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AN OVERVIEW ON NANOEMULSION: A NOVEL APPROACH

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ABSTRACT

The nanoemulsion is one of the most efficient dispersed nanosystems of droplet size ranging to submicron size. **Nanoemulsions/ Sub-micron emulsions (SMEs)/ Mini-emulsions** are thermodynamically stable transparent or translucent dispersions of oil and water stabilized by an interfacial film of surfactant and co surfactant molecules having a droplet size of less than 100 nm. This review provides brief information about method of preparation and evaluation of nanoemulsion as drug carriers for improving the delivery of therapeutic agents. several techniques are to be used for preparation of nanoemulsions like microfluidization, high pressure homogenization, low energy emulsification and solvent evaporation method and parameter that are to be used for its characterization like droplet size analysis, viscosity determination, drug content, refractive index, pH, zeta potential, Transmission electron microscopy, thermal stability, release and *in vitro* skin permeation study.

INTRODUCTION: Nanoemulsions/Sub-micron emulsions (SMEs)/Mini-emulsions/Ultrafine emulsions [1, 2] are thermodynamically stable transparent (translucent) dispersions of oil and water stabilized by an interfacial film of surfactant and cosurfactant molecules having a droplet size of less than 100 nm. Nanoemulsion, which is categorized as multiphase colloidal dispersion, is generally characterized by its stability and clarity. The dispersed phase typically comprises small particles or droplets, with a size range of 5 nm-200 nm, and has very low oil/water interfacial tension. Because the droplet size is less than 25% of the wavelength of visible light, Nanoemulsions are transparent [2]. Nanoemulsion is formed readily and sometimes spontaneously, generally without high-energy input. In many cases a cosurfactant or cosolvent is used in addition to the surfactant, the oil phase and the water phase.

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

- Oil in water Nanoemulsions wherein oil droplets are dispersed in the continuos aqueous phase;
- Water in oil Nanoemulsions wherein water droplets are dispersed in the continuous oil phase;
- Bi-continuous Nanoemulsions wherein microdomains of oil and water are interdispersed within the system.[3]

In all three types of Nanoemulsions, the interface is stabilized by an appropriate combination of surfactants and/or co-surfactants.

The key difference between emulsions and Nanoemulsions are that the former, whilst they may exhibit excellent kinetic stability, are fundamentally thermodynamically unstable and will eventually phase separate. Another important difference concerns their appearance; emulsions are cloudy while Nanoemulsions are clear or translucent. In addition, there are distinct differences in their method of preparation, since emulsions require a large input of energy while Nanoemulsions do not [3, 4].

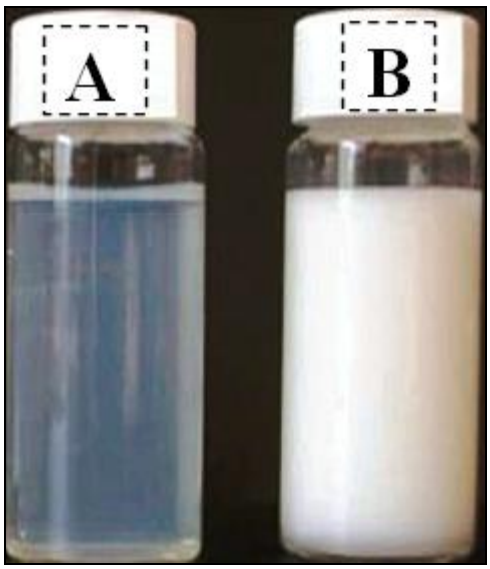

FIG. 1: (A) NANOEMULSION AND (B) MACROEMULSION WITH DROPLET DIAMETERS OF LESS THAN 100 NM AND MORE THAN 1000 NM, RESPECTIVELY[5]

Advantages of Nanoemulsion over Other Dosage Forms [1, 2];

1. Increase the rate of absorption.
2. Eliminates variability in absorption.
3. Helps in solublizing lipophilic drug.
4. Provides aqueous dosage form for water insoluble drugs.
5. Increases bioavailability.
6. Various routes like tropical, oral and intravenous can be used to deliver the product.
7. Rapid and efficient penetration of the drug moiety.
8. Helpful in taste masking.
9. Provides protection from hydrolysis and oxidation as drug in oil phase in O/W Nanoemulsion is not exposed to attack by water and air.
10. Liquid dosage form increases patient compliance.
11. Less amount of energy requirement.
12. Nanoemulsions are thermodynamically stable system and the stability allows self emulsification of the system whose properties are not dependent on the process followed.
13. Same Nanoemulsions can carry both lipophilic and hydrophilic drugs.
14. The use of Nanoemulsion as delivery systems can improve the efficacy of a drug, allowing the total dose to be reduced and thus minimizing side effects.

Disadvantages of Nanoemulsion Based Systems [1, 2];

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. These parameters change upon Nanoemulsion delivery to patients.

Theory of the Formation of Nanoemulsion: In Nanoemulsion which is categorized as multiphase colloidal dispersion which is generally characterized by its stability and clarity. There is an application of high shear generally obtained by micro fluid or ultrasonic approach generally used to reduce the droplet size to nanoscale. There is a marginal difference between the terms Nanoemulsion and microemulsion also known as micellar phase or mesophase. The microemulsion generally forms through thermodynamic self assembly whereas nanoemulsion requires external shear for rupturing the droplets.

In retrospect, the historical choice of the word "microemulsion" to describe the nanoscale is unfortunate since they are structurally between 1 to 100 nm as for Nanoemulsion. Micro emulsions are not the emulsions of micro scale droplets. They are formed by self assembled equation phase in which the surface tension dose not play a significant role. The Nanoemulsions underlines the basic principle in its formulation. They generally comprises of two immiscible phase with an interfacial tension between them reduced by addition of surfactant [3].

Components of Nanoemulsion [2]: Main three components of Nanoemulsions are as follows:

1. Oil **(Table 1)**
2. Surfactant/Cosurfactant **(Table 2, Table 3)**
3. Aqueous phase

TABLE 1: LIST OF OILS USED IN NANOEMULSIONS [2, 5]

Name	Chemical Name	Manufacture
Captex 355	Glyceryl Tricaorylate/Caprate	Abitec
Captex 200	Propylene Dicaprylate/Dicaprate Glycol	Abitec
Captex 8000	Glyceryl Tricaprylate (Tricaprylin)	Abitec
Witepsol	90:10 % w/w c12 Glyceride tri: diesters	Sasol pharmaceutical excipient
Myritol 318	c8/c10 triglycerides	Russia
Isopropyl myristate	Myristic acid isopropyl ester	Fluka

TABLE 2: LIST OF SURFACTANT USED IN NANOEMULSIONS [2, 5]

Sr. No.	Solubilizing agents, surfactants, emulsifying agents adsorption enhancers
1	Caproyl 90
2	Gelucire 44/14, 50/13
3	Cremophor RH 40
4	Imwitor 191, 308(1), 380, 742, 780 K, 928, 988
5	Labrafil M 1944 CS, M 2125 CS
6	Lauroglycol 90
7	PEG MW > 4000
8	Plurol Oleique CC 497
9	Poloxamer 124 and 188
10	Tween 80

TABLE 3. LIST OF CO-SURFACTANT USED IN NANOEMULSION [2, 5]

Sr. No.	Co Surfactant
1	TranscutolP
2	Glycerin, Ethylene glycol
3	Propylene glycol
4	Ethanol
5	Propanol

Factors affecting the Formulation of Nanoemulsion:

- Appropriate composition is required to avoid Oswald ripening the dispersed phase should be highly insoluble in the dispersed medium.
- 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.
- The presence of excess surfactants enables new surface area of nanoscale to be rapidly coated during emulsification there by inhibiting induced coalescence.
- 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. Out of various methods ultrasonication is widely used in laboratory [3].

Techniques of Preparation of Nanoemulsions [1, 2, 3]: Nanoemulsions have very small particle size range; they can be most effectively produced using high-pressure equipment. The most commonly used methods for producing nanoemulsions are 'High-pressure homogenization' and 'Microfluidization' used at both laboratory and industrial scale. Other methods like 'Ultrasonification' and 'In-situ emulsification' are also suitable for preparation of nanoemulsion.

1. **High-Pressure Homogenization:** The preparation of nanoemulsions requires high- pressure homogenization. This technique makes use of high-pressure homogenizer/piston homogenizer to produce nanoemulsions of extremely low particle

size (up to 1nm). The dispersion of two liquids (oily phase and aqueous phase) is achieved by forcing their mixture through a small inlet orifice at very high pressure (500 to 5000 psi), which subjects the product to intense turbulence and hydraulic shear resulting in extremely fine particles of emulsion.

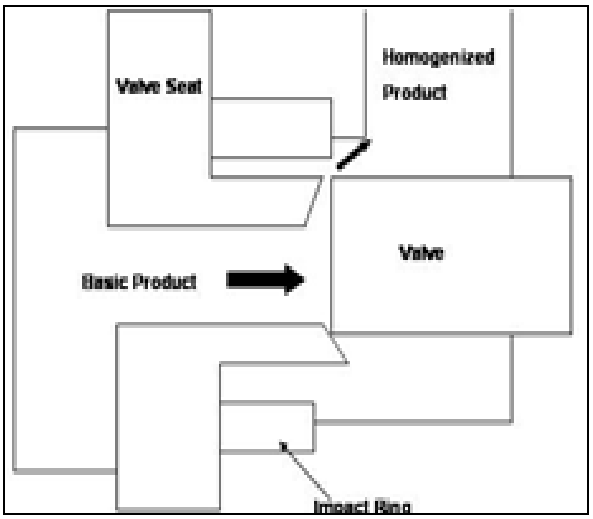

FIG. 2: HIGH PRESSURE HOMOGENIZATION SHOWING THE FORMATION OF NANOEMULSION i.e., THE HOMOGENISED PRODUCT FROM THE BASIC PRODUCT

The particles which are formed exhibit a liquid, lipophilic core separated from the surrounding aqueous phase by a monomolecular layer of phospholipids. This technique has great efficiency, the only disadvantage being high energy consumption and increase in temperature of emulsion during processing.

To obtain the optimized formulation following process variables should be investigated:

- **Effect of Homogenization Pressure:** It is optimized the process parameter ranging from 100 to 150 bars. The higher is the size the lower is the particle size obtained e.g., RMRP 22.

- **No. of Homogenization cycles:** The higher the homogenization cycles the smaller is the particle size obtained. The cycles are carried out in 3, 4 or 10 cycles. The number of cycles is analyzed by polydispersity index of drug after each cycle.

Advantages:

- Ease of scale-up and little batch-to-batch variation.
- Narrow size distribution of the nanoparticulate drug.
- Flexibility in handling the drug quality.
- Effectively used for thermolabile substances.

2. **Microfluidization:** Microfluidization is a mixing technique, which makes use of a device called microfluidizer. This device uses a high-pressure positive displacement pump (500 to 20000psi), which forces the product through the interaction chamber, which consists of small channels called 'microchannels'. The product flows through the microchannels on to an impingement area resulting in very fine particles of sub- micron range.

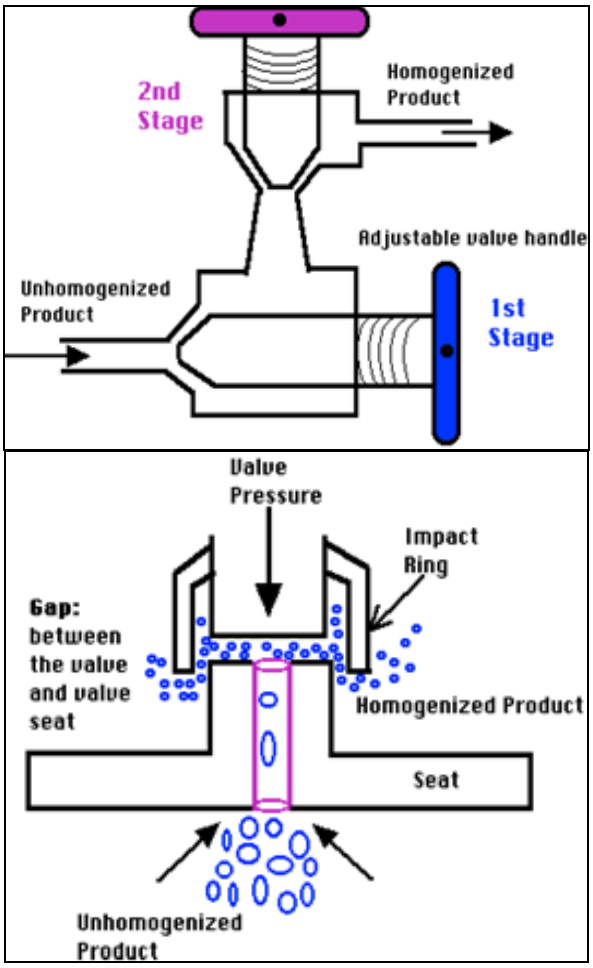

FIG. 3: MICRO FLUIDIZER WITH THE MECHANISM OF WORKING

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 into a microfluidizer where it is further processed to obtain a stable nanoemulsion.

The coarse emulsion is passed through the interaction chamber microfluidizer repeatedly until 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.

3. **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.

FIG. 4: PROBE SONICATOR USED IN LABORATORY SCALE FOR PREPARATION OF NANOEMULSION

4. **Phase inversion method:** In this method, fine dispersion is obtained by chemical energy resulting of phase transitions produced by emulsification pathway. The phase transition is produced by varying the composition of the emulsion and keeping temperature constant or vice versa. The phase inversion temperature was first done by Shinoda *et al*. it was concluded that increase in temperature results in the chemical changes of polyoxyethelene surfactants by degradation of the polymer chain with the temperature.

5. **Spontaneous Emulsification:** It involves three main steps:

   i. Preparation of homogeneous organic solution composed of oil and lipophilic surfactant in water miscible solvent and hydrophilic surfactant.

   ii. The organic phase was injected in the aqueous phase under magnetic stirring the o/w emulsion was formed.

   iii. The water-miscible solvent was removed by evaporation under reduced pressure.

6. **Solvent Evaporation Technique:** This technique involves preparing a solution of drug followed by its emulsification in another liquid that is non-solvent for the drug. Evaporation of the solvent leads to precipitation of the drug. Crystal growth and particle aggregation can be controlled by creating high shear forces using a high-speed stirrer.

7. **Hydrogel Method:** It is similar to solvent evaporation method. The only difference between the two methods is that the drug solvent is miscible with the drug anti-solvent. Higher shear force prevent crystal growth and Ostwald ripening.

Construction of Phase Diagram: Pseudo-ternary phase diagrams of oil, water, and co-surfactant/surfactants mixtures are constructed at fixed cosurfactant/ surfactant weight ratios. Phase diagrams are obtained by mixing of the ingredients, which shall be pre-weighed into glass vials and titrated with water and stirred well at room temperature. Formation of monophasic/biphasic system is confirmed by visual inspection. In case turbidity appears followed by a phase separation, the samples shall be considered as biphasic. In case monophasic, clear and transparent mixtures are visualized after stirring; the samples shall be marked as points in the phase diagram.

The area covered by these points is considered as the Nanoemulsion region of existence [2].

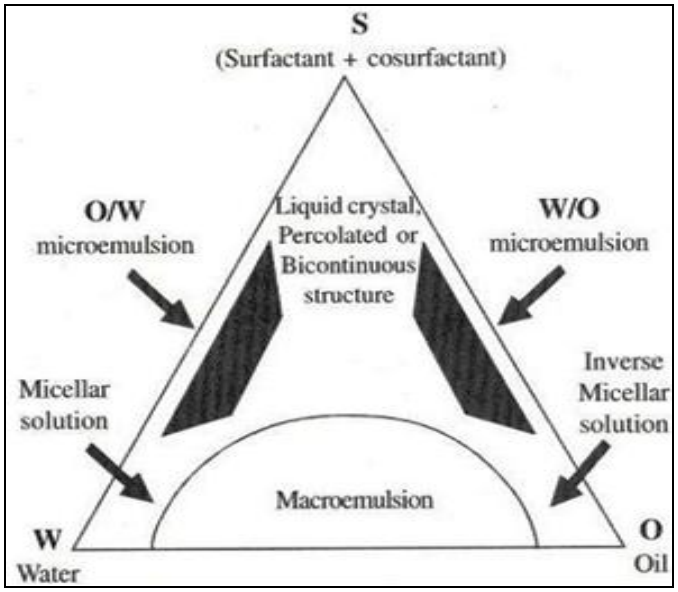

FIG. 5: HYPOTHETICAL PHASE REGIONS OF MICROEMULSION SYSTEMS [2]

Mechanism of Transmembrane Permeation: Nanoemulsion permeation involves various factors they are;

- Solubility of the drug.
- Hair follicles in percutaneous absorption
- The presence of stratum corneum and lipid layer.

Presence of surfactant and cosurfactants too plays a role in the formation of nanoemulsion [6].

Characterization of Nanoemulsion: 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 [2, 7].

1. **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 [1, 8, 9].
2. **Dilutability Test:** O/W Nanoemulsions are dilutable with water whereas W/O are not and undergo phase inversion into O/W Nanoemulsion [2, 3, 10].
3. **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 nature of the continuous phase and to detect phase inversion phenomena, the electrical conductivity measurements are highly useful [1, 4]. 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 [11, 12].
4. **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 [13, 14].
5. **Polydispersity:** The average diameters and polydispersity index of samples were measured by Photon Correlation Spectroscopy. The measurements were performed at 25^{o}C using a He-Ne laser [1, 5].
6. **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 [4, 6].
7. **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 [2].

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 [3].

8. **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 [1].

9. **pH:** The apparent pH of the formulation was measured by pH meter.[3]

10. **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 [2, 3].

11. **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 was performed as, a drop of the nanoemulsion was directly deposited on the holey film grid and observed after drying [1].

12. ***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 37oC 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 [7].

    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.

13. **Thermodynamic Stability Studies:** During the thermodynamic stability of drug loaded Nano-emulsions following stress tests as reported:

    a. **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.

    b. **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.

    c. **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 [1, 2].

Applications of Nanoemulsions:

1. **Parenteral Delivery:** Nanoemulsion are advantages for intravenous administration, due to the strict requirement of this route of administration, particularly the necessity for the formulation droplet size lower than 1 micrometer. Parenteral (or Injectable) administration of nanoemulsion is employed for a variety of purposes, namely nutrition eg. Fats, Carbohydrates, Vitamins etc. [2, 6].

Nanoemulsions of natural oils(soyabean, sesame and olive) with the non toxic surfactant Pluronic F-68 via ultrasound for parentral feeding.Lipid nanoemulsion has been widely explored for parentral delivery of drugs. Nanoemulsion formulations have distinct advantages over macroemulsion systems when delivered parenterally because of the fine particle Nanoemulsion is cleared more slowly than the coarse particle emulsion and, therefore, have a longer residence time in the body. Both O/W and W/O Nanoemulsion can be used for parenteral delivery [15].

2. **Oral Delivery:** Nanoemulsion formulations offer the several benefits over conventional oral formulation for oral administration including increased absorption, improved clinical potency and decreased drug toxicity. Therefore, Nanoemulsion have 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 [17].

   Primaquine when incorporated into oral lipid nanoemulsion showed effective antimalarial activity against Plasmodium bergheii infection in mice at a 25% lower dose level as compared to conventional oral dose.Lipid nanoemulsion of primaquine improved oral bioavailability by the liver with drug concentration higher at least by 45% as compared with the plain drug [18].

3. **Topical Delivery:** Topical administration of drugs can have advantages over other methods for several reasons, one of which is the avoidance of hepatic first pass metabolism of the drug and related toxicity effects. Another is the direct delivery and targetability of the drug to affected area of the skin or eyes. The nanoemulsion can achieve a level of topical antimicrobial activity that has only been previously achieved by systemic antibiotics. The nanoemulsion has broad spectrum activity against bacteria(e.g. *E.coli, S. aureus*) fungi (e.g. Candida, Dermatophytes) [19].

4. **Ocular Delivery:** For the treatment of eye diseases, drugs are essentially delivered topically. O/W Nanoemulsions have been investigated for ocular administration, to dissolve poorly soluble drugs, to increase absorption and to attain prolong release profile [4, 20].

5. **In Cosmetic:** The aesthetic properties, i.e. low viscosity and transparent visual aspects of nanoemulsion with droplet sizes below 200nm, its high surface area allowing effective transport of the active ingredient to the skin make them especially attractive for their application in cosmetics [21]. Nanoemulsions are acceptable in cosmetics because there is no inherent creaming, sedimentation, flocculation or coalescence that are observed with macro 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 protection and penetration of active ingredient. It would be useful for sun care products, moisturing and antiageing creams. It helps to give skin care formulations a good skin feels [22].

6. **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 aceclofenac nanoemulsion (82.2%) as compared to nanoemulsion gel formulation (71.4%) and conventional gel (41.8%) [23, 24].

7. **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 [25].

   Enzymes in low water content display and have –

   - Increased solubility in non-polar reactants.
   - Possibility of shifting thermodynamic equilibria in favour of condensations.
   - Improvement of thermal stability of the enzymes, enabling reactions to be carried out at higher temperatures.[26,27]

Stability Factors of Nanoemulsion: As a general consideration the stability of nanoemulsion largely depends upon the following factors;

a) Coalescence of the two droplets of dispersed phase due to the surface tension and intermolecular attractions. This is mainly reduced by addition of suitable surfactants.

b) If the dispersed phase has high solubility in the dispersed medium. This results in diffusive migration of smaller droplets with low Laplace pressure to larger droplets of high Laplace pressure also known as Ostwald's ripening. The dispersed phase should be selected such that it should have minimum or no solubility in the continuous phase.

The instability of nanoemulsion 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. Vander wall 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. 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 [7].

Some patented Nanoemulsion formulations with their Patent number are given below in **Table 4.**

TABLE 4: PATENTED NANOEMULSIONS [4]

Patent Name	Assignee	US Patent Number
Nanoemulsion based on phosphoric acid fatty acid esters and its uses in cosmetics, dermatological, pharmaceutical and/or ophthalmological fields.	L'Oreal (Paris, FR)	6,274,150
Nanoemulsion based on ethylene oxide and propylene oxide block copolymers and its uses in the cosmetics, dermatological and/or ophthalmological fields.	L'Oreal (Paris, FR)	6,464,990
Method of Preventing and Treating Microbial Infections.	NanoBio Corporation (US)	6,506,803
Non-toxic Antimicrobial Compositions and Methods of Use.	NanoBio Corporation (US)	6,559,189 and 6,635,676
Nanoemulsion based on oxyethylenated or non oxyethylenated sorbitan fatty esters, and its uses in the cosmetics, dermatological and/or ophthalmological fields.	L'Oreal (Paris, FR)	6,335,022
Nanoemulsion based on glycerol fatty esters, and its uses in the cosmetics, dermatological and/or ophthalmological fields	L'Oreal (Paris, FR)	6,541,018

Nanoemulsion based on sugar fatty esters or on sugar fatty ethers and its uses in the cosmetics, dermatological and/or ophthalmological fields.	L'Oreal (Paris, FR)	6,689,371
Transparent nanoemulsion less than 100 nm based on fluid non-ionic amphiphilic lipids and use in cosmetic or in dermopharmaceuticals.	L'Oreal (Paris, FR)	5,753,241

CONCLUSION: NE formulations offer several advantages for the delivery of drugs, biologicals, or diagnostic agents. Traditionally, NEs have been used in clinics for more than four decades as total parenteral nutrition fluids. Several o ther products for drug delivery applications such as Diprivan, Liple and Ropion have also reached the marketplace. Although NEs 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.

Recently, several research papers have been published for the improvement of drug delivery, but still there is a need to emphasis on its characterization part including *in-vitro* evaluation. Besides this, research papers shows higher percentage of surfactant (much higher than CMC level) used for the formation of Nanoemulsion, irrespective of different routes of administration, but there is a lack of toxicological evaluation of the prepared Nanoemulsion, which can be a broad research area in future.

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