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Nanoemulsion: A Novel Approach in Various Pharmaceutical Applications

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ABSTRACT:

Nanoemulsions are nano sized emulsions that are used under high investigation as drug carriers for improving the delivery of therapeutic agents. This advanced technology is used for the systemic delivery of biologically active agents for controlled delivery and targeting. These are the novel drug delivery system consisting of emulsified oil and water system which mean droplet diameter ranging from 5 to 200 nm .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 various aspects of nanoemulsion are highlighted i.e. advantages, disadvantages, method of preparation, characterization techniques like polydispersity, particle size, zeta potential, drug content with special emphasis on various application of nanoemulsion in different areas such as in cancer treatment, drug targeting, as a vehicle for transdermal drug delivery, self nano emulsifying drug delivery system

KEY WORDS: Nanoemulsion, Cosurfactant, Cosolvent, emulsified oil.

INTRODUCTION:

Nowadays, much attention has been focussed on lipid based formulations to improve the permeability and bioavailability of poorly water soluble drugs. By reminding this in mind various novel drug delivery system has been used in which nanoemulsion plays a vital role in delivering the active pharmaceutical at the target organ or site [1]. The role of nanotechnology in drug delivery system has shown remarkable efforts in present pharmaceutical research. Among various technologies nanoemulsions has been showed better enhancement in drug delivery system [2]. These are considered as an ideal alternative for improving the oral bioavailability of BCS (Biopharmaceutical drug classification system) Class II and IV drugs [3]. Nanoemulsions are novel drug delivery system includes an emulsified oil and water systems having mean droplet size ranging from 50 to 1000 nm. 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. 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) [4]. A nanoemulsion is kinetically stable liquid containing 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 [5]. Nanoemulsions have stability against creaming, flocculation, coalescence and sedimentation.

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 [6].

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 [7].

ADVANTAGE OF NANOEMULSION

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

DISADVANTAGES OF NANOEMULSION

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 [10].
4. Expensive process due to size reduction of droplets.

COMPONENTS OF NANOEMULSION

Nanoemulsion contains three main components:

1. Oil (Captex 355, Captex 200, Captex 8000, Myritol 318, Isopropyl Myristate, Witepsol, Castor oil, Cinnamon oil, Eucalyptus oil, Sunflower oil, Olive oil)
2. Surfactant/ co–surfactant (Capryol 90, Gelucire 44/14, 50/13, Cremophor RH 40, Poloxmer 124/ 188, Softigen 701, Tween 80/20, Propylene glycol, Ethanol, Propanol)
3. Aqueous phase [11]

Types of Surfactant

Depending upon their ionization in aqueous solution the surfactant is classified as:

1) **Anionic Surfactant**

Commonly use in soap of alkali, amine & metals, sulphated alcohols and sulphonates.

Examples: Alkali soap – Potassium and Sodium Strearate.

Amino Soap – Ethanolamine, diethanolamine, isopropanolamine and oleic acid.

Metallic Soap – Calcium and Aluminium stearate.

2) **Cationic Surfactant**

Examples: Quaternary Ammonium compound such as cetrimide, benzalkonium chloride.

3) **Ampholytic Surfactant**

Ionic characteristic depend upon pH of the system.

Example: Lecithin, N-dodecylalnine.

4) **Non Surfactant**

These agents include their compatibility with both anionic and cationic surfactant and their resistance to pH change and effect of electrolytes and lower irritancy.

Example: Glycerol and glycol esters i.e. glycerol monosterate, Propylene glycol mono stearate [9].

PREPARATION OF NANOEMULSION

The drug is dissolved in oil phase and the water phase can be combined with a surfactant and cosurfactant is then added at slow rate with gradual stirring until the system

becomes transparent. Appropriate amount of surfactant, cosurfactant and oil must be properly incorporated in the system with the help of pseudo ternary phase diagram [12].

Methods of Preparation of Nanoemulsion

Several methods have been suggested to prepare nanoemulsion. Formation of nanoemulsion system needs a high 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:

Phase Inversion Method: Fine dispersion can be obtained by chemical energy resulting in phase transitions through emulsification method. The adequate 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 [12].

Sonication Method: In this method, the droplet size of conventional emulsion is reduced with the help of sonication mechanism. Only fewer amounts of batches of nanoemulsion can be formed by this method [7].

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 associated 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 [13].

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 [14].

Production with high amplitude ultrasound: This method is an option for high pressure homogenization. High shear forces are necessary for the nanoemulsification are produced by ultrasonic cavitation 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 [4].

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 [15].

CHARACTERIZATION OF NANOEMULSION

1. **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 [16].
2. **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. 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 [16].
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 [6].

4. **Transmission Electron Microscopy (TEM):** Morphology and structure of the nanoemulsion can be studied using transmission electron microscopy (TEM) [17].
5. **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 [18].
6. ***In-vitro* drug release:** The *in vitro* release studies of nanoemulsion containing drug can be investigated through semipermeable 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 covered with the semipermeable membrane. Drug loaded nanoemulsion is placed in the cylindrical tube at the semipermeable 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 milliliter 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 [19].

APPLICATIONS OF NANOEMULSION IN DRUG DELIVERY SYSTEM

1. Nanoemulsions are widely used for the proper delivery of active pharmaceutical ingredient by various routes like oral, parentral, topical, ocular, transdermal etc.
2. Nanoemulsions can be greatly used in cosmetics because of its small particle size which leads to faster absorption and finally better effect. They can be used as moisturisers and creams as an elegant product.
3. These can be used to enhance the oral bioavailability of poorly water soluble drugs due to small particle size.
4. These can be used in transdermal drug delivery due to high permeability through the skin and having a non irritant effect [6].
5. These can produce a topical antimicrobial activity that can previously only attained by systemic antibiotics.
6. These can also be used in ocular drug delivery system to retain the pharmacological effect of the drug [6].
7. Nanoemulsion formulation can be administered orally as they increases absorption, improved clinical potency and reduce drug toxicity over conventional formulation.
8. Direct delivery and target ability of drug to effected area of skin in topical administration [20].
9. Nanoemulsions can be used in cancer therapy for target drug delivery [21].

CONCLUSION

Nano-emulsions are projected for several applications in pharmacy as drug delivery systems because of their capability of solubilizing non polar active compounds. Nanoemulsion formulations propose numerous advantages for the delivery of drugs, biologicals, or diagnostic agents and have been shown to be able to defend labile drug, control drug release, raise drug solubility, enhance bioavailability and diminish patient variability and are thus getting growing attention as drug carriers for improving the delivery of active pharmaceutical ingredients.. Nanoemulsions are mostly seen as vehicles for administering aqueous unsolvable drugs, they have more recently received rising attention as colloidal carriers for targeted delivery. The applications of nanoemulsion are restricted 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. This new technology could be developed to beat the poor absorption of some phyto pharmaceuticals and poor miscibility of these compounds with the lipid contents of cell membrane linings. It is estimated that further research and development work will be carried out in the near future for clinical realization of the targeted delivery vehicles.

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