NANOEMULSION: A NEW SYSTEM FOR DRUG DELIVERY

*Nitin P. Kanwale, Datta Gavali, Dhananjay Patil, Rohit Bhaskar, Abhijit Dhas, Anurag Dwivedi.

Department Of Quality Assurance Techniques, NDMVP Collage Of Pharmacy Nasik, 422002.

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 nm. 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.

KEYWORDS: Nanoemulsion, Submicron size droplet, Self emulsifying agent, Drug delivery system.

INTRODUCTION
Nanoemulsions can be defined as oil-in-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 nanoemulsion in 1940s, it can be of three 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 components of the emulsions.

Due to their small droplet size, nanoemulsions possess stability problem against sedimentation or creaming with Ostwald ripening forming the main mechanism of Nanoemulsion breakdown. The main application of Nanoemulsions is the preparation of nanoparticles using a polymerizable monomer as the disperse phase (the so-called miniemulsion polymerization method) where Nanoemulsion droplets act as nanoreactors.

**Fig1: Structure of Nanoemulsion**

**TYPES OF NANOEMULSION**

Three types of Nanoemulsions are most likely to be formed depending on the composition:

1. **O/w Nanoemulsion**: Wherein oil droplets are dispersed in the continuous aqueous phase.
2. **W/O Nanoemulsions**: Wherein water droplets are dispersed in the continuous oil phase.
3. **Bi-continuous Nanoemulsions**: Wherein 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/or co-surfactants. The main difference between emulsions and nanoemulsion 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.

**COMPONENTS OF NANOEMULSION**

Main Four components of Nanoemulsions are as follows.

1. Oil phase
2. Aqueous phase
3. Surfactant
4. Co-surfactant
Nanoemulsions are colloidal dispersions composed of an oil phase, aqueous phase, surfactant and cosurfactant at appropriate ratios. Unlike coarse emulsions micronized with external energy nanoemulsions are based on low interfacial tension. This is achieved by adding a cosurfactant, which leads to spontaneous formation of a thermodynamically stable Nanoemulsion. The droplet size in the dispersed phase is very small, usually below 140 nm in diameter, which makes the nanoemulsions transparent liquids.

The surfactants used to stabilise such systems may be

1) Non-ionic surfactants:
   Examples: Brij 35 (C12E35), sorbitan monooleate (Span 80).
2) Zwitterionic surfactants:
   Example: Phospholipids.
3) Cationic surfactants:
   Example: Lecithin, 21 Quaternary ammonium alkyl salts.
4) Anionic surfactants.

ADVANTAGES OF NANOEMULSIONS AS DRUG DELIVERY SYSTEMS
The attraction of nanoemulsions for application in personal care and cosmetics as well as in health care is due to the following advantages:
1) The very small droplet size causes a large reduction in the gravity force and the Brownian motion may be sufficient for overcoming gravity. This means that no creaming or sedimentation occurs on storage.
2) The small droplet size also prevents any flocculation of the droplets. Weak flocculation is prevented and this enables the system to remain dispersed with no separation.
3) The small droplets also prevent their coalescence, since these droplets are elastic, surface fluctuations are prevented.
4) Nanoemulsions are suitable for efficient delivery of active ingredients through the skin. The large surface area of the emulsion system allows rapid penetration of actives.
5) The transparent nature of the system, their fluidity (at reasonable oil concentrations) as well as the absence of any thickeners may give them a pleasant aesthetic character and skin feel.
6) Unlike microemulsions (which require a high surfactant concentration, usually in the region of 20% and higher), nanoemulsions can be prepared using reasonable surfactant concentration. For a 20% o/w nanoemulsion, a surfactant concentration in the region of 5%
10% may be sufficient. Nanoemulsions are usually formulated with surfactants, which are approved for human consumption (GRAS), they can be taken by enteric route.

7) The small size of the droplets allows them to deposit uniformly on substrates. Wetting, spreading and penetration may be also enhanced as a result of the low surface tension of the whole system and the low interfacial tension of the o/w droplets.

8) Nanoemulsions can be applied for delivery of fragrants, which may be incorporated in many personal care products. This could also be applied in perfumes, which are desirable to be formulated alcohol free.

9) Nanoemulsions may be applied as a substitute for liposomes and vesicles (which are much less stable) and it is possible in some cases to build lamellar liquid crystalline phases around the nanoemulsion droplets.

**DISADVANTAGES OF NANOEMULSION DRUG DELIVERY SYSTEMS**

Inspite of the above advantages, nanoemulsions have only attracted interest in recent years for the following reasons.

1) Preparation of nanoemulsions requires in many cases special application techniques, such as the use of high pressure homogenisers as well as ultrasonics. Such equipment (such as the Microfluidiser) became available only in recent years.

2) There is a 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 concentrations of emulsifiers.

3) Lack of understanding of the mechanism of production of submicron droplets and the role of surfactants and cosurfactants.

4) Lack of demonstration of the benefits that can be obtained from using nanoemulsions when compared with the classical macroemulsion systems.

5) Lack of understanding of the interfacial chemistry that is involved in production of nanoemulsion.

**METHODS OF PREPARATION OF NANOEMULSION**

1. **High Pressure Homogenization**

   This technique makes use of high pressure homogenizer/ piston homogenizer to produce nanoemulsions of extremely low particle size (up to 1 nm). During this process, several forces, such as hydraulic shear, intense turbulence and cavitation, act together to yield nanoemulsions with extremely small droplet size. The resultant product can be resubjected to
high pressure homogenization until nanoemulsion with desired droplet size and polydispersity index is obtained. The production of small droplets (submicron) requires application of high energy. Several procedures may be applied to enhance the efficiency of emulsification when producing nanoemulsions. The emulsion is preferably prepared at high volume faction of the disperse phase and diluted afterwards. However, very high phase volume ratios may result in coalescence during emulsification, but more surfactant could be added to create a smaller reduction in effective surface tension and possibly diminishing recoalescence. Surfactant mixtures that show more reduction in surface tension than the individual components could also be used. If possible the surfactant is dissolved in the disperse phase, rather than the continuous phase this often leads to smaller droplets. It may be useful to emulsify in steps of increasing intensity, particularly with emulsions having highly viscous disperse phase.

![Fig. 2: high pressure homogenization showing the formation of nanoemulsion](image)

2. Microfluidization
Microfluidization is a patented mixing technology, which makes use of a device called microfluidizer. This device uses a high pressure positive displacement pump (500 - 20,000 psi), which forces the product through the interaction chamber, consisting of small channels called “microchannels”. The product flows through the microchannels on to an impingement area resulting in very fine particles of submicron 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 introduced into a microfluidizer where it is further processed to obtain a stable nanoemulsion. The coarse emulsion is passed through the interaction chamber of the microfluidizer repeatedly until the desired particle size is obtained. The bulk emulsion is then filtered through a filter under nitrogen to remove large droplets resulting in a uniform nanoemulsion. High pressure homogenization and microfluidization
can be used for fabrication of nanoemulsions at laboratory and industrial scale, whereas ultrasonic emulsification is mainly used at laboratory scale.

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 solubilization of the oil in a microemulsion bicontinuous phase independently of whether the initial phase equilibrium is single or multiphase. Due to their small droplet size nanoemulsions possess stability against sedimentation or creaming with Ostwald ripening forming the main mechanism of nanoemulsion breakdown. Phase inversion in emulsions can be one of two types: transitional inversion induced by changing factors which affect the HLB of the system, e.g. temperature and/or electrolyte concentration, and catastrophic inversion, which can also be induced by changing the HLB number of the surfactant at constant temperature using surfactant mixture Phase inversion temperature (PIT) method employs temperature dependent solubility of nonionic surfactants, such as polyethoxylated surfactants, to modify their affinities for water and oil as a function of the temperature. It has been observed that polyethoxylated surfactants tend to become lipophilic on heating owing to dehydration of polyoxyethylene groups. This phenomenon forms a basis of nanoemulsion fabrication using the PIT method. In the PIT method, oil, water and nonionic surfactants are mixed together at room temperature. This mixture typically comprises o/w microemulsions coexisting with excess oil, and the surfactant monolayer exhibits positive curvature. When this macroemulsion is heated gradually, the polyethoxylated surfactant becomes lipophilic and at higher temperatures, the surfactant gets completely solubilized in the oily phase and the initial o/w emulsion undergoes phase inversion to w/o emulsion. The surfactant monolayer has negative curvature at this stage. This method involves heating of the components and it may be difficult to incorporate thermolabile drugs, such as tretinoin and peptides, without affecting their stability. Although it may be possible to reduce the PIT of the dispersion using a mixture of components (surfactants) with suitable characteristics, in order to minimize degradation of thermolabile drugs.

4. Solvent Displacement Method
The solvent displacement method for spontaneous fabrication of nanoemulsion has been adopted from the nanoprecipitation method used for polymeric nanoparticles. In this method, oily phase is dissolved in watermiscible organic solvents, such as acetone, ethanol and ethyl
methyl ketone. The organic phase is poured into an aqueous phase containing surfactant to yield spontaneous nanoemulsion by rapid diffusion of organic solvent. The organic solvent is removed from the nanoemulsion by a suitable means, such as vacuum evaporation. Spontaneous nanoemulsification has also been reported when solution of organic solvents containing a small percentage of oil is poured into aqueous phase without any surfactant.

Solvent displacement methods can yield nanoemulsions at room temperature and require simple stirring for the fabrication. Hence, researchers in pharmaceutical sciences are employing this technique for fabricating nanoemulsions mainly for parenteral use. However, the major drawback of this method is the use of organic solvents, such as acetone, which require additional inputs for their removal from nanoemulsion. Furthermore, a high ratio of solvent to oil is required to obtain a nanoemulsion with a desirable droplet size. This may be a limiting factor in certain cases. In addition, the process of solvent removal may appear simple at laboratory scale but can pose several difficulties during scaleup.

5. Phase Inversion Composition Method (Self-Nanoemulsification Method)

This method has drawn a great deal of attention from scientists in various fields (including pharmaceutical sciences) as it generates nanoemulsions at room temperature without use of any organic solvent and heat. Kinetically stable nanoemulsions with small droplet size (~50 nm) can be generated by the stepwise addition of water into solution of surfactant in oil, with gentle stirring and at constant temperature. The spontaneous nanoemulsification has been related to the phase transitions during the emulsification process and involves lamellar liquid crystalline phases or D-type bicontinuous microemulsion during the process. Nanoemulsions obtained from the spontaneous nanoemulsification process are not thermodynamically stable, although they might have high kinetic energy and long-term colloidal stability.

APPLICATIONS OF NANOEMULSIONS IN DRUG DELIVERY

1. Nanoemulsions And 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.

2. Nanoemulsions And Transdermal Delivery

Drug delivery through the skin to the systemic circulation is convenient for a number of clinical conditions due to which there has been a considerable interest in this area. It offers the advantage of steady state controlled drug delivery over extended period of time, with self administration also being possible, which may not be the case with parenteral route. The drug input can be eliminated at any time by the patient just by removing the transdermal patch. Their transparent nature and fluidity, confers on nanoemulsions a pleasant skin feel. An extra advantage is the total absence of gastrointestinal side effects like irritation and bowel ulcers which are invariably associated with oral delivery. Transdermal drug products have been developed for a number of diseases and disorders including cardiovascular conditions, Parkinsons’ and Alzheimer diseases, anxiety, depression, etc. However, the fundamental disadvantage which limits the use of this mode of administration is the barrier imposed by the skin for effective penetration of the bioactives. The three routes by which drugs can primarily penetrate the skin are through the hair follicles, sweat ducts or directly across stratum corneum, which restricts their absorption to a large extent and limits their bioavailability. For improved drug pharmacokinetics and targeting, the primary skin barriers need to be overcome. Also the locally applied drug redistribution through cutaneous blood and lymph vessel system needs to be controlled. Nano sized emulsions are able to easily penetrate the pores of the skin and reach the systemic circulation thus getting channelized for effective delivery. Caffeine has been used for treatment of different types of cancer by oral delivery. Water-in-oil nanoemulsion formulations of caffeine have been developed for transdermal drug delivery.

3. Nanoemulsions And Parenteral Drug Delivery

This is one of the most common and effective routes of drug administration usually adopted for actives with low bioavailability and narrow therapeutic index. Their capacity to dissolve large quantities of hydrophobics, together with their mutual compatibility and ability to pro-
tect the drugs from hydrolysis and enzymatic degradation make nanoemulsions ideal vehicles for the purpose of parenteral transport. Further, the frequency and dosage of injections can be reduced throughout the drug therapy period as these emulsions guarantee the release of drugs in a sustained and controlled mode over long periods of time. Additionally, the lack of flocculation, sedimentation and creaming, combined with a large surface area and free energy, offer obvious advantages over emulsions of larger particle size, for this route of administration. Their very large interfacial area positively influences the drug transport and their delivery, along with targeting them to specific sites.

4. Nanoemulsions And Drug Targeting

Another interesting application, which is experiencing an active development, is the use of nanoemulsion formulations, for controlled drug delivery and targeting. Because of their submicron size, they can easily be targeted to the tumor area. Although nanoemulsions 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. The development of magnetic nanoemulsions is an innovative approach for cancer therapy. These can deliver photosensitizers like Foscan® to deep tissue layers across the skin thereby inducing hyperthermia for subsequent free radical generation. This methodology can be used for the treatment of cancer in the form of photodynamic therapy.

5. Nanoemulsions And Vaccine Delivery

A vaccine carrier system using nanoemulsions is currently being researched. This medication delivery system uses nanotechnology 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. The oil-based emulsion is administered in the nose, as opposed to traditional vaccine routes. Research is demonstrating that genital mucosal immunity may be attained with vaccines that are administered into the nasal mucosa.

6. Nanoemulsions And Pulmonary Drug Delivery

Until now, the submicron emulsion system has not yet been fully exploited for pulmonary drug delivery and very little has been published in this area. Emulsion systems have been introduced as alternative gene transfer vectors to liposomes. Other emulsion studies for gene delivery (non-pulmonary route) have shown that binding of the emulsion/DNA complex was
stronger than liposomal carriers. This stable emulsion system delivered genes more efficiently than liposomes. Bivas-Benita et al. reported that cationic submicron emulsions are promising carriers for DNA vaccines to the lung since they are able to transfect pulmonary epithelial cells, which possibly induce cross priming of antigen-presenting cells and directly activate dendritic cells, resulting in stimulation of antigen specific T-cells. Therefore the nebulization of submicron emulsions will be a new and upcoming research area. However, extensive studies are required for the successful formulation of inhalable submicron emulsions due to possible adverse effects of surfactants and oils on lung alveoli function (adverse interactions with lung surfactant).

7. Prophylactic In Bio-Terrorism Attack
Based on their antimicrobial activity, research has begun on use of nanoemulsion as a prophylactic medication, a human protective treatment, to treat people exposed to bio attack pathogens such as anthrax and ebola. A broad spectrum nanoemulsion was tested on surfaces by the USA army in Dec 1999 for decontamination of Anthrax spore surrogates. It was tested again by RestOps in March 2001 as a chemical decontamination agent. All tests were successful. The technology has been tested on gangrene and Clostridium botulism spores and can even be used on contaminated wounds to salvage limbs. The nanoemulsion technology can be formulated into a foam, liquid, cream, or spray to decontaminate a variety of materials as has been done by NanoBio Corporation.

Other Applications of Nanoemulsion
1. Use of nanoemulsions in cosmetics.
2. Antimicrobial Nanoemulsions.
4. Nanoemulsions as Mucosal Vaccines.
5. Nanoemulsion as Non-Toxic Disinfectant Cleaner.
7. Nanoemulsion formulations for improved oral delivery of poorly soluble drug
9. Nanoemulsions as a vehicle for transdermal deliver.
10. Nanoemulsion 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. Nanoemulsion in cancer therapy and in targeted drug delivery.

CHARACTERIZATION AND EVALUATION OF NANOEMULSION

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

1. Nanoemulsion Droplet Size Analysis

Droplet size distribution is one of the important physicochemical characteristics of a nanoemulsion, 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 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 nanoemulsions, 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.

2. Polydispersity Index

The average diameters and polydispersity index of samples were measured by photon correlation spectroscopy. The measurements were performed at 25°C using a He-Ne laser.

3. 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.
4. **Refractive Index**

The refractive index, n, of a medium is defined as the ratio of 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. 

\[ n = \frac{c}{v_p} \]

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

5. **pH**

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

6. **Transmission Electron Microscopy (TEM)**

Morphology and structure of the nanoemulsion 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 nanoemulsion droplets. Observations were performed as, a drop of the nanoemulsion was directly deposited on the holey film grid and observed after drying.

7. **Drug Content**

Drug content was determined by reverse phase HPLC method using C18 column.

8. **Zeta Potential**

Zeta potential is a technique which is used to measure the surface charge properties and further the long term physical stability of nanoemulsions, the instrument which is used to measure the surface charge is known as ZetaPALS. The measurements were carried out with diluted nanoemulsion formulations 16 and its values were determined from the electrophoretic mobility of the oil droplets. The minimum zeta potential of ±20mv is desirable.

9. **Percentage Transmittance**

Percentage transmittance of the prepared nanoemulsion formulations was determined spectrophotometrically using UV-VIS Spectrophotometer.

10. **In Vitro Skin Permeation Studies**

In vitro skin permeation studies were performed by using Keshary Chien diffusion cell. It was performed on abdominal skins and was obtained from male rats weighing 250±10 gm with 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 37°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. 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.

11. Thermodynamic Stability Studies
During the thermodynamic stability of drug loaded Nanoemulsions following stress tests as reported.

11.1 Heating Cooling Cycle
Nanoemulsion formulations were subjected to six cycles between refrigerator temperature (4°C) and 45°C. Stable formulations were then subjected to centrifugation test.

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

11.3 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°C at ambient humidity. The samples were withdrawn at regular intervals of 0, 1, 2 and 3 months.

NANOEMULSION INSTABILITY AND ITS PREVENTION METHODS
months and were analyzed for drug content by stability-indicating HPLC method. The instability of nanoemulsions is due to some main factors including creaming, flocculation, coalescence and Ostwald ripening. Among them ostwald ripening is the main mechanism of nanoemulsion instability because rest of the problem are minimized by the small size of nanoemulsion and use of nonionic type of surfactant. Creaming of nanoemulsion is prevented by the faster diffusion rate of smaller droplets. Vanderwall force is responsible for the
attraction of droplets and leads to the flocculation of emulsion. But in case of nanoemulsion nonionic surfactant, it does not create any kind of attractive force, hence no flocculation occurs. The droplet size of nanoemulsion also prevent the flocculation because these small droplets show high curvature and laplace pressure opposes the deformation of large droplets. Coalescence of droplets of nanoemulsion can be prevented by a thick multilamellar surfactant film adsorbed over the interface of droplets.

The only problem of instability of nanoemulsion can arise by the ostwald ripening. In ostwald ripening small droplets with high radius of curvature converted into large droplets with low radius of curvature. Two droplets diffuse and become one large droplet. Thus, after the storage for a long time period, droplets size distribution shifted to large sizes and the transparency of nanoemulsion become turbid. It is also identified that ostwald ripening create a problem during the delivery of formulations. Several theories have been suggested for the demonstration of ostwald ripening, among them LSW theory properly justified the factors affecting the ostwald ripening. Tadros et al demonstrated the addition of a small amount of insoluble oil (squalane) can reduce the diffusion of the smaller oil droplets from the small to the large droplet. Another method to prevent the effect of ostwald ripening is addition of polymeric surfactant on the interface which increase the elasticity of droplets and further reduce the effect of ostwald ripening.

Paqui Izquier do et al successfully demonstrates the influence of surfactant mixing ratio on the stability of nanoemulsion when phase inversion transition method are used as a nanoemulsion preparation method. The formation of O/W nanoemulsions by the PIT emulsification method in water/mixed nonionic surfactant/oil systems was studied. The hydrophilic-lipophilic properties of the surfactant were varied by mixing polyoxyethylene 4-lauryl ether (C₁₂E₁₄) and polyoxyethylene 6-lauryl ether (C₁₂E₆). Emulsification was performed in samples with constant oil concentration (20 wt%) by fast cooling from the corresponding HLB temperature to 25 °C. Nanoemulsions with droplet radius 60-70 nm and 25-30 nm were obtained at total surfactant concentrations of 4 and 8 wt%, respectively. The nanoemulsion with 8% surfactant ratio was showing high stability over the nanoemulsion with 4% surfactant concentration. In another study Sher L. et al successfully demonstrated the effect of process variables over the droplet size of nanoemulsion which further leads to the stability of nanoemulsion. In the work they studied the formation and stability of n-decane in water nanoemulsion produced by the PIT method by using polyoxyethylene lauryl
ether as a surfactant. The result of this work clearly indicate that the droplet size of nanoemulsion depends on the various process variables such as heating and cooling temperature of formulations and final temperature to which the mixture is cooled after phase inversion.

In another investigation the influence of both, the nature of the surfactant and surfactant concentration on the processes of droplet breakup and coalescence in the formation of decane in water nanoemulsions in a high-pressure homogenizer were investigated. Food proteins, phosphatidylglycerol and phosphatidylcholine were used as surfactant by varying concentration and droplet size were investigated for each formulation. It was found that for the proteins the increase in droplet volume was shown to be linear with respect to time, indicating an Ostwald ripening process. Although there was coalescence on storage at the lowest concentrations of phospholipids used, there was no observed ripening at any emulsifier concentration showing that phospholipids interfaces are structured in such a way as to resist ripening. It is demonstrated that the mixture of surfactant enhances the stability a compared to single surfactant by Porras M. It was also demonstrated that the stability of the electrostatically- and sterically stabilized dispersions can be controlled by the charge of the electrical double layer and the thickness of the droplet surface layer formed by nonionic emulsifier.

**FUTURE INDUSTRIAL PERSPECTIVES**

Nanoemulsion since its emergence has proved to be versatile and useful novel drug delivery system. Nanoemulsions are proposed for numerous applications in pharmacy as drug delivery systems because of their capacity of solubilizing non polar active compounds. Future perspectives of nanoemulsion are very promising in different fields of therapeutics or application in development of cosmetics for hair or skin. One of the versatile applications of nanoemulsions is in the area of drug delivery where they act as efficient carriers for bioactives, facilitating administration by various routes. Their parenteral delivery has been adopted for supplying nutriational requirements, controlled drug release, vaccine delivery and for drug targeting to specific sites. The advantages and applications of oral drug delivery through these vehicles are numerous where the droplet size is related to their absorption in the gastrointestinal tract. Pulmonary and transdermal routes are other successful ways of administering nanoemulsified delivery system. Although there have not been many reports of nanoemulsion applications in other fields, there is a great potential for nanoemulsion
applications in other areas, such as in chemical and physical sciences, agriculture and engineering.

CONCLUSION
Nanoemulsion 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, Nanoemulsions have been used in clinics for more than four decades as total parenteral nutrition fluids. Nanoemulsions 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 tumor area. Moreover, targeting moiety has opened new avenues for targeted delivery of drugs, genes, photosensitizers, and other molecules to the tumor area. It is expected that further research and development work will be carried out in the near future for clinical realization of these targeted delivery vehicles.

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