Review Article

Nanoemulsion: As Pharmaceutical Overview

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ABSTRACT

Nanoemulsions are thermodynamically stable transparent nano-sized dispersions of oil-in-water (o/w) or water-in-oil (w/o) stabilized by an interfacial film of surfactant and cosurfactant molecule having the droplet size 10–100 nm. One of the unique characteristics of the NE technology is the relatively high percentage of total particle volume occupied by the internal hydrophobic oil core of the droplets. The efficacy of the nanoemulsion is enhanced by the nature and type of surfactant and co-surfactant used. This review specially focuses on the components used, merits and demerits of nanoemulsions, method of preparation and application of nanoemulsions as efficient drug delivery system. The applications of nanoemulsion are limited by the instability. Stability of formulation may be enhanced by controlling factors such as type and concentration of surfactant and cosurfactant, type of oil phase, methods used, process variables and addition of additives.

Keywords: Nanoemulsion, Oil-in-water (o/w), Water-in-oil (w/o), surfactant.

INTRODUCTION

The nanoemulsion is one of the most efficient dispersed nanosystems of droplet size ranging to submicron size. Nanoemulsion are generally transparent or semitransparent system characterized by high stability. Submicron droplet size and high surfactant concentration makes it an efficient transdermal delivery vehicle.

Research works proves that nanoemulsion is far more efficient drug delivery system than other transdermal drug delivery system.

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.

Transdermal route using nanoemulsion technique has been investigated to eliminate oral GI adverse effects, maintains the plasma drug level for longer period of time, improve patient compliance and suitable for long treatment of arthritis.

Nanoemulsions are thermodynamically stable transparent or translucent nano-sized dispersions of oil-in-water (o/w) or water-in-oil (w/o) stabilized by an interfacial film of surfactant and cosurfactant molecule having the droplet size 10–100 nm.

One of the unique characteristics of the NE technology is the relatively high percentage of total particle volume occupied by the internal hydrophobic oil core of the droplets. This provides high solubilization of lipophilic compound as compared to other lipoidal vehicle such as liposomes.

Nanoemulsions are also referred to as miniemulsions, ultrafine emulsions and submicron emulsions.

Advantages of Nano Emulsion[1-8]

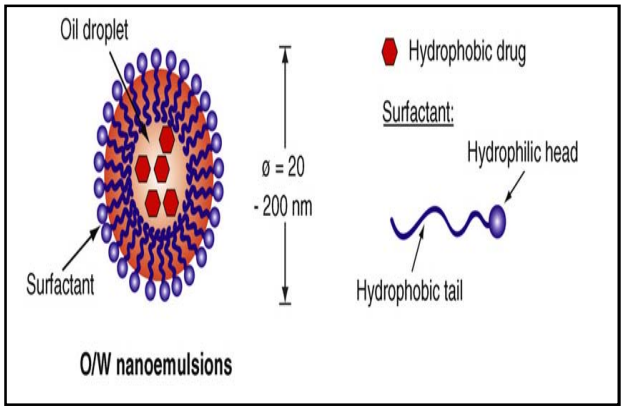

Figure 1: O/W nanoemulsion

1. Nanoemulsion is the approach to improve water solubility and ultimate bioavailability of lipophilic drugs. The nano-sized droplets leading to enormous interfacial areas associated with nanoemulsions would influence the transport properties of the drug, an important factor in sustained and targeted drug delivery.
2. Nanoemulsions have been reported to make the plasma concentration profiles and bioavailability of drugs more reproducible.
3. Fine oil droplets empty rapidly from the stomach and promote wide distribution of the drug throughout the intestinal tract and thereby minimizing irritation frequently encountered with extended contact of the drug and gut wall.
4. Higher solubilization capacity than simple micellar solutions and their thermodynamic stability offers advantages over unstable dispersions such as emulsions and suspensions because they can be

manufactured with little energy input (heat or mixing) and have a long shelf life.

5. They also provide ultra-low interfacial tension and large o/w interfacial areas.
6. They also offer an advantage over existing self-emulsifying system in terms of rapid onset of action (no extra time for dispersion) and reduced inter subject variability in terms of GIT fluid volume.
7. They possess high kinetic stability and optical transparency resembling to Microemulsions.
8. The structures in the nanoemulsions are much smaller than the visible wavelength, so most nanoemulsions appear optically transparent, even at large loading.
9. They have potential to deliver peptides that are prone to enzymatic hydrolysis in GIT.
10. Nanoemulsions have higher surface area and higher free energy than macro emulsions that make them an effective transport system.
11. Problems of inherent creaming, flocculation, coalescence, and sedimentation are not seen in nanoemulsions, which are commonly associated with macroemulsions.
12. Nanoemulsions can be formulated in numerous dosage foam such as creams, liquids, sprays and foams.
13. It is non-toxic and non-irritant so can be easily applied to skin and mucous membranes.
14. Nanoemulsions are formulated with surfactants, which are approved for human consumption (GRAS) so they can be taken by enteric route.
15. It is do not damage healthy human and animal cells, so nanoemulsions are suitable for human and veterinary therapeutic purposes.

Disadvantages of Nano Emulsion[1,20]

1. Use of a large concentration of surfactant and co-surfactant necessary for stabilizing the nanodroplets.
2. Limited solubilizing capacity for high-melting substances.
3. The surfactant must be nontoxic for using pharmaceutical applications.
4. Nanoemulsion stability is influenced by environmental parameters such as temperature and pH.
5. 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.
6. Lack of understanding of the mechanism of production of submicron droplets and the role of surfactants and cosurfactants.
7. Lack of demonstration of the benefits that can be obtained from using nanoemulsions when compared with the classical macroemulsions systems.
8. Lack of understanding of the interfacial chemistry that is involved in production of nanoemulsions.

Components of Nano Emulsion[12,15]

Nanoemulsions contain three main components.

1. Oil
2. Surfactant/cosurfactant
3. Aqueous Phase

Oil

Solubility of the drug in the oil phase is an important criterion for the selection of oils. This is particularly important in the case of oral formulation development, as the ability of 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 cosurfactant is contributing to drug solubilization, there could be a risk of precipitation, as dilution of nanoemulsion in the gastrointestinal tract will lead to lowering of the solvent capacity of the surfactant or cosurfactant.

Surfactant

Surfactants used for stabilizing the systems there are three types of surfactant anionic, cationic, and nonionic. Nonionic surfactants are relatively less toxic than their ionic counterparts and typically have lower CMCs. Also, o/w nanoemulsion dosage forms for oral or parenteral use based on nonionic surfactants are likely to offer *in vivo* stability. Therefore, proper selection of surfactants becomes a crucial factor. Another important criterion is the selection of surfactant with proper HLB value. Hydrophilic surfactant and cosurfactant are considered to prefer the interface and to lower the necessary energy to form the nanoemulsions, consequently improving the stability. For example, the required HLB value to form o/w nanoemulsions is greater than 10. The right blend of low and high HLB surfactants leads to the formation of a stable nanoemulsion upon dilution with water.

Classification of surfactant[13]

1. Nonionic - Fatty alcohols, Glycerol esters, Fatty acid esters.
2. Anionic - Carboxylate groups, Soaps, Sulfonates, Divalent ions.
3. Cationic Amines and quaternary ammonium compounds.

Cosurfactant

Cosurfactants are added to obtain nanoemulsion systems at low surfactant concentration. Short- to medium-chain-length alcohols (C3–C8) are commonly added as

cosurfactants, which further reduce the interfacial tension and increase the fluidity of the interface. They also increase the mobility of the hydrocarbon tail and allow greater penetration of the oil into this region. Alcohols may also increase the miscibility of the aqueous and oily phases due to its partitioning between these phases. Therefore, ethanol, isopropyl 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.

Table 1: Cosurfactant used in preparation of nanoemulsion[19]

S.No	oil	surfactant	Cosurfactants
1	Captex 355	Capryol 90	Transcutol p
2	Captex 200	Tween 80	Glycerin, Ethylene glycol
3	Captex 8000	Lauroglycol 90	Propylene glycol
4	Witepsol	PEG MW > 4000	Ethanol
5	Isopropyl Myristate	Poloxamer 124 and 188	Propanol

Factors Affecting Formulation of Nano Emulsion[18]

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 nano scale to be rapidly coated during emulsification there by inhibiting induced 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 of 10-100 atm.

Methods of Preparation of Nano Emulsion[13-15, 19, 20]

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 re-subjected 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.

Figure 2: High pressure homogenizer

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 micro-channels 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.

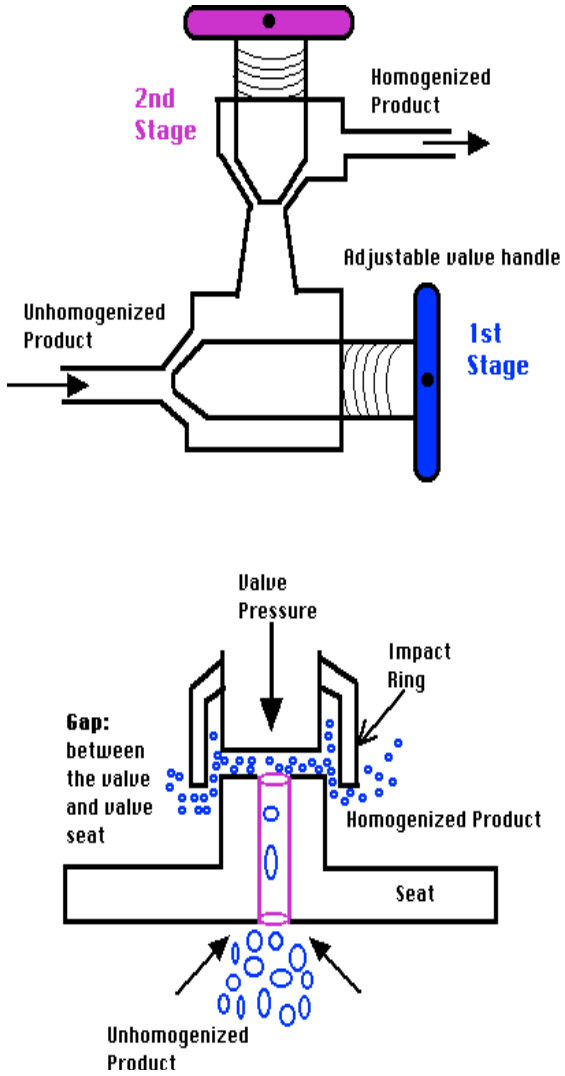

Figure 3: Microfluidizer

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 mixtures.

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 macroemulsions 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.

Solvent Displacement Method

The solvent displacement method for spontaneous fabrication of nanoemulsion has been adopted from the nano- precipitation method used for polymeric nanoparticles. In this method, oily phase is dissolved in water-miscible 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 scale-up.

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.

Ultrasonication

The preparation of Nanoemulsion is reported in various research papers which aim to use the ultrasonic sound frequency for the reduction of the droplet size. Another approach is the use of a constant amplitude sonotrode at system pressures 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 increases the collapse pressure of cavitations bubbles. This means that the collapse of the bubbles when cavitation occurs becomes stronger and more violent than when the pressure is at atmospheric conditions. As cavitation is the most important mechanism of power dissipation in a 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.

Figure 4: Probe Sonicator Used in Laboratory Scale for Preparation of NanoEmulsion

Characterization of NanoEmulsions[16-19]

The droplet size, viscosity, density, turbidity, refractive index, phase separation and pH measurements shall be performed to characterize the Nanoemulsion. The droplet size distribution of Nanoemulsion vesicles can be determined by either light scattering technique or electron microscopy. This technique has been advocated as the best method for predicting Nanoemulsion stability.

Dye Solubilization

A water soluble dye is solubilized within the aqueous phase of the W/O globule but is dispersible in the O/W globule. An oil soluble dye is solubilized within the oil phase of the O/W globule but is dispersible in the W/O globule.

Dilutability Test

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

Conductance Measurement

O/W Nanoemulsion where the external phase is water are highly conducting whereas W/O are not, since water is the internal or dispersal phase. To determine the temperature of the continuous phase and to detect phase inversion phenomena, the electrical conductivity measurements are highly useful.

A sharp increase in conductivity in certain W/O Nanoemulsion systems was observed at low volume fractions and such behaviour was interpreted as an indication of a 'percolative behaviour' or exchange of ions between droplets before the formation of bicontinuous structures.

Dielectric measurements are a powerful means of probing both structural and dynamic features of Nanoemulsion systems.

Dynamic light-scattering measurements

The DLS measurements are taken at 90° in a dynamic light scattering spectrophotometer which uses a neon laser of wavelength 632 nm. The data processing is done in the built-in computer with the instrument.

Polydispersity

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.

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.

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 refractrometer (Nirmal International) at 25±0.5°C.

Interfacial Tension

The formation and the properties of Nanoemulsion 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°C by a thermobath and the samples for the measurement are to be immersed in it before testing.

Thermodynamic Stability Studies

During the thermodynamic stability of drug loaded Nano-emulsions following stress tests as reported.

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.

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.

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.

In-vitro Drug Permeation Studies

Release studies can be performed using vertical passive diffusion cells (HTD 96, HT Dialysis, USA), with a cellulose membrane. The cellulose (molecular weight<12 000) membrane was first hydrated in the buffer solution at 20°C for 24 hours. The receptor solution will contain 0.20 mL of phosphate buffer pH 7.4 containing 1% SLS (Sodium laurylsulphate) to, and it will be maintained at 37°C ± 0.5°C using a thermostatic shaker bath and stirr at 200 rpm throughout the experiment. The donor compartment will contain 0.2 ml of nanoemulsion sample.

The release can be modulated (or) altered based on pharmacokinetic needs by selecting appropriate Formulation excipients at right composition. For example the formulation scientist can tailor the formulation for Sustained or immediate release by choosing high solubilizing oil or low solubilizing oil respectively. Also by reducing the oil content with respect to the aqueous content will give slightly enhanced flux with high solubilizing oil. The flux can be further increased by using high amount of surfactant in the nanoemulsion system irrespective of the solubilizing nature of the oil, since drug will be soluble in the surfactant solution. Another way of increasing the flux would be selection of low solubilizing oil with high amount of aqueous content for highly lipophilic compound. The sustained release can be achieved either by means of using high amount of medium/high solubilizing oils. There are several biological factors should be considered like thickness of the diffusion membrane, unionized state of the molecule at the absorption site because their degree of ionization depends upon the pH of the biological fluid. Only the unionized fraction of the drug, if sufficiently lipid soluble can permeate the membrane passively until the concentration of unionized drug on either side of the membrane becomes equal until equilibrium is attained. Also the amount of fluid available at the site, where dilution can takes place after ingestion of nanoemulsion will determine the effective formation of micro droplets. The existence of bile salts and few surfactants in biological system will also help in the effective formation of micro droplets along with the peristaltic movement present in the stomach.

Determination of permeability coefficient and flux

Excised human cadaver skin from the abdomen can be obtained from dead who have undergone postmortem not more than 5 days ago in the hospital. The skin is stored at 4°C and the epidermis separated. The skin is first immersed in purified water at 60°C for 2 min and the epidermis then peeled off. Dried skin samples can be kept at 20°C for later use. Alternatively the full thickness dorsal skin of male hairless mice may be used. The skin shall be excised, washed with normal saline and used. The passive permeability of lipophilic drug through the skin is investigated using Franz diffusion cells with known effective diffusional area. The hydrated skin samples are used. The receiver compartment may contain a complexing agent like cyclodextrin in the receiver phase, which shall increase the solubility and allows the maintenance of sink conditions in the experiments. Samples are withdrawn at regular interval and analyzed for amount of drug released.

Applications of NanoEmulsions[13,14,17-19]

Nanoemulsions containing pharmaceutically active agents can be utilized for the production of pharmaceutical preparations. If desired a special galenic form can be imparted to the mixture. Ampoules, especially sterile injection and infusion solutions; solutions, especially oral liquids, eye drops and nose drops which can contain various auxiliary substances can be formulated in the form of nanoemulsion; aerosols without metering feature and dosing aerosols, which can contain propellant gas and stabilizers besides the nanoemulsion; hydrophilic and hydrophobic gels and ointments containing the nanoemulsion; o/w or w/o creams containing the nano-

emulsion; lotions and pastes containing the nanoemulsion are available in the market.

Ocular delivery

Oil in water emulsions are being explored for improved topical lipophilic drug delivery to the eye. Examples: Piroxicam, Pilocarpine, Indomethacin, cyclosporine - A.

Percutaneous route

Many drugs exhibit low skin permeation, which results in poor efficacy. Common chemical skin penetration enhancers, organic solvents are generally associated to some degree with skin irritation, toxicity and sensitization. A solvent free topical vehicle based on drug entrapment in the o/w emulsion droplets of submicron size is more efficacious in terms of percutaneous absorption with possibly devoid of adverse effects. Examples: NSAIDs, Diazepam, α-tocopherol antifungal drugs (Econazole or Miconazole nitrate) EMLA (Eutectic Mixtures of local anesthetic) have proven to be useful medication by this route.

Nasal route

The nasal route has received great attention due to number of advantages over parenteral and oral administration especially by bypassing the liver. Nanoemulsions increase absorption by solubilizing the drug in the inner phase of an emulsion and prolonging contact time between emulsion droplets and nasal mucosa. Examples: Lipid soluble renin inhibitor was incorporated into an O/W emulsion, insulin and testosterone can also be delivered by this route.

Use of nanoemulsion in cosmetics

Nanoemulsions are recently becoming increasingly important as potential vehicles for the controlled delivery of cosmetics and for optimized dispersion of active ingredients into skin. Nanoemulsion gain increasing interest due to their own bioactive effects. Nanoemulsions are acceptable in cosmetics because there is no inherent creaming, sedimentation, flocculation or coalescence observed with macro emulsions.

Antimicrobial Nanoemulsions

Antimicrobial nanoemulsions are oil in water droplets with size range from 200-600n.m. The nanoemulsion particles are thermodynamically driven to fuse with lipid containing organisms.

When enough nano particles fuse with the pathogens, they release part of the energy trapped within the emulsion. Both the active ingredient and the energy released destabilize the pathogen lipid membrane, resulting in cell lysis and death.

Nanoemulsion has broad spectrum activity against bacteria (e.g. E. Coli, Salmonella, S. aureus) enveloped viruses (e.g. HIV, Herpes Simplex), Fungi (e.g. Candida, Dermatophytes) and spores (e.g. anthrax).

In Biotechnology

Many enzymatic and biocatalytic reactions are conducted in pure organic or aqua-organic media. Biphasic media are also used for these types of reactions. The use of pure apolar media causes the denaturation of biocatalysts. The use of water-proof media is relatively advantageous.

Transdermal

Indomethacin a potent NSAID, the anti-inflammatory effects of true optimized nanoemulsion formulation were compared with marketed gel in carragenan induced paw edema in rats. The % inhibition value was significant for developed Nanoemulsion, so great potential for transdermal application of Indomethacin. Nanoemulsions for transdermal delivery of celecoxib. Formulation which consisted of 2% celecoxib 10% oil phase (Sefsol 218 and Triacetin) 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 aceclofenacnano emulsion (82.2%) as compared to nanoemulsion gel formulation (71.4%) and conventional gel.

CONCLUSION

Overall nanoemulsion formulation may be considered as effective, safe and patient compliance formulation for the delivery of pharmaceuticals. One of the unique characteristics of the NE technology is the relatively high percentage of total particle volume occupied by the internal hydrophobic oil core of the droplets. This provides high solubilization of lipophilic compound as compared to other lipoidal vehicle such as liposomes. This review specially focuses on the components used, merits and demerits of nanoemulsions, method of preparation and application of nanoemulsions as efficient drug delivery system. The applications of nanoemulsion are limited by the instability. Stability of formulation may be enhanced by controlling factors such as type and concentration of surfactant and cosurfactant, type of oil phase, methods used, process variables and addition of additives.

Future Industrial Prospectives

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 nutritional 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. Nanoemulsions have also been studied for their use in ocular delivery where pharmacological drugs are more sustained compared to their respective solutions. 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.

Table 2: Patents on nanoemulsion formulations.

Patent Claim	Assignee	Patent Number
Transparent nanoemulsion less than 100 nm based on fluid non-ionic amphiphilic lipids and use in cosmetics or in dermopharmaceuticals	L'Oreal (Paris, FR)	US Patent number: 5,753,241
Nanoemulsions based on sugar fatty ethers and its uses in the cosmetics, dermatological and/ophthalmological fields	L'Oreal (Paris, FR)	US Patent number: 6,689,371
Non-toxic antimicrobial compositions and methods of use	NanoBio Corporation US	Patent Number: 6,559.189 and 6,635,676
Method of preventing and treating microbial infections	NanoBio Corporation US	Patent Number: 6,506,803
Nanoemulsion of 5-aminolevulinic acid	ASAT AG Applied Science and Technology (Zug, CH)	PCT/EP99/08711
Nanoemulsion of poorly soluble pharmaceutical active ingredients and methods of making the same	WO/2007/103294	
Nanoemulsion based on ethylene oxide & propylene oxide block copolymers and its use in the cosmetics, dermatological & ophthalmological fields	L'Oreal (Paris, FR)	Patent Number: 6,464,990
Nanoemulsion based on glycerol fatty esters and its uses in cosmetics, dermatological & ophthalmological fields	L'Oreal (Paris, FR)	Patent Number: 6,541,018
Nanoemulsions based on oxyethylenated or non-oxyethylenatedsorbitan fatty esters and its uses in cosmetics, dermatological and ophthalmological fields	L'Oreal (Paris, FR)	Patent Number: 6,335,022
Nanoemulsions based on phosphoric acid fatty acid esters and its uses in cosmetics, dermatological and/ ophthalmological fields	L'Oreal (Paris, FR)	Patent Number: 6,274,150

Table 3: Marketed nanoemulsion formulations.

Drug/Bioactive	Brand Name	Manufacturer	Indication
Palmitatealprostadil	Liple	Mitsubishi Pharmaceutical, Japan	Vasodilator, platelet inhibitor
Dexamethason	Limethason	Mitsubishi Pharmaceutical, Japan	Steroid
Propofol	Diprivan	Astra Zaneca	Anesthetic
Flurbiprofenaxtil	Ropion	Kaken Pharmaceutical, Japan	NSAID
Vitamins A, D, E and K	Vitalipid	Fresenius Kabi Europe	Parenteral nutrition

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