WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 7, Issue 2, 522-531. Review Article ISSN 2277 – 7105

NANOEMULSION: A WAY TO ENHANCE BIOAVAILABILITY

Wasim Khan*[1,2], Dr. Zeashan Hussain[2] and Noor Fatima Siddique[3]

[1]Asst. Professor Mahatma Gandhi Institute of Pharmacy, Lucknow.

[2]Professor, Mahatma Gandhi Institute of Pharmacy, Lucknow.

[3]Asst.Professor, Babasaheb Bhimroa Ambedkar University Lucknow.

Article Received on
02 December 2017,

Revised on 23 Dec. 2017,
Accepted on 13 Jan 2018

DOI: 10.20959/wjpr20182-10807

***Corresponding Author**
Wasim Khan
Asst. Professor Mahatma Gandhi Institute of Pharmacy, Lucknow.

ABSTRACT

Poor water solubility is still the main problem for the formulator which can be overcome by nanonization to larger extent which in turn increase drug loading and enhanced bioavailability. Nanoemulsions have attracted great attention in research, dosage form design and pharmacotherapy .Nanoemulsions are composed of oil droplets dispersed in an aqueous medium and stabilized by surfactant molecules. 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. The methods used for the production of nanoemulsions include HPH, microfluidization, ultrasonication and spontaneous emulsification. Nanoemulsions have widespread applications in different fields such as pharmaceutics, food technology and cosmetics. In this paper various aspects of nanoemulsion have been discussed including advantages, limitations and methods of preparation.

KEYWORDS: Microfluidization, nanoemulsion, droplet, surfactant, immiscible.

INTRODUCTION

Nanoemulsions (NEs) are defined as the dispersions of water and oil in the presence of combination of surfactant and co-surfactant (Smix) in a manner to reduce interfacial tension. On the basis of nature of dispersion and disperse phase, NEs were classified as: o/w, w/o & bi-continuous type. These systems are usually characterized by clear appearance, higher thermodynamic stability, small droplet size (< 200 nm), high drug solubility, and drug

reservoir for lipophilic and hydrophilic drugs. The capacity of nanoemulsions to dissolve large quantities of hydrophobics, along with their mutual compatibility and ability to protect the drugs from hydrolysis and enzymatic degradation make them ideal vehicles for the purpose of parenteral transport. Further, the frequency and dosage of injections can be reduced throughout the drug therapy period as these emulsions guarantee the release of drugs in a sustained and controlled mode over long periods of time. Additionally, the lack of flocculation, sedimentation and creaming, combined with a large surface area and free energy, offer obvious advantages over emulsions of larger particle size, for this route of administration. Their very large interfacial area positively influences the drug transport and their delivery, along with targeting them to specific sites. 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.

Components of Nanoemulsion[3]: Main three components of nanoemulsions are as follows:

1. Oil
2. Surfactant/Co-surfactant
3. Aqueous phase

Advantages

The attraction of nanoemulsion formulation in pharmaceuticals and cosmetics is due to following reasons.[4]

1. 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 possess creaming and sedimentation of emulsion.
2. 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 prevents the coalescence among them and also the deformation and surface fluctuation.

3. 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.
4. 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.
5. Nanoemulsion formulation required low amount of surfactant compared to microemulsion. For exampleabout 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.
6. Nanoemulsion has a transparent and fluidity property which improves the formulation patient compliance and safe for administration due to the absence of any thickening agent and colloidal particles.
7. It is also reported that nanoemulsion may be used for the target delivery of active ingredient especially in cancer therapy.
8. Nanoemulsion formulation may become the stable alternate for the liposomes and vesicle type of delivery systems.
9. Nanoemulsion formulation can be administered by the various routes of body. There are various reported methods which support the administration of nanoemulsion formulation through parenteral [5-8], oral [9-11], topical[12,13], nasal[14] and ocular[15,16] route.
10. These formulations may be used to increase the bioavailability of poor water soluble drug by developing oil in water type of nanoemulsion.[17,18]

Limitations of nanoemulsion[19,20]

1. Preparation of nanoemulsions requires in many cases special application techniques, such as the use of high pressure homogenizers as well as ultrasonics. Such equipment (such as the microfluidizer) became available only in recent years.
2. There is a perception in the personal care and cosmetic industry that nanoemulsions are expensive to pro- duce. Expensive equipment are required as well as the use of high concentrations of emulsifiers.
3. Lack of understanding of the mechanism of production of submicron droplets and the role of surfactants and co-surfactants.

4. Lack of demonstration of the benefits that can be obtained from using nanoemulsions when compared with the classical macroemulsion systems.
5. Lack of understanding of the interfacial chemistry that is involved in production of nanoemulsions.

METHODS OF PREPARATION OF NANOEMULSIONS

1. 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.

Certain factors affect the above process which are stated below:

(i) Effect of homogenization pressure: It is optimized the process parameter ranging from 100 to 150 bars. The higher is the size the lower is the particle size obtained.

(ii) No. of homogenization cycles: The higher the homogenization cycles the smaller is the particle size obtained. The cycles are carried out in 3, 4 or 10 cycles. The number of cycles is analyzed by polydispersity index of drug after each cycle.

Advantages

(a) Ease of scale-up and little batch-to-batch variation.
(b) Narrow size distribution of the nanoparticulate drug.
(c) Flexibility in handling the drug quality.
(d) Effectively used for thermolabile substances.

2. Microfluidization[21]: Microfluidization is a mixing technique, which makes use of a device called microfluidizer. This device uses a high-pressure positive displacement pump (500 to 20000 psi), 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.

3. Ultrasonication[22]: The preparation of Nanoemulsion is reported in various research papers which aim to use the ultrasonic sound frequency for the reduction of the droplet size. Another approach is the use of a constant amplitude sonotrode at system pressures in excess of the ambient value. It is well known that increasing the external pressure increases the cavitation threshold within an ultrasonic field and thus fewer bubbles form. However, increasing the external pressure also increases the collapse pressure of cavitation bubbles. This means that the collapse of the bubbles when cavitation occurs becomes stronger and more violent than when the pressure is at atmospheric conditions. As cavitation is the most important mechanism of power dissipation in a low frequency ultrasonic system, these changes in navigational intensity can be related directly to changes in the power density. The system also uses a water jacket to control the temperature to optimum level.

4. **Phase inversion method[23]:** In this method, fine dispersion is obtained by chemical energy resulting of phase transitions produced by emulsification pathway. The phase transition is produced by varying the composition of the emulsion and keeping temperature constant or vice versa. The phase inversion temperature was first done by Shinoda *et al*. it was concluded that increase in temperature results in the chemical changes of polyoxyethelene surfactants by degradation of the polymer chain with the temperature.

5. Spontaneous emulsification[24]: 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 was injected in the aqueous phase under magnetic stirring the o/w emulsion was formed.
c) The water-miscible solvent was removed by evaporation under reduced pressure.

6. **Solvent evaporation technique[25]:** 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[26,27]: 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.

EVALUATION

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.[28]

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

2. 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.

3. 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.

4. Transmission electron microscopy (TEM): This method is used to observe the morphology in the nanoemulsion.

5. Drug content: 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.

6. Viscosity: Viscosity should be measured to ensure the better delivery of the formulation.

APPLICATIONS OF NANOEMULSIONS[29]

1. Parenteral delivery: Nanoemulsion is advantages for intravenous administration, due to the strict requirement of this route of administration, particularly the necessity for the formulation droplet size lower than 1 micrometer. Parenteral (or Injectable) administration of nanoemulsion is employed for a variety of purposes, namely nutrition eg. fats, carbohydrates, vitamins etc. Nanoemulsions of natural oils (soyabean, sesame and olive) with the non-toxic surfactant Pluronic F-68 via ultrasound for feeding lipid nanoemulsion has been widely

explored for parenteral delivery of drugs. 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.

2. 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 has 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. Primaquine when incorporated into oral lipid nanoemulsion showed effective antimalarial activity against Plasmodium Bergheim infection in mice at a 25% lower dose level as compared to conventional oral dose lipid nanoemulsion of primaquine improved oral bioavailability by the liver with drug concentration higher at least by 45% as compared with the plain drug.

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 of the drug to affected area of the skin or eyes. The nanoemulsion can achieve a level of topical antimicrobial activity that has only been previously achieved by systemic antibiotics. The nanoemulsion has broad spectrum activity against bacteria (e.g. *E.coli, S. aureus*) fungi (e.g. Candida, Dermatophytes) .

4. Ocular delivery[30]: 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.

5. In cosmetics: The aesthetic properties, i.e. low viscosity and transparent visual aspects of nanoemulsion with droplet sizes below 200nm, its high surface area allowing effective transport of the active ingredient to the skin make them especially attractive for their application in cosmetics. Nanoemulsions are acceptable in cosmetics because there is no inherent creaming, sedimentation, flocculation or coalescence that can be observed with macro emulsion. The incorporation of potentially irritating surfactants can be avoided by

using high energy equipment during manufacturing. Nanogel technology to create miniemulsion from oil-in water concentrate suited to minimizing transepidermal water loss, enhanced skin protection and penetration of active ingredient. It would be useful for sun care products, moisturing and antiageing creams. It helps to give skin care formulations a good skin feels.

6. **Transdermal[31]:** Indomethacin a potent NSAID, the anti-inflammatory effects of true optimized nanoemulsion formulation were compared with marketed gel in carragenan induced paw edema in rats. The %inhibition value was significant for developed Nanoemulsion, so great potential for transdermal application of indomethacin for transdermal delivery of celecoxib formulation which consist of 2% celecoxib 10% oil phase (Sefsol 218 and Triacetin) 50% surfactant mixture (Tween 80 and Transcutol –P) and 40% water. The anti-inflammatory effect and percent inhibition value after 24h administration was found to be high for nanoemulsion formulation (81.2%) as compared to celecoxib gel (43.7%) and nanoemulsion gel (64.5%). The in vitro- in vivo studies revealed a significant increase in the anti-inflammatory effects of aceclofenac nanoemulsion (82.2%) as compared to nanoemulsion gel formulation (71.4%) and conventional gel (41.8%).

7. 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 apolar media causes the denaturation of biocatalysts. The use of water-proof media is relatively advantageous. Enzymes in low water content display and have –

(i) Increased solubility in non-polar reactants.
(ii) Possibility of shifting thermodynamic equilibria in favour of condensations.
(iii) Improvement of thermal stability of the enzymes, enabling reactions to be carried out at higher temperatures.

REFERENCES

1. T. P. U. Ravi and T. Padma, “Nanoemulsions for Drug Delivery through Different Routes,” Research in Bio-technology, 2011; 2(3): 1-13.
2. N. Anton and T. Vandamme, “The Universality of Low- Energy Nano-Emulsification,” International Journal Phar-maceutics, 2009; 377(1-2): 142-147. doi:10.1016/j.ijpharm.2009.05.014.

3. Liu, P; Kurihara-Bergstrom, T and Good, WR, "Cotransport of estradiol and ethanol through human skin in vitro: understanding the permeant/enhancer flux relationship", Pharm Res, 1991; 8: 938-944.
4. Tharwat F, Colloids in cosmetics and personal care, 2003; (4): 36-39.
5. Nakajima, Hideo O, Miyuki T, Emulsified composition, US patent 5,098,606, 1992.
6. European patent 0363928 Bl, 1994.
7. Ping L, Ghosh A, Wagner R.F., Krill S, Joshi Y.M and Serajuddin A.T.M., Effect of combined use of nonionic surfactant on formation of oil-in-water microemulsions, Int. J. Pharm, 2005; (288): 27–34.
8. Chronicles of Young Scientists, 1(2): 2010.
9. Mbela TKM, Deharo E, Haemers A, Ludwig A, Submicron oil-in-water emulsion formulations for mefloquine and halofantrine: Effect of electric-charge inducers on antimalarial activity in mice, J Pharm Pharmacol, 1998; (50): 1221-1225.
10. Bhalani VT, Satishchandra SP, Pharmaceutical composition for cyclosporines, US Patent 5858401 A. 1999.
11. Ghosh PK. and Murthy RSR, Microemulsions: A potential drug delivery system, Current Drug Delivery, 2006; (3): 167–180.
12. Calvo P, Lopez R, Vila-Jato JL, Alonso MJ, Evaluation of cationic polymer-coated nanocapsules as ocular drug carriers, Colloid polym Sci, 1997; (275): 46-53.
13. Restel S, Cauwet-Martin D, Eur patent appl EP 842652 Al., 1998.
14. Schwartz JS, Weisspapir MR, Friedman DI, Enhanced transdermal delivery of diazepam by submicron emulsion creams, Pharm Res, 1995; (12): 687-692.
15. Ko KT, Needham TE, Zia H, Emulsion formulations of testosterone for nasal administration, Journal of microencapsulation, 1998; (15): 197-205.
16. Sznitowska M, Zurowaska-Pryczkowska K, Janiki S, Jarvinen T, Miotic effect and irritation potential of pilocarpine prodrug incorporated into a submicron emulsion vehicle, Int J Pharm, 1999; (184): 115-120.
17. Shinoda K. Lindman B. Organized surfactant systems: microemulsions, Langmuir, 3(1987): 135–179.
18. T. Tadros, P. Izquierdo, J. Esquena and C. Solans, "For-mation and Stability of Nanoemulsions," Advances in Colloids and Interface Science, 2004; 108-109: 303-318. doi:10.1016/j.cis.2003.10.023.
19. R. Aboofazeli, "Nanometric Scaled Emulsions (Nano- emulsions)," Iranian Journal of Pharmaceutical Re-search, 2010; 9(4): 325-326.

20. Hadgraft, J, “Skin: the final frontier”, Int J Pharm, 2001; 224: 1-18.
21. Bhatt P and Madhav S: A Detailed Review on Nanoemulsion Drug Delivery System. International Journal of Pharmaceutical Sciences and Research, 2011; 2(10): 2482-2489.
22. Kh. Hussan R: Nanoemulsion as a Novel Transdermal Drug Delivery System. International Journal of Pharmaceutical Sciences and Research, 2011; 2(8): 1938-1946.
23. Devarajan V and Ravichandran V: Nanoemulsions: As Modified Drug Delivery Tool. International Journal of Comprehensive Pharmacy, 2011; 4(01): 1-6.
24. Shah P, Bhalodia D: Nanoemulsion: A Pharmaceutical Review. Sys Rev Pharm, 2010; 1(1): 24-32.
25. Gupta P, Pandit J: Pharmaceutical Nanotechnology Novel Nanoemulsion –High Energy Emulsification Preparation, Evaluation and Application. The Pharma Research (T. Ph. Res.), 2010; 3: 117-138.
26. Simonnet et al.: Nanoemulsion based on ethoxylated fatty ethers or on ethoxylated fatty esters and its uses in the cosmetics, dermatological and/or ophthalmological fields, 2002.
27. Morales D, Gutie´rrez JM, Garcı´a-Celma MJ, Solans YC, A study of the relation between bicontinuous microemulsion and O/W nanoemulsion formulation, Langmuir, 2003; (19): 7196-7200.
28. Kemken J, Ziegler A, Muller BW. Influence of supersaturation on the pharmacodynamic effect of bupranolol after dermal administration using microemulsions as vehicle. Pharm Res, 1992; 9: 554Y558.
29. Kreilgaard M, Kemme MJB, Burggraaf J, Schoemaker RC, Cohen AF. Influence of a microemulsion vehicle on cutaneous bioequivalence of a lipophilic model drug assessed by microdialysis and pharmacodynamics. Pharm Res, 2001; 18: 593Y599.
30. Kreilgaard M, Pedersen EJ, Jaroszewski JW. NMR characterization and transdermal drug delivery potentials of microemulsion systems. J Control Rel, 2000; 69: 421Y433.