Review Article
NANO-EMULSION IN PHARMACEUTICALS: A REVIEW
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Abstract
Nano-emulsion 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 with the average droplet size ranging from 5nm to 100nm. Nanoemulsions show great promise for the future of cosmetics, diagnostics, drug therapies and biotechnologies. In this review, is a brief about the formulation, methods of preparation and characterization techniques with emphasis on the pharmaceutical applications of the nano-emulsion.

Keywords: Nano-emulsion; Characterization; Pharmaceutical application

INTRODUCTION
Nanotechnology comprises technological developments on the nanometer range of usually 0.1 -100nm. The pharmaceutical developed on the basis of nanotechnology is referred to as “NANOPHARMACEUTICALS”. Various nanopharmaceuticals currently being used or in the process of development are Nanoemulsions, Nanosuspensions, Nanospheres, Nanotubes, Nanoshells, Nanocapsules, lipid nanoparticles and dendrimers.[1] A nanoemulsion is considered to be a thermodynamically or kinetically stable liquid dispersion of an oil phase and a water phase, in combination with a surfactant. 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.[2] The Nanoemulsions are made from surfactants approved for human consumption and common food substances that are “Generally Recognised As Safe” (GRAS) by the FDA.[3] A nanoemulsion offers a promising vehicle for increasing the aqueous solubility of poorly water-soluble drugs. Nanoemulsions can enhance drug solubility, has perfect thermodynamic stability and ease of manufacturing and permeation over conventional formulations that convert them to important drug delivery systems. The design & development of Nanoemulsions aimed at controlling or improving required bioavailability levels of therapeutic agents.

CLASSIFICATION OF NANOEMULSIONS:
1. **Oil in Water Nanoemulsion (O/W):** Oil droplets are dispersed in the continuous aqueous phase.
2. **Water in Oil Nanoemulsion (W/O):** Water droplets are dispersed in the continuous oil phase.
3. **Bi- Continuous Nanoemulsion:** micro domains of oil and water are inter-dispersed within the system.

Advantages of nano-emulsion [4 5 6 7 8]

1. It improves water solubility and bioavailability of lipophilic drugs.
2. It increases the rate of absorption.
3. Fine oil droplets empty rapidly from the stomach thus providing wide distribution of drug throughout the intestinal tract by minimising the irritation.
4. Has higher solubilisation capacity and is thermodynamically stable over emulsions and suspensions.
5. It is non-toxic; non-irritant so can be applied in the skin and the mucous membranes.
6. Rapid and efficient penetration of the drug moiety.
7. Nanoemulsions are formulated with surfactants that are approved for human consumption so can be used in enteric route.

Figure 1: Nano-emulsion Formulation

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8. It does not damage healthy human and animal cells so can be used for human and veterinary therapeutic purpose.
9. Various routes like topical, oral and intravenous can be used to deliver the product.
10. Liquid dosage forms increases patient compliance.
11. Can be formulated in various formulations like spray, foam, liquid and creams.
12. Does not show problems of coalescence, creaming, flocculation and sedimentation such as that of macroemulsions.

FORMULATION OF NANOEMULSION [9, 10]
Nanoemulsions consist of main 3 components:
1. Oil
2. Surfactants / co-surfactants.
3. Aqueous phase

Oils: include Captex 355, Captex 200, Captex 8000, Witepsol, Isopropyl Myristate.

Surfactants include Capryol 90, Gelucire 44/14, 50/13, Cremophor RH 40, Imwitor 191, 308(1), 380, 742, 780 K, 928, 988, Labrafil M 1944 CS, M 2125 CS, Lauruglycol 90, PEG MW > 4000, Plurol Oleique CC 497, Poloxamer 124 and 188, Softigen 701, 767, Tagat TO and Tween 80.

Co-surfactant includes Transcutol P, Glycerine, Ethylene glycol, Propylene glycol, Ethanol, Propanol.

Construction of phase diagram: Pseudo-ternary phase diagrams of oil, water and co-surfactant/surfactant mixtures are constructed at fixed co-surfactant/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 is confirmed by visual inspection. In case turbidity appears followed by a phase separation, the samples are considered as biphasic. In case of monophasic, clear and transparent mixtures are visualised after stirring.

PREPARATION OF NANOEMULSION
Nanoemulsion can be prepared by both high and low energy methods. Both high and low energy methods can produce stable nanoemulsions. High-pressure homogenizer and Microfluidization can be used for the preparation of nanoemulsion by high energy emulsification methods. Self-emulsification and phase inversion methods are the low energy methods for the preparation of nanoemulsions.

High pressure homogenizer: This method is performed by applying a high pressure over the system having oil phase, aqueous phase and surfactant or co-surfactant. The pressure is applied with the help of homogenizer. Some problems associated with homogenizer are poor productivity, component deterioration due to generation of much heat. With this method only Oil in water (O/W) liquid nanoemulsion of less than 20% oil phase can be prepared.

Micro-fluidization: Micro-fluidization technology makes use of a device called ‘MICRO FLUIDIZER’. This device uses a high pressure positive displacement pump which forces the product through the interaction chamber, consisting of small channels called micro channels. The product flows through the micro channels on to an impingement area resulting in very fine particles of submicron range. The two solutions (aqueous and oily phase) are combined together and processed in an inline homogenizer to yield a course emulsion. The course emulsion is into a micro fluidizer where it is further processed to obtain a stable nanoemulsion.
**Phase Inversion Method**: Fine dispersion is obtained by chemical energy resulting of phase transitions occur through emulsification method. The adequate phase transitions are produced by changing the composition at constant temperature or by changing the temperature at constant composition.

**Figure 4: Phase Inversion**

**Self-emulsification methods**: This method generates nanoemulsions at room temperature without any use of organic solvent and heat. Small droplet size of 50nm can be generated by step wise addition of water into solution of surfactant in oil, with gentle stirring and at constant temperature.\(^{[11]}\)

**CHARACTERIZATION OF NANOEMULSION**\(^{[12]}\)

1. **Particle size analysis**: dynamic light scattering (DLS) methods is used for the measurement of particle size and their distribution.
2. **Zeta potential**: it measures the surface charge of nanoemulsion with the help of a mini electrode.
3. **Transmission Electron Microscopy**: it is used to determine the size, number and structure of nanoemulsions.
4. **Viscosity**: it used to determine the viscosity using Brookfield type rotary viscometer.
5. **Thermodynamic stability studies**:  
   1. Centrifugation: formulations were centrifuged at 3500 rpm for 30 minutes. A sample that does not show phase separation is selected.
   2. Heating and cooling cycle: 6 cycles between refrigerator temperature (4°C) and 45°C with storage not less than 48 hrs were done. Stable formulations were subjected to freeze thaw cycle.
   3. Freeze-thaw cycle: 3 freeze-thaw cycles were done for the formulation between -21°C and 25°C. The formulations that survived thermodynamic stability were selected for further study.

**PHARMACEUTICAL APPLICATIONS OF NANOEMULSIONS**:

1. **Solubilisation of poorly soluble drugs**: solubilisation is the main important parameter for application of nanoemulsions. Lorazepam is injected intravenously for premedication and sedation in an operation. It is usually administered as a solution in organic solvents. A phospholipids stabilised soybean oil emulsion was able to stably emulsify Lorazepam to a 20 fold, which could reduce the volume fort injection.\(^{[13]}\)
2. **Ocular delivery**: for the treatment of eye, drugs are delivered topically. O/W nanoemulsions have been investigated for ocular administration. Eg: Pilocarpine.
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 target ability.
4. **Nasal route**: nanoemulsions increase absorption by solubilising the drug in the inner phase of an emulsion and prolonging contact time between emulsion droplets and nasal mucosa.
5. **Cosmetics**: nanoemulsions are acceptable in cosmetics because there is no inherent creaming, sedimentation, coalescence or flocculation that are observed with macro emulsions. It is also highlighted that it helps to give skin care formulations a good skin feel.
6. **Antimicrobial**: anti-microbial nanoemulsions is oil in water droplets that range from 200 to 600nm. They are composed of oil and water and are stabilized by surfactants and alcohol. The nanoemulsion particles are driven to fuse with lipid containing organisms.
7. **Nanoemulsions in cell culture technology**: cell cultures are used for in vitro assays or to produce biological compounds such as antibodies or recombinant proteins. To optimise cell growth, the culture medium can be supplemented with a number of defined molecules or blood serum. The advantages of using nanoemulsions in cell culture technology are better uptake of oil soluble supplements in cell culture; improve growth and vitality of cultured cells, and allowance of toxicity studies of oil soluble drugs in cell cultures.
8. **Nanoemulsions in cancer treatment**: advantages of formulating various lipophilic anti-cancer drugs in sub micron O/W emulsion are obvious. The oil phase act as the solubilizer for the lipophilic compound. Therefore, solubility of lipophilic drugs can be enhanced in an emulsion system, leading to smaller administration volumes compared to aqueous solution. Emulsion show a promise in cancer chemotherapy, as vehicles for prolonging the drug release after intramuscular and intratumoral injection.\(^{[14]}\)

**CONCLUSION**

Nanoemulsion formulation offers several advantages for the delivery of drugs, biological and diagnostic agents. Nanoemulsions are applicable for all routes and therefore hold promise for different fields. This technology could be developed to overcome the poor absorption of phytopharmaceuticals. Overall nanoemulsion formulation can be considered as effective, safe and patient compliance formulation for the delivery of pharmaceuticals. In the upcoming future, further research work and development will be carried out for the clinical application of nanoemulsion.

**REFERENCES**:


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