A BRIEF INTRODUCTION TO METHODS OF PREPARATION, APPLICATIONS AND CHARACTERIZATION OF NANOEMULSION DRUG DELIVERY SYSTEMS

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ABSTRACT

Nanoemulsions have attracted great attention in delivery of therapeutically active agents since approximately 40% of new chemical entities are hydrophobic in nature and the delivery of these poorly water soluble drugs is a challenge for delivery of drugs. The emulsions and Nanoemulsions differ mainly in the size and shape of the particles dispersed in the continuous phase. The particle size in nanoemulsions is (10-200nm) and those of conventional emulsions are (1-20µm). Nanoemulsions are prepared by high energy emulsification methods like micro fluidic and ultrasonic methods, these methods rupture large micro droplets into nano scale droplets. Oil in water (O/W) and water in oil (W/O) nanoemulsions were prepared by aqueous phase titration method. Nano emulsions can be evaluated for their morphology, droplet size, viscosity, PH, optical clarity, zeta potential, conductivity, transmission electron microscopy and polydispersity. Nanoemulsions find application in controlled drug delivery, targeted drug delivery, nutraceuticals, food products, transdermal and colloidal drug delivery. This article includes preparation, characterization, evaluation and application of nanoemulsions.

Key words: Nanoemulsion, co surfactant, phase inversion, microfluidization

1. INTRODUCTION

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. Nanoemulsion is considered to be a thermodynamically or kinetically stable liquid dispersion of an oil phase and water phase in combination with a surfactant. The dispersed phase droplet size is about 5 nm-200 nm and should have very low oil/water interfacial tension. Cosurfactant or cosolvent is used in many cases in addition to the surfactant, the oil phase and the water phase.

1.2. TYPES OF NANOEMULSION

Depending on the composition there are three types of nanoemulsions:

1. Oil in water nanoemulsions wherein oil droplets are dispersed in the continuous aqueous phase.
2. Water in oil nanoemulsions wherein water droplets are dispersed in the continuous oil phase.
3. Bi-continuous nanoemulsions wherein micro domains of oil and water are interdispersed within the system.

The main difference between emulsions and nanoemulsion are that even though emulsion is having kinetic stability they are thermodynamically unstable. Emulsions are cloudy but nanoemulsions are clear and translucent. They also differ in their method of preparation.

1.3. ADVANTAGES OF NANOEMULSION

1. Increase the rate of absorption.
2. Eliminates variability in absorption
3. Helps solubilize lipophilic drug
4. Increases bioavailability
5. Various routes like topical, oral and intravenous can be used to deliver the product.
6. Helpful in taste masking.
7. Rapid and efficient penetration of the drug moiety.
8. Liquid dosage form increases patient compliance.
9. Nanoemulsions are thermodynamically stable system and the stability allows self emulsification of the system.

1.4. DISADVANTAGES OF NANOEMULSION

1. Use of a large concentration of surfactant and cosurfactant necessary for stabilizing the nano droplets.
2. Limited solubility capacity for high melting substances.
3. The surfactant must be non toxic for using pharmaceutical applications.
4. Nanoemulsion stability is influenced by environmental parameters such as temperature and PH.

1.5. COMPONENTS OF NANOEMULSION

Nanoemulsions contain three main components.

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

1.6. SURFACTANTS USED IN NANOEMULSION

Surfactants used for stabilizing the systems may be

1. Non ionic
2. Zwitterionic
3. Cationic
4. Anionic

1.7. CLASSIFICATION OF SURFACTANTS

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

Surfactants used in nanoemulsions

S.No	Surfactants
1	Capryol 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 in 1944 CS, M, 2125 CS
6	Lauroglycol 90
7	PEG MW > 4000
8	Plurol Oleique CC 497
9	Poloxamer 124 and 188
10	Softigen 701, 767
11	Tween 80

Oils used in nanoemulsions

S.No	Oils
1	Captex 355
2	Captex 200
3	Captex 8000
4	Witepsol
5	Myritol 318
6	Isopropyl Myristate

Cosurfactants used in nanoemulsions

S.No	Cosurfactants
1	Transcutol p
2	Glycerin, Ethyleneglycol
3	Propylene glycol
4	Ethanol
5	Propanol

2. PREPARATION OF NANO EMULSION

The drug is dissolved in the lipophilic part (oil) of the nanoemulsion. The aqueous phase is combined with surfactant and a cosurfactant. The aqueous phase is added at a slow rate with gradual stirring until the system is transparent. The amount of surfactant and cosurfactant that can be incorporated shall be determined with the help of pseudo ternary phase diagram. Finally ultra sonicator can be used to achieve the desired range of dispersed globules. Then it is allowed to equilibrate. Gel may be prepared by adding a gelling agent. Most widely used gelling agent is carbomer.

Factors to be considered during preparation of nanoemulsion:

- The prime requirement in nanoemulsion production is an ultra low interfacial tension should be attained at the oil water interface, so surfactants must be carefully chosen.
- Concentration of surfactant must be high enough to provide the number of surfactant molecules needed to stabilize the nano droplets.
- The interface must be flexible to promote the formation of nanoemulsion.

2.1. METHODS OF PREPARATION OF NANOEMULSION

Several methods have been suggested to prepare nanoemulsion. Formation of nanoemulsion system required a high amount of energy. This energy can be provided either by mechanical equipment or the chemical potential inherent within the component. Some methods used for the preparation of nanoemulsion are

2.2. 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. 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 lipophilic with increase in temperature because of dehydration of polymer chain. At low temperature the surfactant monolayer has a great positive spontaneous curvature forming oil swollen micellar solution phase.

2.3. Sonication Method: In this method the droplet size of conventional emulsion are reduced with the help of sonication mechanism. Only small batches of nanoemulsion can be prepared by this method.

2.4. 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 and cream nanoemulsion of high viscosity or hardness with a mean droplet diameter lower than 200 nm cannot be prepared.

2.5. Microfluidizatiion: Microfluidization technology makes use of a device called 'MICRO FLUIDIZER". This device uses a 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 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 course emulsion. The course emulsion is into a micro fluidizer where it is further processed to obtain a stable nano emulsion.

2.6. Production with high amplitude ultrasound: This method is a viable alternative to high pressure homogenization. Intense shear forces necessary for the nanoemulsification are generated by ultrasonic cavitation which produces violently and asymmetrically imploding vacuum bubbles and break up particles down to the nanometer scale. This method is successfully used in small scale production of nanoemulsions.

3. CHARACTERIZATION OF NANOEMULSIONS

3.1. Phase behavior study: This study is a characterization and optimization of ingredients (surfactant, oil phase and aqueous phase). Generally the study is necessary in case of nanoemulsion formulation prepared by phase inversion temperature method and self emulsification method in order to determine the phase of nanoemulsion and dispersibility. Study is done by placing the different ingredients of nanoemulsion by varying the concentration in glass ampoules and thoroughly homogenized at a certain temperature for a time until equilibrium anisotropic phase can be identified by polarized light.

3.2. Particle size analysis: Generally in case of nanoemulsion dynamic light scattering (DLS) method is used for the measurement of particle size and their distribution.

3.3. Surface Charge Measurement: The surface zeta potential of nanoemulsion is predicted with the help of mini electrode.

3.4. Transmission Electron Microscopy: This method is used to observe the morphology of nanoemulsion.

3.5. Viscosity: Viscosity will be measured to ensure the better delivery of the formulation.

3.6. Stability of Nanoemulsions: Stability studies are performed on nanoemulsions by storing them at refrigerator and room temperatures over a number of months. The viscosity, refractive index and droplet size are determined during this period of storage. Insignificant changes in these parameters indicate formulation stability.

Accelerated stability studies can also be performed. In this case, nanoemulsion formulation is kept at accelerated temperatures and samples are withdrawn at regular intervals and analyzed for drug content by HPLC. The amount of drug degraded and remaining in nanoemulsion formulation is determined at each time interval.

4. APPLICATIONS OF NANOEMULSION

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 aerosois, 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.

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

4.2. 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 Mixturees of local anaesthetic) have proven to be useful medication by this route.

4.3. 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.

4.4. 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.

4.5. 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 with in 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).

5. CONCLUSION

Although high energy emulsification method is traditionally used for the preparation of nanoemulsion formulation but low emulsion emulsification method now create an attraction due to their wide application and advantages as a formulation and stability aspects. 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 phse, methods used, process variables and addition of additives. Overall nanoemulsion formulation may be considered as effective, safe and patient compliance formulation for the delivery of pharmaceuticals.

6. REFERENCES

Gasco M R, Gallarate M, Pattarino F, *In-vitro* permeation of azelaic acid from viscosized microemulsions, Int J Pharm, 69, 1991, 193–196.

Kreilgaard M, Pedersen E J, Jaroszewski J W, NMR characterization and transdermal drug delivery potential of microemulsion systems, J Control Release, 69, 2000, 421-433.

Kriwet K, Müller-Goymann C C, Diclofenac release from phospholipid drug systems and permeation through excised human stratum corneum, Int J Pharm, 125, 1995, 231–242.

Ktistis G, Niopas I, A study on the *in-vitro* percutaneous absorption of propranolol from disperse systems, J Pharm Pharmacol, 1998, 50, 413–418.

Shinoda K, lindman B, organized surfactant systems micro emulsion Langmuir, 3, 1987, 135-149.

Shinoda K, Lindman B, Organised surfactant systems: microemulsions, Langmuir, 3, 1987, 135–149.

Tenjarla SN; Microemulsions, An overview and pharmaceutical applications, Critical Reviews in Therapeutic Drug Carrier Systems, 16, 1999, 461–521.

Tenjarla SN, Microemulsions: An overview and pharmaceutical applications, Critical Review s in Therapeutic Drug carrier, systems 16, 1999, 461-521.

Trotta M, Influence of phase transformation on indomethacin release from microemulsions, J Control Release 60, 1999, 399–405.