Chronicles of Young Scientists 1(2) 2010: 2-6

Available online at www.opubs.com/cys

Chron Young Scientist

Review Article

Nanoemulsion: A new concept of delivery system

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Received 25 January 2010; accepted 15 February 2010

Abstract Nanoemulsion has been identified as a promising delivery system for various drugs including biopharmaceuticals. Nanoemulsion is a heterogeneous system composed of one immiscible liquid dispersed as droplets within another liquid. The droplets size of nano emulsion is between 20 to 500 nm. Diameter and surface properties of droplets of nanoemulsion plays an important role in the biological behavior of the formulation. Small droplet sizes lead to transparent emulsions so that product appearance is not altered by the addition of an oil phase. In this paper various aspects of nanoemulsion have been discussed including advantages, disadvantages and methods of preparation. Furthermore new approaches of stability of formulation, effect of types and concentration of surfactant, process variables and method are also discussed to improve the stability of nanoemulsion formulation

Keywords: Nanoemulsion, Ostwald ripening, Microemulsion

Introduction

Nanoemulsions consist of fine oil-in-water dispersions, having droplets covering the size range of 100–600 nm. Nanoemulsions, usually spherical, are a group of dispersed particles used for pharmaceuticals biomedical aids and vehicles that shows great promise for the future of cosmetics, diagnostics, drug therapies and biotechnologies. [1] The terms sub-micron emulsion (SME), [2] mini-emulsion [3] and ultra fine emulsion [4] are used as synonyms. Nanoemulsion is a heterogeneous mixture of lipid and aqueous phase and stability are achieved by using a suitable material known as emulsifying agents. Nanoemulsion is a translucent system compare to ordinary emulsion or some time microemulsion. It has been demonstrated that with the help of nanoemulsion as a delivery system retention time of a drug in the body can be increased, so low amount of drug is required for the therapeutic action. Past studies shows the utilization of nanoemulsion technology for the enhancement of bioavailability of lipophilic drug [5].

Nowadays this dosage form is frequently used for the delivery of various biopharmaceuticals as vaccines, DNA encoded drugs [6], and antibiotics [7]. Nanoemulsion technology is used as a cosmetics and topical preparations. This technology has a great advantage over the other dosage forms that the formulation can be delivered by various routes including oral [5], ocular [8] and transdermal [9].

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The smaller droplet size of emulsions not only suppresses the coalescence or coagulation of emulsion droplets but also suppresses the precipitation of emulsions and also helps to deliver the active agents [10].Oil in water type of nanoemulsion formulation are prepared since long ago [2,3, 11, 12] but water in oil type of nanoemulsion is recently investigated by K. Landfester [13, 14]. Both of these type of nanoemulsion have various advantages as pharmaceuticals and in cosmetics science as well as. In this paper we are trying to understand various aspects related to the manufacturing of nanoemulsion, type of emulsifying agents, and various problems during the formulation of nanoemulsion delivery system. Due to the very small size of droplets it provides the stability against sedimentation and creaming with Ostwald ripening forming the main mechanism of nanoemulsion breakdown. Structure of o/w nanoemulsion droplets are demonstrated in Fig. 1. [15]

Application of nanoemulsion

Nanoemulsion has become a very attractive formulation for the delivery of pharmaceuticals. Nanoemulsion also shows a good advantage in the field of cosmetics. The attraction of nanoemulsion formulation in pharmaceuticals and cosmetics is due to following reasons [16].

- Nanoemulsion never shows the creaming and sedimentation kind of problems due to its very small droplet size. These problems are very common with conventional emulsion and even microemulsion. Basically both problems are associated with the influence of gravitational force over the droplet of emulsion. But in case of nanoemulsion the droplet size is very small which minimized the working of gravitational force over the droplets and posses creaming and sedimentation of emulsion.

- Again small droplet size of nanoemulsion prevents the coalescence of droplets. In the coalescence process droplets come together and form a large droplet with increased size which is responsible for the instability of emulsion. But the small droplet size of nanoemulsion prevent the coalescence among them and prevent the deformation and than surface fluctuation.
- Dispersibility of nanoemulsion is very high as compared to microemulsion because small droplet size prevents the flocculation of droplets and this process makes the system dispersed without separation.
- Nanoemulsion formulation provides a rapid penetration of active ingredients through skin due to the large surface area of droplets. Even sometimes it is found that nanoemulsion penetrate easily through rough skin. This property of nanoemulsion minimizes the additional utilization of special penetration enhancer which is responsible for incompatibility of formulation.
- Nanoemulsion formulation required low amount of surfactant compared to microemulsion. For example about 20- 25 % surfactant is required for the preparation of microemulsion but 5-10 % surfactant is sufficient in case of nanoemulsion. Again with the help of nanoemulsion surfactant utilization can be minimized.
- Nanoemulsion has a transparent and fluidy property which improves the formulation patient compliance and safe for administration due to the absence of any thickening agent and colloidal particles.
- It is also reported that nanoemulsion may be used for the target delivery of active ingredient especially in cancer therapy.
- Nanoemulsion formulation may become the stable alternate for the liposomes and vesicle type of delivery systems.
- Nanoemulsion formulation can be administered by the various routes of body. There are various reported methods which support the administration of nanoemulsion formulation through paranteral [17-20], oral [21-23], topical [24, 25], nasal [26] and ocular [27, 28] route.
- These formulations may be used to increase the bioavailability of poor water soluble drug by developing oil in water type of nanoemulsion [29, 30].

Limitation of nanoemulsion

Although this formulation provide great advantages as a delivery system for the consumers but sometimes the reduced size of droplets are responsible for the limited use of nanoemulsion formulation. Some limitations of nanoemulsion are as follows [31].

- The manufacturing of nanoemulsion formulation is an expensive process because size reduction of droplets is very difficult as it required a special kind of instruments and process methods. For example, homogenizer (instrument required for the nanoemulsion formulation) arrangement is an expensive process. Again microfludization and ultrasonication (manufacturing process) require high amount of financial support.
- Stability of nanoemulsion is quite unacceptable and creates a big problem during the storage of formulation for the longer time period. Ostwald ripening is the main factor associated with unacceptability of nanoemulsion formulations. This is due to the high rate of curvature of small droplet show greater solubility as compared to large drop with a low radius of curvature.
- Less availability of surfactant and cosurfactant required for the manufacturing of nanoemulsion is another factor which marks as a limitation to nanoemulsion manufacturing.

Preparation Methods of nanoemulsion

Several methods have been suggested for the preparation of nanoemulsion. The basic objectives of the nanoemulsion preparation to achieve the droplet size range of 100-600 nm and another is to provide the stability condition. 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 [32]. Here some methods are discussed which are freely used for the nanoemulsion preparation.

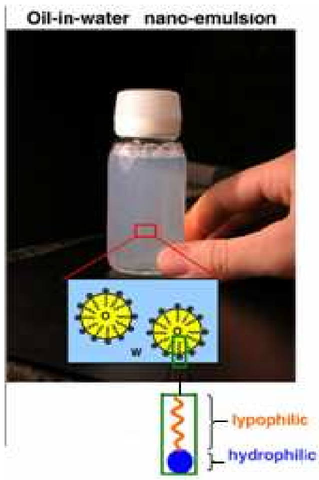

Fig:1. An o/w type nanoemulsion with structural droplets demonstration

1. Phase inversion method

In this method fine dispersion is obtained by chemical energy resulting of phase transitions taking place through emulsification path. The adequate phase transitions are produced by varying the composition at constant temperature or by varying the temperature at constant composition, phase inversion temperature (PIT) method was introduced by Shinoda et al. based on the changes of solubility of polyoxyethylene- type surfactant with temperature. This surfactant becomes lipophilic with increase in temperature due to dehydration of polymer chain. But at low temperature, the surfactant monolayer has a large positive spontaneous curvature forming oil-swollen micellar solution phase [33].

2. Sonication method

Sonication method is another best way to prepare nanoemulsion. In this method the droplet size of conventional emulsion or even microemulsion are reduced with the help of sonication mechanism. This method is not suitable for large batches only small batches of nanoemulsion can be prepared by this method [34].

3. **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 a special equipment know as homogenizer. There are some problems which are associated with homogenizer such as poor productivity, component deterioration due to difficult mass production and 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 [35].

Characterization of nanoparticles

Nano-emulsions are not thermodynamically stable, and, because of that, their characteristics will depend on preparation method. Here some parameters are discussed which should be analyzed at the time of preparation of nanoemulsion [36].

(i) Phase behaviour 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 ampules and thoroughly homogenized at a certain temperature for a time until equilibrium. Anisotropic phase can be identified by polarized light.

(ii) Particle Size Analysis: Formulated nanoemulsion should be analyzed for their hydrodynamic particle size and particle size distribution. Generally in case of nanoemulsion dynamic light scattering (DLS) method are used for the measurement of particles and further particle size distribution.

(iii) Surface charge measurement: Surface zeta potential of nanoemulsion droplets should be measured with the help of mini electrode to predict the surface properties of nanoemulsion.

(iv) Transmission Electron Microscopy (TEM): This method is used to observe the morphology in the nanoemulsion.

(v) Drug contain: This method is used to determine the amount of drug contained in the formulation. Various methods (especially Western Blot method) are used in this order.

(vi) Viscosity: Viscosity should be measured to ensure the better delivery of the formulation.

Nanoemulsion instability and its prevention methods

The instability of nanoemulsion is due to some main factors including creaming [37] flocculation [38, 39], coalescence [40] and Ostwald ripening [41]. Among them ostwald ripening is the main mechanism of nanoemulsion instability because rest of the problem are minimized by the small size of nanoemulsion and use of nonionic type of surfactant. Creaming of nanoemulsion is prevented by the faster diffusion rate of smaller droplets. Vanderwall force is responsible for the attraction of droplets and leads to the flocculation of emulsion. But in case of nanoemulsion nonionic surfactant, it does not create any kind of attractive force, hence no flocculation occurs. The droplet size of nanoemulsion also prevent the flocculation because these small droplets show high curvature and laplace pressure opposes the deformation of large droplets [42].Coalescence of droplets of nanoemulsion can be prevented by a thick multilamellar surfactant film adsorbed over the interface of droplets [43].

The only problem of instability of nanoemulsion can arise by the ostwald ripening. In ostwald ripening small droplets with high radius of curvature converted into large droplets with low radius of curvature [44].Two droplets diffuse and become one large droplet. Thus, after the storage for a long time period, droplets size distribution shifted to large sizes and the transparency of nanoemulsion become turbid. It is also identified that ostwald ripening create a problem during the delivery of formulations. Several theories have been suggested for the demonstration of ostwald ripening, among them LSW theory properly justified the factors affecting the ostwald ripening. Tadros et al demonstrated the addition of a small amount of insoluble oil (squalane) can reduce the diffusion of the smaller oil droplets from the small to the large droplet. Another method to prevent the effect of ostwald ripening is addition of polymeric surfactant on the interface which increase the elasticity of droplets and further reduce the effect of ostwald ripening [45].

Paqui Izquier do et al successfully demonstrates the influence of surfactant mixing ratio on the stability of nanoemulsion when phase inversion transition method are used as a nanoemulsion preparation method. The formation of O/W nanoemulsions by the PIT emulsification method in water/mixed nonionic surfactant/oil systems was studied. The hydrophilic–lipophilic properties of the surfactant were varied by mixing polyoxyethylene 4-lauryl ether ($C_{12}E_{14}$) and polyoxyethylene 6-lauryl ether ($C_{12}E_6$). Emulsification was performed in samples with constant oil concentration (20 wt %) by fast cooling from the corresponding HLB temperature to 25 °C. Nanoemulsions with droplet radius 60–70 nm and 25–30 nm were obtained at total surfactant concentrations of 4 and 8 wt%, respectively. The nanoemulsion with 8% surfactant ratio was showing high stability over the nanoemulsion with 4% surfactant concentration [46]. In another study Sher L. et al successfully demonstrated the effect of process variables over the droplet size of nanoemulsion which further leads to the stability of nanoemulsion. In the work they studied the formation and stability of n-decane in water nanoemulsion produced by the PIT method by using polyoxyethylene lauryl ether as a surfactant. The result of this work clearly indicate that the droplet size of nanoemulsion depends on the various process variables such as heating and cooling temperature of formulations and final temperature to which the mixture is cooled after phase inversion [47].

In another investigation the influence of both, the nature of the surfactant and surfactant concentration on the processes of droplet breakup and coalescence in the formation of decane in water nanoemulsions in a high-pressure homogenizer were investigated. Food proteins, phosphatidylglycerol and phosphatidylcholine were used as surfactant by varying concentration and droplet size were investigated for each formulation. It was found that for the proteins the increase in droplet volume was shown to be linear with respect to time, indicating an Ostwald ripening process. Although there was coalescence on storage at the lowest concentrations of phospholipids used, there was no observed ripening at any emulsifier concentration showing that phospholipids interfaces are structured in such a way as to resist ripening [48]. It is demonstrated that the mixture of surfactant enhances the stability a compared to single surfactant by Porras M [49]. It was also demonstrated that the stability of the electrostatically- and sterically-stabilized dispersions can be controlled by the charge of the electrical double layer and the thickness of the droplet surface layer formed by non-ionic emulsifier [50].

Discussion

Although high energy emulsification method is traditionally used for the preparation of nanoemulsion formulation but low emulsion emulsification method now create an attraction nowadays due to their wide application and advantages as a formulation and stability aspects. Possible application of nanoemulsion formulation has been discussed in the paper, but these applications are limited by the instability of nanoemulsion. 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 over the interfaces of nanoemulsion formulation. Overall nanoemulsion formulation may be considered as effective, safe, and patient compliance formulation for the delivery of pharmaceuticals and in cosmetics science after controlling the instability factors.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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