Nanoemulsion Drug Delivery System: A Review

Ashish B. Budhrani*1, Shubhra R. Rai2, Aarati S. Panchbhai3, Rajshri B. Dongarwar4

1Department of Pharmaceutics, Datta Meghe College of Pharmacy, Datta Meghe Institute of Medical Sciences (DU), Wardha - 442001, Maharashtra, India
2Department of Pharmaceutics, Guru Ramdas Khalsa Institute of Science and Technology, Pharmacy, Jabalpur - 482001, Madhya Pradesh, India
3Department of Oral Medicine and Radiology, Sharad Pawar Dental College, Datta Meghe Institute of Medical Sciences (DU), Wardha - 442001, Maharashtra, India
4Department of Quality Assurance, Dadasaheb Balpande College of Pharmacy, Nagpur - 440034, Maharashtra, India

ABSTRACT

Nano-emulsion dosage forms have nano-sized droplets of disperse phase and are kinetically stable dosage form. Nano-emulsions are included under the category of new drug delivery system containing emulsified water in oil/oil in water system having mean globule size ranges from 10 nm to 1000 nm. In the field of pharmacy, nano-emulsions play an essential role in the delivery of medication through various drug administration routes like parenteral, topical and oral route. Nano-emulsions are nano-sized emulsions which are used under high investigation as a drug carrier for enhancing the delivery of therapeutic agents. They are nowadays growing work for utilizing nano-sized particles in the research of pharmaceuticals, cosmetics and food products. Mainly, intrigue has been creating simultaneously with higher emulsification techniques and mechanisms of stabilization. Nano-emulsions are formulated by both methods like high energy emulsification or low energy emulsification methods. Rapid energy emulsification technique includes high shear mixing, high-pressure homogenization or ultrasonication. In contrast, low energy emulsification technique includes the merit of the physicochemical characteristics of the system, which exploits phase transitions to obtained nano-emulsion. This review article is an effort to summarize comparative aspects like introduction, types, advantages, disadvantages, components, factors affecting, methods of preparations, methods of analysis of nano-emulsion and applications of nano-emulsion.

*Corresponding Author

Name: Ashish B. Budhrani
Phone: +91-8888944700
Email: ashu.budhrani123@gmail.com

INTRODUCTION

The drugs moiety included in Biopharmaceutical Classification System Class II and Class IV has low aqueous solubility and remedy for the solubility problems are nanotechnology techniques. Nanotechnology techniques play an essential role at the molecular level and nano length scale size. To increase the dissolution rate of drug moiety, which directly leads to an increase in the bioavailability of drug depends on decrease drug particles into the nanoscale range. (Jain *et al.*, 2013) The nano-

emulsion dosage form is considered as thermodynamically stable dosage form consisting of a clear solution of two immiscible liquids like water and oil, stabilized by an interfacial film coat of surface-active agent molecules. Nano-emulsions are included under the category of novel drug delivery system containing emulsified water in oil/oil in water system having mean globule size ranges from 10 nm to 1000 nm. Due to nano-globules size of the disperse phase, nano-emulsions are different from emulsions. (Basha *et al.*, 2013) Nano-emulsions are also called colloidal disperse system containing surfactant, co-surfactant, an oil phase and aqueous phase in right proportions. Nano-emulsions are formulated by both methods like high energy emulsification or low energy emulsification methods. (Kumar and Singh, 2012) Nanoemulsion is considered generally as safe by the FDA, which includes non-irritant and non-toxic. (Solè *et al.*, 2010)

Various types of oils like synthetics, semi-synthetics and natural oils are used in the manufacturing of nano-emulsions. Emulsion with the nanoscale size is prepared by using emulsifying agents that are mainly considered as secure and safe for human use. The kind of surfactant and its quantity in the aqueous phase are selected in such a manner to achieve better stability against coalescence. Nano-emulsions have better stability as compare to macroemulsion or microemulsion against flocculation of disperse phase, creaming, sedimentation and coalescence. (Thiagarajan, 2011)

Types of Nanoemulsions

1. **Oil in Water Nanoemulsions:** Oil phase considered as a disperse phase and aqueous phase is considered a continuous phase.

2. **Water in Oil Nanoemulsions:** Oil phase considered as a disperse phase, and the aqueous phase is considered a continuous phase.

3. **Bi-continuous Nanoemulsions:** Microdomains of oil and water are interspersed within the system.

In all these three types of nano-emulsions, the interface is made stabilized by a right proportion of surfactants and co-surfactants.

The significant difference between nano-emulsions and macroemulsions, Nanoemulsion dosage form, are considered as thermodynamically stable dosage form consisting of a clear solution of two immiscible liquids like water and oil, stabilized by an interfacial film coat of surface-active agent molecules. Other differences in their appearance, i.e. nano-emulsions are transparent or translucent biphasic liquid dosage form. Nanoemulsion needs a large amount of energy for its preparation as compared to macroemulsion. (Date and Nagarsenker, 2008)

Advantages of Nanoemulsions

1. Nanoemulsions dosage forms are considered as kinetically and thermodynamically stable dosage form against flocculation of disperse phase, creaming, sedimentation and coalescence.

2. Nanoemulsion is a technique to increase the dissolution rate of drug moiety, which directly leads to an increase in the bioavailability of lipophilic drugs.

3. Nanoemulsion can be given by various routes like topical, transdermal, oral, parenteral etc.

4. Nano-emulsions can be used for administration of both lipophilic and hydrophilic drugs.

5. Nano-emulsions are capable of delivering peptides that are prone to enzymatic hydrolysis in the gastrointestinal tract.

6. Due to nano-size of a droplet of the disperse phase, which increases surface area and therefore enhances the availability of the drug in the systemic circulation.

7. Nano-emulsions protect against oxidation and hydrolysis.

8. Nano-emulsions also increase skin permeation of drugs.

9. Nano-emulsions provide ultra-low interfacial tension. (Sadurní *et al.*, 2005)

Disadvantages of Nanoemulsions

1. Surfactants/co-surfactants concentration required for stabilization of nano-emulsions may be more extensive.

2. Change in pH and temperature may affect the stability of nano-emulsions.

3. Due to Oswald ripening effect, instability of nano-emulsion may be observed.

4. Cost of nano-emulsion is more because of the size reduction of disperse phase globules. (Bhatt and Madhav, 2011)

Components of Nanoemulsion

Various components of nano-emulsion are as follows, (Reza, 2011)

Oils

The choice of a correct oily or disperse phase is significant because it may affect the choice of another excipient of nano-emulsions, mainly just in case of oil in water type of nano-emulsions. Generally, the oil having the best solubilizing property can be referred to as a dispersed phase for the preparation of nano-emulsions. These provide to get increased drug-carrying within the nano-emulsions. Naturally developed oils and fats include a mixture of triglycerides that contain fatty acids of varying chain lengths and degrees of unsaturation. Triglycerides are divided as long-chain (>12 carbons), medium-chain (6 to 12 carbons) and short-chain (<5 carbons) and should be synthetically hydrogenated to minimize the degree of unsaturation, thereby conferring resistance to oxidative degradation. The choice of the oily phase is additionally a compromise between its capability to solubilize the drugs moiety and its capability to ease the preparation of nano-emulsion of required properties. Various oil phases are Myritol 318, modified vegetable oils, Captex 355, IPM, digestible or non-digestible oils and fats like hydrogenated as well as non-hydrogenated soybean oil, olive oil, oleic acid, palm oil, peanut oil, beeswax and sesame oil.

Surfactants

The surfactant should be able for micro emulsification of the oily or disperse phase and will also have the best solubilizing property for the aqueous insoluble drug moiety. The selection of the surfactants is very important for the nano-emulsion preparation. A surface-active agent having an HLB value less than ten-value are water insolubility like sorbitan monoesters and get water in oil type of nano-emulsion and surfactants having higher HLB value (>10) like polysorbate 80 are water-soluble and form oil in water type of nano-emulsion. The hydrophobic core increases the entrapment of drug, hence increasing its solubility. When the oil content is more, surfactant concentrates on the oil/water interface forming emulsions, and thus the drug is solubilized in the internal oil phase. On the other hand, when the oil content is less, minute oil entrapped surfactant globules are developed, which are referred to as nano-emulsions.

The surfactant utilized in nano-emulsion formation might be ionic or non-ionic surfactants aren't preferred due to its toxic effects. Many surfactants are mostly utilized like polysorbate 80, poloxamers and lecithins. Determination of surfactant concentration is crucial because a large quantity of it may act gastrointestinal irritation. The size of the globule and concentration of surface-active agents are interrelated. In some instances, greater the surfactant concentration may lead to smaller globules like within the case of a mixture of saturated C8-C10 polyglycolized glycerides. However, by enhancing the concentration of surfactant, the mean globule size also is increased.

Co-surfactants

Various times, surfactant individually cannot decrease the oil-water interfacial or surface tension completely to get a nano-emulsion which necessitates the addition of a co-surfactant to bring about the interfacial tension on the brink of zero. Co-surfactants enter into the monolayer of surfactant, giving additional fluidity to interfacial film and hence distracting the liquid crystalline phases developed when surfactant film is just too rigid. Generally, a lower HLB co-surfactant is employed with a higher HLB surfactant to switch or adjust the overall HLB value of the system. Similar to surfactant, the co-surfactant might not be able to form self-associated structures like micelles on its own. Hydrophilic co-surfactants mainly alcohols of intermediate chain length like pentanol, octanol and hexanol, which are known to scale back the oil/water interface and permit the rapid preparation of nano-emulsion.

Factors affecting the Formulation of Nanoemulsion

1. The emulsifying agent is the vital agent of any nano-emulsion. They ought to not form lyotropic liquid crystalline "micro-emulsions" phases. Systems including short-chain alkanes, water, surfactants and alcohols form the phases which are usually used with the co-surfactant.

2. The desired quantity is required to avoid Oswald ripening, and therefore the dispersed phase should be highly insoluble in the dispersion medium.

3. The existence of more amounts of surface-active agents develops a new surface area of nanoscale to be fast coated during emulsification, thereby prohibiting induced coalescence. (Thakur *et al.*, 2013)

METHODS OF FORMULATION OF NANOEMULSION

There are various methods available to prepare nanoemulions. A comparatively higher amount of energy is needed for the development of nano-emulsion than regular emulsions or other dosage

forms. Various methods utilized for the formulation of nano-emulsion are:

Sonication technique

In the sonication technique, the size of the globules of a normal emulsion is made compact by using sonication mechanism. This method is utilized to develop a few quantities of batches of nano-emulsion. (Shah *et al.*, 2010)

High-Pressure Homogenizer

In this technique, a huge amount of pressure is applied to the system containing aqueous or oil phase and co-surfactant or surfactant. The higher pressure is applied by using a homogenizer. Homogenization may sometimes cause certain problems like poor productivity, component deterioration, which are a result of the high-pressure application. By this technique, only oil/water type of nano-emulsion having concentration lower than 20% oily phase may be prepared. Higher viscosity cream nano-emulsion and thickness having a mean globule diameter lower than 200 nm couldn't be formulated. (Pratap *et al.*, 2012)

Phase Inversion technique

This technique was based on the mechanism of changes of solubility of a surface-active agent such as polyoxyethylene with temperature. This surface-active agent is initially insoluble in lipids but changes into lipid-soluble by increasing temperature due to polymer chain dehydration. At a lower temperature, the surface-active agent monolayer has a better positive, spontaneous curvature producing oil swollen micellar solution phase. (Pey *et al.*, 2006)

Production with high amplitude ultrasound

This technique is nowadays used as a substitute against high-pressure homogenization for small scale production of nano-emulsion. For Nanoemulsification, more shear forces are essential which are developed by ultrasonic cavitations. This develops violently and asymmetrically imploding vacuum bubbles and decreases molecule length to the nanometer scale. For small scale manufacturing of nano-emulsions, this technique is efficaciously used. (Jafari *et al.*, 2007)

Solvent Displacement technique

In this technique, the non-aqueous phase is mixed with various water-miscible organic solvents like ethanol, acetone, etc. The aqueous and organic phases are mixed with the help of emulsifying agents to develop nano-emulsion by using rapid diffusion of organic solvent. Vacuum evaporation technique is then utilized to evaporate the organic solvent from the mixture. (Narang *et al.*, 2007)

Microfluidizatiion

A microfluidizer is a piece of equipment that includes a high-pressure positive displacement pump (200 to 500 PSI). This pump pressurizes the material through the interaction chamber, comprising of small channels referred to as microchannels. The material moves through the microchannels directly to an impingement area which brings about extremely fine particles of submicron extend. Aqueous and oily phase are combined and formed in an inline homogenizer to obtain a coarse emulsion. To obtain a resultant stable nano-emulsion, the coarse emulsion is processed further into a microfluidizer. (Savardekar and Bajaj, 2016)

CHARACTERIZATION OF NANOEMULSION

Zeta potential

An instrument named Zeta PALS is utilized to calculate Zeta Potential. Zeta Potential is the electrokinetic potential difference on the surface of the globule in nano-emulsion. Surfactant develops surface charges; however, additionally, act as a mechanical barrier. Zeta potential develops electrical forces which are repulsive around oil globules and which produce restricts coalescence in some instances. The process of Zeta Potential is shown in Figure 1. (Gupta *et al.*, 2010)
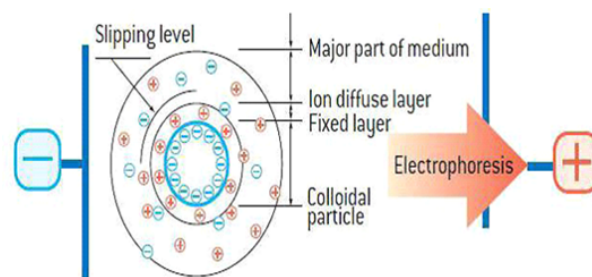

Figure 1: Processes of Zeta Potential

Polydispersity

Polydispersity specifies the uniformity of globules size within the preparation. It is the ratio of the standard deviation to mean droplet size. Polydispersity represents a direct relation between globule sizes in the preparation, i.e. more will be the polydispersity, less will be the uniformity of the globule size in the preparation. Malvern Zetasizer worked on dynamic light scattering mechanism and used to calculates polydispersity. (Suyal *et al.*, 2018)

Particle size analysis

For analysis of particles distribution and particle size, dynamic light scattering (DLS) mechanism id

---

utilized. This is the most suitable method to measure particle size and dispersion. Electron microscopic examination can also be done for this, but it is not used very frequently. (Pouton and Porter, 2008)

Percent of drug loading

By dissolving determined quantity of nano-emulsion in 25 ml of a suitable solvent. The collected extract is analyzed by High-Performance Liquid Chromatography (HPLC) with a reference solution of the drug. The content of the drug is then calculated by reverse-phase High-Performance Liquid Chromatography by utilizing various columns of suitable porosity. (Gursoy and Benita, 2004)

Transmission electron microscopy (TEM)

Transmission Electron Microscopy (TEM) is used for investigation structure and morphology of the nano-emulsion. (Chime *et al.*, 2014)

In-vitro drug release

The *In-vitro* release investigation of nano-emulsion, including drug, may be completed by semi-permeable membrane utilized in dissolution equipment. For this research, a round glass tube, 6 cm in length and 1.25 cm in radius, is connected rather than the basket and is firmly covered with the semi-permeable membrane. Nano-emulsion (drug-loaded) is kept in the round glass tube at the semi-permeable membrane surface. A round glass tube ought to dip in 100 ml buffer keeping the pH to permit the establishment of the sink situation and to preserve everlasting solubilization. The drug release investigation may be achieved for 24 hours at 32°C. The stirring shaft ought to rotate at a speed of a 100 rpm. At predetermined time intervals (1, 2, 4, 6, 8, 12, 20, 24 hours) aliquots of one millilitre of the delivery medium is withdrawn and diluted then filtered for evaluation and changed with an equivalent extent of the buffer medium for keeping up a regular volume. UV spectrometer is utilized for measurement of absorbance of the collected samples. (Nirmala *et al.*, 2013)

APPLICATIONS OF NANO-EMULSIONS

Various Applications of Nano-emulsions are as follows, (Tamilvanan, 2004)

1. Nano-emulsions increase the solubility of poorly soluble drugs.

2. Nanoemulsions dispensing system eliminates the requirement of co-solvent, as well as encapsulating drug that would, in any other case, be irritants; thus, nano-emulsion can minimize irritation upon injection.

3. Nanoemulsions dispensing system decreases the toxicity of drugs.

4. Improving pharmacokinetic parameters for greater beneficial medication performance is an essential goal of drug transport studies in normal and for nano-emulsion specifically, one specific parameter that will be referenced on various times is the zone below the concentration-time curve, abbreviated AUC.

CONCLUSION

Nanoemulsions, drug delivery system, offer several merits for effective drugs delivery, biological, or diagnostic agents. Nanoemulsion technology can protect labile drug, increase bioavailability, enhances drug solubility and control the release of the drug. In this review article, Nanotechnology-based drug delivery system, i.e. Nanoemulsion, has been presented with the efforts that they can serve as the building blocks for much more success in the field. Stability of nano-emulsion preparation might be prevented by preventing various factors like type and concentration of surface-active agent as well as co-surfactant, type of oily phase, techniques utilized, procedure variables and excipients are added which are utilized over the interphases formulation of nano-emulsion. Recently, nano-emulsions with globules size of less than 100 nm have attracted significant attention because of their potential merits in pharmaceutical, biotechnology, cosmetics and food industries as a better drug delivery system due to their small globule size, clear, and higher kinetic stability. But still, there is a requirement to emphasize on the toxicological characterization of the formulated nano-emulsions, which may be a vast research field in future.

REFERENCES

Basha, S. P., Rao, K. P., Vedantham, C. 2013. A brief introduction to methods of preparation, applications and characterization of nano-emulsion drug delivery systems. *Indian journal of research in pharmacy and biotechnology*, 1(1):25–25.

Bhatt, P., Madhav, S. 2011. A detailed review of nano-emulsion drug delivery system. *International Journal of Pharmaceutical Sciences and Research*, 2(10):2482–2482.

Chime, S. A., Kenechukwu, F. C., Attama, A. A. 2014. Nano-emulsions—advances in the formulation, characterization and applications in drug delivery . volume 3, pages 1–51.

Date, A. A., Nagarsenker, M. S. 2008. Parenteral microemulsions: An overview. *International Journal of Pharmaceutics*, 355(1-2):19–30.

Gupta, P. K., Pandit, J. K., Kumar, A., Swaroop, P., Gupta, S. 2010. Pharmaceutical nanotechnology novel nanoemulsion-high energy emulsification preparation, evaluation and application. *The Pharma Research*, 3(3):117–138.

Gursoy, R. N., Benita, S. 2004. Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. *Biomedicine & Pharmacotherapy*, 58(3):173–182.

Jafari, S. M., He, Y., Bhandari, B. 2007. Optimization of nano-emulsions production by microfluidization. *European Food Research and Technology*, 225(5-6):733–741.

Jain, K., Kumar, R. S., Sood, S., Gowthamarajan, K. 2013. The enhanced oral bioavailability of atorvastatin via oil-in-water nano-emulsion using an aqueous titration method. *Journal of Pharmaceutical Sciences and Research*, 5(1):18–18.

Kumar, S. H., Singh, V. 2012. Nanoemulsification-a novel targeted drug delivery tool. *Journal of Drug Delivery and Therapeutics*, 2(4).

Narang, A. S., Delmarre, D., Gao, D. 2007. Stable drug encapsulation in micelles and microemulsions. *International Journal of Pharmaceutics*, 345(1-2):9–25.

Nirmala, M. J., Shivashankar, M., Mukherjee, A., Chandrasekaran, N. 2013. Fluconazole: a simple nano-emulsion drug delivery system. *Int J Pharm Pharm Sci*, 5(3):716–717.

Pey, C. M., Maestro, A., Solé, I., González, C., Solans, C., Gutiérrez, J. M. 2006. Optimization of nano-emulsions prepared by low-energy emulsification methods at constant temperature using a factorial design study. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, 288(1-3):144–150.

Pouton, C. W., Porter, C. J. 2008. Formulation of lipid-based delivery systems for oral administration: Materials, methods and strategies. *Advanced Drug Delivery Reviews*, 60(6):625–637.

Pratap, S. B., Brajesh, K., Jain, S. K., Kausar, S. 2012. Development and characterization of a nano-emulsion gel formulation for transdermal delivery of carvedilol. *International Journal of Drug Development & Research*, 4(1):151–161.

Reza, K. H. 2011. Nano-emulsion as a novel transdermal drug delivery system. *International Journal of Pharmaceutical Sciences and Research*, 2(8):1938–1938.

Sadurní, N., Solans, C., Azemar, N., García-Celma, M. J. 2005. Studies on the formation of O/W nano-emulsions, by low-energy emulsification methods, suitable for pharmaceutical applications. *European Journal of Pharmaceutical Sciences*, 26(5):438–445.

Savardekar, P., Bajaj, A. 2016. Nanoemulsions-a review. *Inter J Res Pharm and Chem*, 6(2):312–322.

Shah, P., Bhalodia, D., Shelat, P. 2010. Nanoemulsion: A pharmaceutical review. *Systematic Reviews in Pharmacy*, 1(1):24–24.

Solè, I., Pey, C. M., Maestro, A., González, C., Porras, M., Solans, C., Gutiérrez, J. M. 2010. Nano-emulsions prepared by the phase inversion composition method: Preparation variables and scale up. *Journal of Colloid and Interface Science*, 344(2):417–423.

Suyal, J., Bhatt, G., Singh, N. 2018. Formulation and evaluation of nano-emulsion for enhanced bioavailability of Itraconazole. *Int J Pharm Sci & Res*, 9:2927–2931.

Tamilvanan, S. 2004. Review article submicron emulsions as a carrier for topical (ocular and percutaneous) and nasal drug delivery. *Indian Journal Of Pharmaceutical Education*, 38(2):73–80.

Thakur, A., Walia, M. K., Kumar, S. L. 2013. Nanoemulsion in the enhancement of bioavailability of poorly soluble drugs: a review. *Pharmacophore*, 4(1):15–25.

Thiagarajan, P. 2011. Nano-emulsions for drug delivery through different routes. *Research in Biotechnology*, 2(3).