Indian J.Pharm.Biol.Res. 2014; 2(1):122-127

CODEN (USA): IJPB07 ISSN: 2320-9267

Indian Journal of Pharmaceutical and Biological Research (IJPBR)

Journal homepage: www.ijpbr.in

Review Article

Nanoemulsion: A Review on Novel Profusion in Advanced Drug Delivery

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ARTICLE INFO:

Article history:

Received: 25 December 2013

Received in revised form:

8 January 2014

Accepted: 10 January 2014

Available online7 March 2014

Keywords:

Nanoemulsion,

Submicron size droplet,

Self-emulsifying agent,

Drug delivery system.

ABSTRACT

Nanoemulsions are submicron sized emulsion that is under extensive investigation as drug carriers for improving the delivery of therapeutic agents. These are by far the most advanced nanoparticle systems for the systemic delivery of active pharmaceutical for controlled drug delivery and targeting. These are the thermodynamically stable isotropic system in which two immiscible liquid (water and oil) are mixed to form a single phase by means of an appropriate surfactants or it mixes with a droplet diameter approximately in the range of 0.5-100 µm. Nanoemulsion droplet size falls typically in the range of 20-200 nm and shows a narrow size distribution. Nanoemulsion show great promise for the future of cosmetics, diagnostics, drug therapies and biotechnologies. Thus the aim of this review is focused on nanoemulsion advantage and disadvantage, various methods of preparation, characterization techniques and the various applications of sub micron size emulsion in different areas such as various route of administration, in chemotherapy, in cosmetic, etc.

1. Introduction

Nanoemulsions can be defined as oil-in-water (o/w) emulsions with mean droplet diameters ranging from 50 to 1000 nm. Usually, the average droplet size is between 100 and 500 nm, terms sub-micron emulsion (SME) and mini-emulsion are used as synonyms. Since, the preparation of the first nanoemulsion in 1940s, it can be of three types such as oil-in-water (o/w), water-in-oil (w/o), and bi-continuous. The transformation between these three types can be achieved by varying the components of the emulsions. Each type of the nanoemulsions serves as a template for preparing polymer latex particles, nonporous polymeric solids etc. Apart from this, the nanoemulsions with pharmaceutically accepted ingredients are utilized in the development of drug formulations for oral drug delivery. The nanoemulsions are also referred as miniemulsions, ultrafine emulsions and submicron emulsions. Phase behaviour studies have shown that the size of the droplets is governed by the surfactant phase structure (bicontinuous microemulsion or lamellar) at the inversion point induced by either temperature or composition. Studies on Nanoemulsion formation by the phase inversion temperature method have shown a relationship between minimum droplet size and complete solubilization of the oil in a microemulsion bicontinuous phase independently of whether the initial phase equilibrium is single or multiphase. Due to their small droplet size, nanoemulsions possess stability against sedimentation or creaming with Ostwald ripening forming the main mechanism of nanoemulsion breakdown. The main application of nanoemulsions is the preparation of nanoparticles using a polymerizable monomer as the disperse phase (the so-called miniemulsion polymerization method) where nanoemulsion droplets act as nanoreactors. Another interesting application which is experiencing an active development is the use of Nanoemulsions as formulations, namely, for controlled drug delivery and targeting. The main application of nanoemulsions is the preparation of nanoparticles using a polymerizable monomer as the disperse phase where nanoemulsion droplets act as nanoreactors [1].

1.1 *Advantages of Nanoemulsion*

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1. Nanoemulsions have higher surface area and free energy that make them an effective transport system.
2. They do not show the problems of inherent creaming, flocculation, coalescence and sedimentation.
3. It can be formulated in variety of formulations such as foams, creams, liquids and sprays.
4. They are non-toxic; non-irritant hence can be easily applied to skin and mucous membranes.
5. It can be administered orally if the formulation contains surfactants which are biocompatible.
6. It do not damage healthy human and animal cells hence are suitable for human and veterinary therapeutic purposes.
7. It provides better uptake of oil-soluble supplements in cell cultures technology to improve growth of cultured cells and allows toxicity studies of oil-soluble drugs.
8. It may be applied as a substitute for liposomes and vesicles and it is possible to build lamellar liquid crystalline phases around the nanoemulsion droplets.
9. Due to their small size, nanoemulsions can penetrate through the "rough" skin surface and this enhances penetration of actives.
10. It constitutes the primary step in nanocapsules and nanospheres synthesis using nano precipitation and the interfacial poly-condensation [2].

1.2 *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 [3].

1.3 *Components of Nanoemulsion*

Main three components of Nanoemulsions are as follows:
1. Oil
2. Surfactant/Co-surfactant
3. Aqueous phase

Nanoemulsions are colloidal dispersions composed of an oil phase, aqueous phase, surfactant and cosurfactant at appropriate ratios. Unlike coarse emulsions micronized with external energy nanoemulsions are based on low interfacial tension. This is achieved by adding a cosurfactant, which leads to spontaneous formation of a thermodynamically stable nanoemulsion. The droplet size in the dispersed phase is very small, usually below 140 nm in diameter, which makes the Nanoemulsions transparent liquids. In principle, nanoemulsions can be used to deliver drugs to the patients via several routes, but the topical application of nanoemulsions has gained increasing interest. The three main factors determining the transdermal permeation of drugs are the mobility of drug in the vehicle, release of drug from the vehicle, and permeation of drug into the skin. These factors affect either the thermodynamic activity that drives the drug into the skin or the permeability of drug in the skin, particularly stratum corneum. Nanoemulsions improve the transdermal delivery of several drugs over the conventional topical preparations such as emulsions and gels. Mobility of drugs in Nanoemulsions is more facile as compared to the Nanoemulsion with gel former which will increase its viscosity and further decrease the permeation in the skin. The superior transdermal flux from Nanoemulsions has been shown to be mainly due to their high solubilization potential for lipophilic and hydrophilic drugs. This generates an increased thermodynamic activity towards the skin. Nanoemulsions may affect the permeability of drug in the skin. In this case, the components of nanoemulsions serve as permeation enhancers. Several compounds used in nanoemulsions have been reported to improve the transdermal permeation by altering the structure of the stratum corneum. For example, short chain alkanols are widely used as permeation enhancers. It is known that oleic acid, a fatty acid with one double bond in the chain structure, perturbs the lipid barrier in the stratum corneum by forming separate domains which interfere with the continuity of the multilamellar stratum corneum and may induce highly permeable pathways in the stratum corneum. Isopropyl myristate (IPM) is used as a permeation enhancer in transdermal formulations, but the mechanism of its action is poorly understood. Nonionic surfactants are widely used in topical formulations as solubilizing agents but some recent results indicate that they may affect also the skin barrier function. It is of interest to explore the effects of these components in the organized nanoemulsion structures. The aim of the present study was to investigate the potential of several Nanoemulsion formulations in transdermal delivery of lipophilic drugs. A unique attempt was made to emulsify coconut oil with the help of polyoxyethylene 2-cetyl ether and isopropanol or ethanol, forming stable isotropic dispersion thus paving way for use of plant and vegetable oil to be used as oil phase in Nanoemulsion [3].

1.4 *Methods of Preparation of Nanoemulsion*

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 [4].

Factors to be considered during preparation of nanoemulsion:

a. Surfactants must be carefully chosen so that an ultra low interfacial tension (< 10-3 mN/m) can be attained at the oil / water interface which is a prime requirement to produce nanoemulsions.
b. Concentration of surfactant must be high enough to provide the number of surfactant molecules needed to stabilize the microdroplets to be produced by an ultra low interfacial tension.
c. The interface must be flexible or fluid enough to promote the formation of nanoemulsions.

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. 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 [4].

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. 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 [5].

Spontaneous Emulsification

It involves three main steps-

a. Preparation of homogeneous organic solution composed of oil and lipophilic surfactant in water miscible solvent and hydrophilic surfactant.
b. The organic phase is injected in the aqueous phase under magnetic stirring the o/w emulsion was formed.
c. The water-miscible solvent is 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. Other method used for Nanoemulsion preparation is the phase inversion temperature technique [8].

1.5 *Characterization of Nanoemulsion*

Nanoemulsion Droplet Size Analysis

Droplet size distribution is one of the important physicochemical characteristics of a nano-emulsion, was measured by a diffusion method using a light-scattering particle size analyzer Coulter LS-230. It measures the size distribution using the diffusion of laser light by particles. Polarization intensity differential scattering (PIDS) is the assembly consists of an incandescent light source and polarizing filters, a PIDS sample cell and an additional seven photodiode detectors. It is used to measure the droplets size distribution, like 0.5 ml emulsion is introduced in the measure compartment (125 ml of water). The results are presented as the volume distribution [9].

Polydispersity Index

The average diameters and polydispersity index of samples are measured by photon correlation spectroscopy. The measurements are performed at 25^{o}C using a He-Ne laser [9].

pH

The apparent pH of the formulation is measured by pH meter [9].

Transmission Electron Microscopy (TEM)

Morphology and structure of the nanoemulsion are studied using transmission electron microscopy. Combination of bright field imaging at increasing magnification and of diffraction modes is used to reveal the form and size of nanoemulsion droplets. Observations are performed as a drop of the nanoemulsion is directly deposited on the holey film grid and observed after drying [9].

Drug Content

Drug content is determined by reverse phase HPLC method using C18 column [9].

Zeta Potential

Zeta potential is a technique which is used to measure the surface charge properties and further the long term physical stability of nanoemulsions, the instrument which is used to measure the surface charge is known as ZetaPALS [10].

Thermal Conductivity Technique

In this technique, named 3 -wire method is developed to measure nanoemulsion by the thermal conductometer [10].

Dynamic Light Scattering Spectrophotometer

Dynamic light scattering measurements are done at 90° using a neon laser of wavelength 632nm. The particle size and particle size distribution is determined by dynamic light scattering spectrophotometer [11].

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 [11].

Dilutability Test

o/w Nanoemulsions are dilutable with water whereas w/o are not and undergo phase inversion into o/w nanoemulsion [11].

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. 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].

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 [11].

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. 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 [12].

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 [12].

In-Vitro Skin Permeation Studies

In-vitro skin permeation studies are performed by using Keshary Chien-diffusion cell. It is performed on abdominal skins and is obtained from male rats weighing 250±10 g with a recirculating water bath and 12 diffusion cells. The skins are placed between the donor and the receiver chambers of vertical diffusion cells. The receiver chambers are filled with freshly water containing 20% ethanol. The receiver chambers are set at 37^{o}C and the solution in the receiver chambers is stirred continuously at 300 rpm. The formulations are placed in the donor chamber. At 2, 4, 6, 8 h, 0.5 ml of the solution in the receiver chamber is removed for GC analysis and replaced immediately with an equal volume of fresh solution. The permeation rates of drug at a steady-state through rat skins can be calculated from the slope of linear portion of the cumulative amount permeated through the rat skins per unit area versus time plot [12].

2. Applications of Nanoemulsion

Parenteral Delivery

Parenteral administration (especially via the intravenous route) of drugs with limited solubility is a major problem in industry because of the extremely low amount of drug actually delivered to a targeted site. 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. The literature contains the details of the many Nanoemulsion systems, few of these can be used for the parenteral delivery because the toxicity of the surfactant and parenteral use. An alternative approach was taken by Von Corsewant and Thoren in which C3-C4 alcohols were replaced with parenterally acceptable co-surfactants, polyethylene glycol (400) / polyethylene glycol (660) 12-hydroxystearate / ethanol, while maintaining a flexible surfactant film and spontaneous curvature near zero to obtain and almost balanced middle phase nanoemulsion. The middle phase structure was preferred in this application, because it has been able to incorporate large volumes of oil and water with a minimal concentration of surfactant [13].

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. However, most are difficult to administer orally. With on oral bioavailability in conventional (i.e. non-nanoemulsion based) formulation of less than 10%, they are usually not therapeutically active by oral administration. Because of their low oral bioavailability, most protein drugs are only available as parenteral formulations. However, peptide drugs have an extremely short biological half life when administered parenterally, so require multiple dosing. A nanoemulsion formulation of cyclosporine, named Neoral® has been introduced to replace Sandimmune®, a crude oil-in-water emulsion of cyclosporine formulation. Neoral® is formulated with a finer dispersion, giving it a more rapid and predictable absorption and less inter and intra patient variability [14].

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. Both o/w and w/o nanoemulsions have been evaluated in a hairless mouse model for the delivery of prostaglandin E1. The nanoemulsions were based on oleic acid or Gelucire 44/14 as the oil phase and were stabilized by a mixture of Labrasol (C8 and C10 polyglycolysed glycerides) and Plurol Oleique CC 497 as surfactant. Although enhanced delivery rates were observed in the case of the o/w nanoemulsion, the authors concluded that the penetration rates were inadequate for practical use from either system. The use of lecithin/IPP/water nanoemulsion for the transdermal transport of indomethacin and diclofenac has also been reported. Fourier transform infra red (FTIR) spectroscopy and differential scanning calorimetry (DSC) showed the IPP organogel had disrupted the lipid organisation in human stratum corneum after a 1 day

incubation. The transdermal delivery of the hydrophilic drug diphenhydramine hydrochloride from a w/o nanoemulsion into excised human skin have also been investigated. The formulation was based on combinations of Tween 80 and Span 20 with IPM. However two additional formulations were tested containing cholesterol and oleic acid, respectively. Cholesterol increased drug penetration whereas oleic acid had no measurable effect, but the authors clearly demonstrated that penetration characteristics can be modulated by compositional selection [15].

Ocular and Pulmonary 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. The nanoemulsions containing pilocarpine were formulated using lecithin, propylene glycol and PEG 200 as co-surfactant and IPM as the oil phase. The formulations were of low viscosity with a refractive index lending to ophthalmologic applications. The formation of a water-in-HFA propellent Nanoemulsion stabilized by fluorocarbon non-ionic surfactant and intended for pulmonary delivery has been described[15].

Nanoemulsions 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 a polar media causes the denaturation of biocatalysts. The use of water-proof media is relatively advantageous. Enzymes in low water content display and have-

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

Many enzymes, including lipases, esterases, dehydrogenases and oxidases often function in the cells in microenvironments that are hydrophobic in nature. In biological systems many enzymes operate at the interface between hydrophobic and hydrophilic domains and these usually interfaces are stabilized by polar lipids and other natural amphiphiles. Enzymatic catalysis in nanoemulsions has been used for a variety of reactions, such as synthesis of esters, peptides and sugar acetals transesterification; various hydrolysis reactions and steroid transformation. The most widely used class of enzymes in microemulsion-based reactions is of lipases [16].

3. Conclusion

Nanoemulsion formulations offer several advantages for the delivery of drugs, biologicals, or diagnostic agents and able to protect labile drug, control drug release, increase drug solubility, increase bioavailability and reduce patient variability. Traditionally, Nanoemulsions have been used in clinics for more than four decades as total parenteral nutrition fluids. Nanoemulsions 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. Moreover, targeting moiety has opened new avenues for targeted delivery of drugs, genes, photosensitizers, and other molecules to the tumor area. It is expected that further research and development work will be carried out in the near future for clinical realization of these targeted delivery vehicles.

Conflict of interest statement

We declare that we have no conflict of interest.

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Cite this article as: Rohit Rajendra Bhosale, Riyaz Ali Osmani, Prasanna Prasad Ghodake, Sabir Majjid Shaikh , Sarika Raghunath Chavan. Nanoemulsion: A Review on Novel Profusion in Advanced Drug Delivery. **Indian J. Pharm. Biol. Res.2014;2(1):122-127.**