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An introductory review article on nanoemulsion

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Abstract
In pharmaceutical observation, nanoemulsion is one of the chief dosage forms in delivering active ingredients to the objective area which has engrossed a great attention in recent years for its application in various fields. In the pharmaceutical field, nanoemulsions have been used as a drug delivery system through various systemic routes such as oral, topical and parenteral. Nanoemulsions are submicron sized emulsions which are used under high investigation as drug carriers for improving the delivery of therapeutic agents. The small droplets size 10-200 nm, high solubilization capacity, high interfacial area, low viscosity, transparent or translucent appearance, and high kinetic stability, make nanoemulsions used for various applications. These emulsions are easily produced in large quantities by mixing a water immiscible oil phase into an aqueous phase with high stress. These are prepared from surfactants, cosurfactants or cosolvents.
In this review diverse aspects of nanoemulsion are highlighted i.e. method of preparation, characterization techniques like particle size, zeta potential, polydispersity, drug content advantages, disadvantages and particular importance on various application of nanoemulsion in different areas such as in cancer treatment, drug targeting, as a vehicle for transdermal drug delivery, selfnano emulsifying drug delivery system.

Keywords: Nanoemulsion, surfactant, co-solvent, emulsified oil, applications

1. Introduction
At the present time, a lot of interest has been directed on lipid based formulations to progress the permeability and bioavailability of poorly water soluble drugs. By reminding this in mind a choice of different novel drug delivery system has been used in which nanoemulsion plays an essential role in delivering the active pharmaceutical ingredient at the target organ or site. Among diverse technologies nanoemulsions has been showed better development in drug delivery system. These are considered as an ideal alternative for improving the oral bioavailability of BCS (Biopharmaceutical drug classification system) Class II and IV drugs [1]. The role of nanotechnology in drug delivery system has exposed notable efforts in present pharmaceutical research. The term Nanoemulsion is said to a thermodynamically stable clear solution of two non soluble liquids, such as oil and water, stabilized by an interfacial film of surfactant molecules. Nanoemulsions are novel drug delivery system includes an emulsified oil and water systems having mean droplet size which ranges from 50 to 1000 nm. The emulsions and nanoemulsions differ mainly in the size and shape of the particles dispersed in continuous phase. The particle size in nanoemulsions is (10-200 nm) and those of conventional emulsions are (1-20µm) [2]. A nanoemulsion is kinetically stable liquid which consists an oil phase and water phase with an appropriate surfactant. The dispersed phase mainly comprises small particles having a size range of 5 nm-200 nm, and has less oil/water interfacial tension. Nanoemulsions are colloidal dispersions having an oil phase, aqueous phase, surfactant and co surfactant in correct ratios [3]. Nanoemulsions were shaped both by high energy emulsification methods or low energy emulsification methods. High energy emulsification methods engage high shear mixing, high-pressure homogenization or ultrasonification, while low energy emulsification methods used the advantage of the physicochemical properties of the system which exploits phase transitions to produce nanoemulsion [4]. Nanoemulsion prepared with oil, surfactant and cosurfactant are non toxic, non-irritant and approved for human consumption that are "generally recognized as safe" by the FDA. Several types of oils such as natural, semi-synthetic and synthetic are used in the formulation of nanoemulsions. Nanoemulsions are made from pharmaceutical surfactants that are generally regarded as safe for human intake. The surfactant type and concentration in the aqueous phase are chosen to provide good stability against coalescence. Nanoemulsions have stability against creaming, flocculation, coalescence and sedimentation [5].

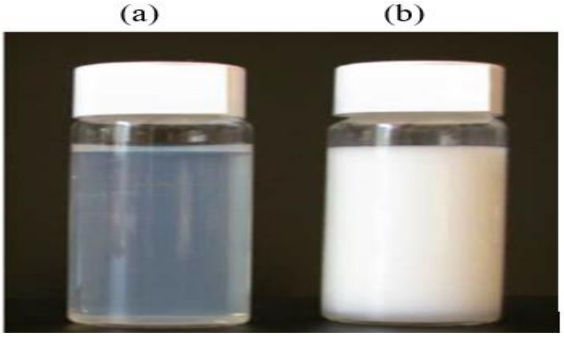

Fig 1: a) Nanoemulsion b) Macroemulsion

Types of Nanoemulsions

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

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

Advantages of Nanoemulsions

1. Nanoemulsions are thermodynamically and kinetically stable thus preventing flocculation, aggregation, creaming and coalescence.
2. Nanoemulsion is an approach to improve water solubility and bioavailability of lipophilic drugs.
3. Nanoemulsion can be administered by various routes, such as oral, topical, parenteral and transdermal etc.
4. Nanoemulsions can deliver both hydrophilic and lipophilic drugs.
5. Nanoemulsions have potential to deliver peptides that are prone to enzymatic hydrolysis in GIT.
6. Droplet size are nano, so surface area is large thus increases the rate of absorption and decreases variability, thus enhances bioavailability of drug [7].
7. Nanoemulsions are appropriate for human and veterinary uses because they do not damage human or animal cell.
8. It protects the drug from hydrolysis and oxidation due to encapsulation in oil-droplet. It also provides taste masking.
9. Nanoemulsion also enhances permeation of drug through skin
10. They also provide ultra-low interfacial tension and large o/w interfacial areas [8].

Disadvantages of Nanoemulsions

1. Large concentration of surfactants /cosurfactants is required for stabilization.
2. Its stability is affected by temperature and pH.
3. Instability can be caused due to Oswald ripening effect.
4. Expensive process due to size reduction of droplets [9].

Components of Nanoemulsion

Oils

Selection of a proper oily phase is very essential as it influences the selection of other ingredients of nanoemulsions, generally in case of o/w nanoemulsions. Usually, the oil having greatest solubilising potential has selected as an oily phase for the formulation of nanoemulsions. This helps to attain maximum drug loading in the nanoemulsions [6]. Naturally occurring oils and fats contains a mixture of triglycerides which contain fatty acids of varying chain lengths and degrees of unsaturation. Triglycerides are classified as short (<5 carbons), medium (6-12 carbons), or long chain (>12 carbons) and may be synthetically hydrogenated to decrease the degree of unsaturation, thereby conferring resistance to oxidative degradation. The selection of oily phase is also a compromise between its ability to solubilize the drugs and its ability to ease the formation of nanoemulsion of desired properties [10]. Some suitable oil phases are Captex 355, Myritol 318, IPM, modified vegetable oils, digestible or non-digestible oils and fats such as olive oil, palm oil, corn oil, oleic acid, sesame oil, soybean oil, hydrogenated soybean oil, peanut oil and beeswax [11].

Surfactants

The surfactant should capable of microemulsification of the oily phase and should also possess good solubilising potential for the hydrophobic drug compounds. The choice of the surfactant is critical for the nanoemulsion formulation. Surfactants with an HLB value <10 are hydrophobic (such as sorbitan monoesters) and form w/o nanoemulsion where as high HLB (>10) surfactants such as polysorbate 80 are hydrophilic and form o/w nanoemulsion [12]. The hydrophobic core enhances the entrapment of drug, thus increasing its solubility. When the oil content is high, surfactant concentrate on the oil/water interface forming emulsions, where in the drug is solubilized in the internal oil phase. On the other hand when the oil content is low, minute oil entrapped surfactant globules are produced, which are known as nanoemulsions [13]. The surfactant used in nanoemulsion formation could be ionic or non-ionic but ionic surfactants are not preferred due to toxicological effects. Various surfactants are mostly used such as lecithins, poloxamers and polysorbate 80. It is very important to determine the surfactant concentration properly as large amounts of surfactants may cause GI irritation. There is a relationship between the droplet size and the concentration of the surfactant being used. In some cases, increasing the surfactant concentration could lead to smaller droplets such as in the case of a mixture of saturated C8-C10 polyglycolized glycerides. On the other hand, in some cases the mean droplet size may increase with increasing surfactant concentrations [14].

Co-surfactants

Many times, surfactant alone cannot lower the oil-water interfacial tension adequately to yield a nanoemulsion which necessitates the addition of a co-surfactant to bring about the surface tension close to zero. Co-surfactants penetrate into the surfactant monolayer providing additional fluidity to interfacial film and thus distracting the liquid crystalline phases which are formed when surfactant film is too rigid [6]. Usually a very low HLB co-surfactant is used with a high HLB surfactant to modify the overall HLB of the system. Unlike surfactant, the co-surfactant may not be capable of forming self-associated structures like micelles on its own. Hydrophilic co-surfactants preferably alcohols of intermediate chain length such as hexanol, pentanol and octanol, which are known to reduce the oil/water interface and allow the spontaneous formation of nanoemulsion [11].

Co-solvents

The production of finest nanoemulsions requires relatively high concentrations (generally more than 30% w/w) of surfactants. Organic solvents such as ethanol, glycerol, propylene glycol (PG), polyethylene glycol(PEG) are suitable for oral delivery, and they enable dissolution of large quantity of either the hydrophilic surfactant or the drug in the lipid base by co-solvency and by making the environment more hydrophobic by reducing the dielectric constant of water [15].

Aqueous Phase

The droplet size and stability of nanoemulsion is influenced by the nature of aqueous phase. Hence, pH and ionic content of aqueous phase should be given due importance while designing nanoemulsion. The physiological system has various pH ranges varying from pH 1.2 (pH in stomach) to 7.4 and greater (pH of blood and intestine). It is well known that electrolytes can have influence on the nanoemulsion characteristics, such as droplet size and physical stability. Hence, it is advisable to evaluate the nanoemulsion and the characteristics of the resultant nanoemulsion in aqueous phases with varying pH and/or electrolyte concentration (depending upon the type of application). In addition to plain water, Ringer's solution, simulated gastric fluid (pH 1.2), simulated intestinal fluid (pH 6.8) and phosphate buffered saline can be used as aqueous phase to evaluate spontaneous nano emulsification of self-nano emulsifying drug delivery system. These studies indicate that the pH of the aqueous phase can have a great influence on the phase behavior of this system, especially when a drug with pH-dependent solubility is loaded in the system [16].

Types of Surfactant

1. **Anionic Surfactant:** ex. Potassium and Sodium stearate, Calcium and Aluminium stearate, Ethanolamine etc.
2. **Cationic Surfactant:** ex. Quaternary Ammonium compound such as cetrimide, benzalkonium chloride.
3. **Ampholytic Surfactant:** ex. Lecithin, N-dodecylalnine.
4. **Non Surfactant:** ex. Glycerol and glycol esters i.e. glycerol monosterate, Propylene glycol mono stearate

Methods of Preparation of Nanoemulsion

Numerous methods have been optional to practise nanoemulsion. Development of nanoemulsion system needs an elevated amount of energy. This energy can be obtained either by mechanical equipment or by the chemical potential inherent within the component. Some methods used for the preparation of nanoemulsion are:

1. **Sonication Method**: In this technique, the droplet size of usual emulsion is compact with the help of sonication mechanism. Only fewer amounts of batches of nanoemulsion can be produced by this method [18].
2. **High Pressure Homogenizer:** This method is based on by applying a large pressure over the system consisting an oil phase, aqueous phase and surfactant or co-surfactant. The high pressure is applied with the help of homogenizer. Some problems allied with homogenizer are poor productivity, component deterioration due to production of much heat. From this method, only oil in water (o/w) liquid nanoemulsion of less than 20% oil phase can be formed and cream nanoemulsion of high viscosity or hardness having a mean droplet diameter less than 200 nm cannot be prepared [19].
3. **Phase Inversion Method**: Fine dispersion can be obtained by chemical energy resulting in phase transitions through emulsification method. The sufficient phase transitions are produced by changing the composition at constant temperature or by changing the temperature at constant composition. The phase inversion temperature (PIT) method was introduced based on the principle of changes of solubility of polyoxyethylene type surfactant with temperature. This surfactant becomes lipid soluble with increase in temperature because of dehydration of polymer chain. At low temperatures the surfactant monolayer has a great positive spontaneous curvature forming oil swollen micellar solution phase [20].
4. **Production with high amplitude ultrasound**
   This method is an alternative for high pressure homogenization. High shear forces are necessary for the nanoemulsification are produced by ultrasonic cavitations which produces violently and asymmetrically imploding vacuum bubbles and reduce the particle size to the nanometer scale. This method is successfully used in small scale production of nanoemulsions [2].
5. **Solvent Displacement Method**
   In this method, oily phase is dissolved in water miscible organic solvents such as acetone, ethanol. The organic phase is mixed into an aqueous phase containing surfactant to produce nanoemulsion by rapid diffusion of organic solvent. Organic solvent is removed from nanoemulsion by vaccum evaporation [21].
6. **Microfluidizatiion:** Microfluidization technology makes use of a device called ‘MICRO FLUIDIZER”. This device consist of high pressure positive displacement pump (500-200 PSI) which forces the product through the interaction chamber, consisting of small channels called micro channels. The product moves through the micro channels on to an impingement area which results in very fine particles of submicron range. The two solutions (aqueous phase and oily phase) are mix together and processed in an inline homogenizer to get a coarse emulsion. The coarse emulsion is into a micro fluidizer where it is further processed to get a stable nanoemulsion [22].

Characterization of Nanoemulsion

1. **Zeta potential:** Zeta potential is measured by an instrument known as Zeta PALS. It is used to measure the charge on the surface of droplet in nanoemulsion. Emulsifiers not only act as a mechanical barrier but also through formation of surface charges. Zeta potential can produce repulsive electrical forces among approaching oil droplets and this hinders coalescence. The more

negative zeta potential, greater the net charge of droplets and more stable the emulsion is. Zeta potential values lower than -30 mV generally indicate a high degree of physical stability. Malvern Zetasizer is based on dynamic light scattering and measures Zeta potential.

2. **Polydispersity:** Polydispersity is the ratio of standard deviation to mean droplet size, so it indicates the uniformity of droplet size within the formulation. The higher the polydispersity, the lower the uniformity of the droplet size in the formulation. Malvern Zetasizer is based on dynamic light scattering and measures polydispersity [23].
3. **Particle Size Analysis:** Generally in case of nanoemulsion dynamic light scattering (DLS) method is used for the measurement of particle size and their distribution [24].
4. **Percent Drug Loading:** Pre-weighed nanoemulsion is extracted by dissolving in 25ml suitable solvent, extract is than analyzed spectrophotometrically/ H.P.LC. against the standard solution of drug. Drug content determine by reverse phase HPLC method using different columns of appropriate porosity [25].
5. **Transmission Electron Microscopy (TEM):** Morphology and structure of the nanoemulsion can be studied using transmission electron microscopy (TEM).
6. **In-vitro drug release:** The *in vitro* release studies of nanoemulsion containing drug can be investigated through semi permeable membrane used in a dissolution apparatus. A glass cylindrical tube (2.5 cm in diameter and 6 cm in length) is attached instead of the basket and should tightly cover with the semi permeable membrane. Drug loaded nanoemulsion is placed in the cylindrical tube at the semi permeable membrane surface. The cylindrical tube should dip in 100 ml buffer maintaining the pH to allow the establishment of the sink conditions and to sustain permanent solubilization. The release study can be carried out for 24 hrs. at 32°C.Tthe stirring shaft should rotate at speed of 100 r.p.m. At predetermined time intervals (1, 2, 4, 6, 8, 12, 20, 24 hrs.) aliquots of one millilitre of the release medium is withdrawn and diluted then filtered for analysis and replaced with equal volume of the buffer solution to maintain a constant volume. The absorbance of the collected samples can be measured by UV spectrometer [26].

Applications of Nanoemulsion

Nanoemulsions containing active pharmaceutical ingredients can be utilized for the invention of pharmaceutical preparations, the nanoemulsion consist of an active component, with a suitable vehicle for therapeutic administration. If desired, a special galenic form can be imparted to the mixture. The following galenic forms of administration are ampoules, especially sterile injection and infusion solutions; solutions, especially oral liquids, eye drops and nose drops which can contain various secondary substances in addition to the 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 nanoemulsion; lotions and pastes containing the nanoemulsion.

1. **Ocular Delivery:** Oil in water emulsions are being used for improved topical lipophilic drug delivery to the eye. Lipophilic drug loaded o/w ocular emulsions provide a better balance between ocular bioavailability improvement and patient comfort following topical installation into the eye e.g. pilocarpine, indomethacin, piroxicam cyclosporine A [27].
2. **Nasal Route:** The nasal route has received great attention due to number of advantages over parenteral and oral administration especially by passing 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. Drugs which have been formulated for nasal delivery are insulin and testosterone [27].
3. **Use of Nanoemulsions in Cosmetics:** Nanoemulsions have recently become increasingly important as potential vehicles for the controlled delivery of cosmetics and for the optimized dispersion of active ingredients in particular skin layers. Due to their lipohilic nature, nanoemulsions are more suitable for the transport of lipophilic compounds than liposomes. Similar to liposomes, they support the skin penetration of active ingredients and thus increase their concentration in the skin. Another advantage is the small-sized droplet with its high surface area allowing effective transport of the active to the skin. Furthermore, nanoemulsions gain increasing interest due to their own bioactive effects. This may reduce the trans epidermal water loss, indicating that the barrier function of the skin is strengthened. Nanoemulsions are acceptable in cosmetics because there is no creaming, sedimentation, flocculation or coalescence observed within macroemulsions.
4. **Antimicrobial Nanoemulsions:** Antimicrobial nanoemulsions are oil in water droplets having size range from 200-600 nm. The nanoemulsion particles are thermodynamically fused with lipid containing organisms. When sufficient 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) [24].

Conclusion

Nanoemulsions propose several advantages for the delivery of drugs and are thus receiving growing attention as drug carriers for improving the delivery of active pharmaceutical

ingredients. They are applicable for almost all routes of delivery and therefore provide the promising effect for different fields like therapeutics, cosmetics and biotechnology. This new technology is developed to overcome the poor absorption of some pharmaceuticals and poor miscibility of these compounds with the lipid contents of cell membrane.The conventional approaches to bioavailability enhancement can hardly meet the challenges presented by the growing number of insoluble drugs. The effectiveness of nanoemulsion based drug delivery in overcoming current bioavailability challenges are well documented in this literature. In this review, the modern strategies and considerations for successful nanoemulsion based drug delivery have been presented with the hope that they can serve as the foundation for many more success in the field. The applications of nanoemulsion are limited by the instability. Stability of formulation may be enhanced by controlling various factors such as type and concentration of surfactant and co surfactant, type of oil phase, methods used, process variables and addition of additives used over the inter phases of nanoemulsion formulation.

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