyoxy ethylated castor oil (cremophor EL). Cremophor EL has been associated with Bronchospasms, hypotension, and other hypertensive reactions. To reduce the toxicity associated with cremophor EL, incorporation of paclitaxel into a wide variety of drug delivery vehicles including liposomes, micelles, emulsions and cyclodextrins, has been investigated. For the commercially available taxoll formulation the Maximum Tolerated Dose (MTD) was approximately 20mg/kg where as for the nanoemulsion formulation it was approximately 70mg/kg, over three times greater. The efficacy of the nanoemulsion formulation was assessed with B16 melanoma, a fast growing solid murine tumor. Nanoemulsion showed increasing efficacy at increasing dosage amounts and were better than the commercial formulation in all cases.

4. Improved pharmacokinetics

Pharmacokinetic is concerned with the fate of external substances introduced to the body, specially the extent and rate of absorption, distribution, metabolism and excretion of compounds. Improving these parameters for more favourable drug performance drug performance is a primary objective of drug delivery research in general and for nanoemulsion specially one specific parameter that will be mentioned multiple times is the area under the concentration time curve, abbreviated AUC.

Eg: Nalbuphine is morphine like drug and once of its advantages over morphine is that it lacks significant withdrawal symptoms. However, due to its short elimination half-life and poor oral bioavailability it needs to be injected every 3-6 hours prodrug ognalbuphine have been investigated for parenteral administration, and Fang and coworkers sought to use Nanoemulsion for both nalbuphine and its prodrugs.

Applications of Nanoemulsion in Drug Delivery System

Nanoemulsion containing pharmaceutically active agent can be utilized for the production of pharmaceutical preparations. If desired special galvanic form can be imported to the mixture. Ampules, especially sterile injection and infusion solution; solutions, especially oral liquids, eye drops and nose drops which can contain various auxiliary substances can be formulated in the form of nanoemulsion.

(A) Ocular Delivery

Oil in water emulsion is being explored for improved topical lipophilic drug delivery to the eye. Examples: Piroxicam, Pilocarpine, Cyclosporine-A.

(B) Oral Delivery

Nanoemulsion formulation offer the several benefits over conventional oral formulation for oral administration for including increased absorption, improved clinical potency, and decreased drug toxicity. Therefore, Nanoemulsionhas been reported to be ideal delivery of drugs such as steroids, hormones, diuretic and antibiotics. Pharmaceutical drugs of peptides and proteins are highly potent and specific in their physiological functions. However, most are difficult to administer orally. With on oral bioavailability in conventional (i.e. non-nanoemulsion based) formulation of less than 10%, they are usually not therapeutically

active by oral administration. Because of their oral bioavailability, most protein drugs are only available as parenteral formulation. However peptide drugs have an extremely short biological half-life when administered parenterally, so required multiple dosing. A nanoemulsion formulation of cyclosporine, named Neoral has been introduced to replace and immune, a crude oil-in-water emulsion of cyclosporine formulation. Neoral is formulated with a finer dispersion, giving it more rapid and predictable absorption and less inner and intra patient variability.

(C)Topical Delivery

Topical administration of drugs can have advantages over other methods for several reasons, one of which is avoidance of hepatic first pass metabolism of drug and related toxicity effects. Another is the direct delivery and target ability of the drug and affected area of the skin or eyes. Both O/W or W/O Nanoemulsions have been evaluated in a hairless mouse model for the delivery of prostaglandin E1. The nanoemulsion were based on oleic acid or Gelucire 44/14 as the oil phase and were stabilized by a mixture of Labrasol (C8 and C10 polyglycolysed glycerides) and PlurolOleique CC 497 as a surfactant. Although enhanced delivery rates were observed in case of the O/W Nanoemulsions, the others concluded that the penetration rates were inadequate for practical use from either system. The use of lecithin /IPP/water Nanoemulsions for the transdermal transport of indomethacin and diclofenac has also been reported Fourier infra-red (FTIR) spectroscopy and differential scanning colourimetry (DSC) showed the IPP organogel had disrupted the lipid organization in human stratum corneum after a one day incubation. The transdermal delivery of the hydrophilic drug diphenhydramine hydrochloride from a W/O Nanoemulsions into excised human skin have also been investigated. The formulation was based on combination of Tween 80 and span 20 with IPM. However two additional formulations were tested containing cholesterol and oleic acid, respectively. Cholesterol increased drug penetration whereas oleic acid had no measurable effect, but the authors clearly demonstrated that penetration characteristics can be modulated by compositional selection.

(D) In Cosmetics [10,13,17]

The aesthetic properties, i.e. low viscosity and transparent visual aspects of Nanoemulsions with droplet size 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 are observed with micro emulsion. 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 penetration of active ingredient. It would be useful for sun care products, moisturing and antiageing creams. It helps to give skin care formulation a good skin feels.

(E) Nanoemulsionin Biotechnology

Many enzymatic and biocatalytic reactions are connected in pure organic or aqua-organic media. Biphasic media are also used for these types of reactions. The used of pure a polar media causes the denaturation of biocatalyst. The used of water-proof media is relatively advantageous. Enzymes in low water content display and have

-Increased solubility of non-polar reactant

-Possibility of shifting thermodynamic equilibria in favour of condensation

-Improvement of thermal stability of the enzymes, enabling reactions to be carried out at higher temperatures.

Many enzymes including lipases, esterases, dehydrogenases and oxides often function in the cells in microenvironments that are hydrophobic in nature. In biological systems many enzyme operated at the interface between hydrophobic and hydrophilic domains and these usually interfaces are stabilized by polar lipids and other natural amphiphiles. Enzymatic catalysis in Nanoemulsions has been used of variety of reactions, such as synthesis of esters, peptides and sugar acetals transesterification various hydrolysis reactions and steroid transformation. The most widely used class of enzymes in microemulsions-based reaction is of lipases.

CONCLUSION:

Nanoemulsion formulation offers several advantages for the drug delivery of the drugs, biological, or diagnostic agents and able to protect labile drug, control drug release, increase drug solubility, increase bioavailability and reduce variability. Traditionally, Nanoemulsions have been used in clinics more than decades as total parenteral nutrition (TPN) fluids. Nanoemulsions are chiefly seen as vehicles for administering aqueous insoluble drugs, they have more recently received increasing attention as colloidal carriers for targeted drug delivery of various anticancer drug, photosensitizers, and neutron capture therapy agents. Because of their submicron size, they can be easily targeted to the tumor area. Moreover, targeting delivery of drugs, genes, photosensitizers, and other molecule to the tumor area. It is expected that further research and development work will be carried out the near future for clinical realization of these targeted delivery vehicles.

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