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Current Medical and Drug Research

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Mini-review article

Nanoemulsion - An ideal drug delivery for nose-to-brain targeting

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Article history

Received : July 25, 2017
Accepted : October 20, 2017

Keywords

Nanoemulsion
Drug delivery system
Drug targeting
Nose-to-brain targeting
Phase inversion point

ABSTRACT

Nanoemulsions are well-liked drug delivery system in the pharmaceutical world. These are clear, thermodynamically stable and isotropic liquid-in-liquid dispersion with an average size range of 20 to 200 nm. They are having elevated surface area, strong stability, optically clear appearance, acceptable rheology and good drug loading capacity because of their characteristic droplet size. The methods used for the preparation of nanoemulsions include bubble bursting method, micro-fluidization, phase inversion temperature, emulsion inversion point, ultrasonication and spontaneous emulsification high-pressure homogenization etc. In the present paper, the advantages, methods of preparation and applications of nanoemulsions are critically reviewed.

INTRODUCTION

The introduction of any drug delivery system is the outcome of some demerits associated with existing one. Researchers of this field faced the biggest problem of solubility with APIs. Additionally, Drug loading capacity, diffusivity through the membrane, poor bioavailability issues, poor stability issues, poor drug targeting issues, etc. are responsible for the birth of nanoemulsion drug delivery system (neDDS).

Nanoemulsions are thermodynamically stable, isotropic and clear dispersion of oil and water with a typical droplet size of 50-200 nm. The emulsifier is also added in nanoemulsion for the creation of small-sized droplets as it decreases the interfacial tension. Emulsifier also plays a role in stabilizing nanoemulsions through repulsive electrostatic interactions and steric hindrance (Mason et al., 2006). Nanoemulsions are also popular as mini-emulsion, submicron emulsion and ultrafine emulsion.

Nanoemulsions are gaining popularity over other drug delivery systems as it increases the rate of absorption by eliminating variability in absorption, facilitate the solubility of lipophilic drug, make available the aqueous preparations for water-insoluble drugs, increases bioavailability, rapid and efficient diffusion of the drug, helpful in taste masking, protect the drug from hydrolysis and oxidation, thermodynamically stability of nanoemulsions allows self-emulsification of the system, both lipophilic and hydrophilic drugs could be loaded with same nanoemulsions, the total dose to be reduced and thus minimizing side effects (Trotta et al., 1999). Nanoemulsions stability is influenced by environmental parameters such as temperature and pH which may change upon nanoemulsions delivery to patients and this makes nanoemulsions use limited (Alvarez-Figueroa and Blanco-Méndez, 2001).

Three types of nanoemulsions are most likely to be formed depending on the composition: oil in water nanoemulsions, water in oil nanoemulsions and bi-continuous nanoemulsions wherein microdomains of oil and water are interdispersed within the system (Kriwet and Müller-Goymann, 1995). Nanoemulsions are characterised by the droplet size, polydispersity, viscosity, density, zeta potential, turbidity, refractive index, phase separation, interfacial tension, pH measurements, permeation and stress stability testing (Kazimiera et al., 2009; Pershing et al., 1993).

MANUFACTURING OF NANOEMULSION

The distinct size range of nanoemulsions makes their manufacturing typical. Nanoemulsions are prepared either by preparing microemulsion or microemulsion converted to a nanoemulsion. There are two popular techniques for the manufacturing of nanoemulsions, high energy method and low energy method (Tadros et al., 2004; Solans et al., 2005).

High energy method

The high energy method is more efficient for the manufacturing of nanoemulsion. It requires power density in the range of 106-1010 W/kg. Its only drawback is that it increased the temperature of preparation during the process.

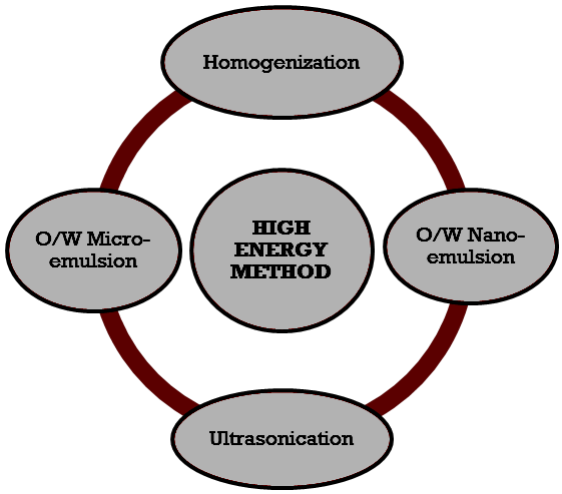

Fig. 1. Manufacturing of nanoemulsions by high energy method

Based on this method high-pressure homogenization, micro-fluidization, ultrasonication, etc processes are reported (Hadgraft, 2001; Bhatt and Madhav, 2011). The nanoemulsions are prepared by high energy method by preparing O/W microemulsion which turns into nanoemulsion via homogenization or ultrasonication process (Fig. 1).

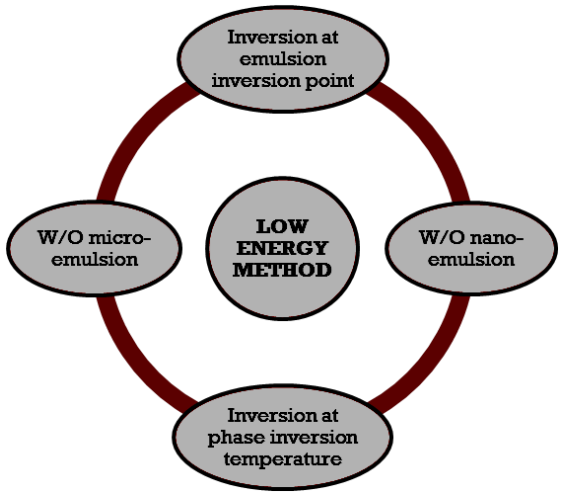

Fig. 2. Manufacturing of nanoemulsion by low energy method

Low energy method

It is a safe and suitable method of nanoemulsion manufacturing. It requires power density of 102-106 W/kg. The sound knowledge of inversion point is required for obtaining desired outcomes. Phase inversion method, spontaneous emulsification method, a solvent evaporation method, hydrogel method, etc. are reported under low energy methods (Reza, 2011; Devarajan and Ravichandran, 2011; Shah and Bhalodia, 2010). The nanoemulsions are prepared by low energy method by preparing W/O microemulsion which converts into nanoemulsion either by inverting it at phase inversion point or emulsion inversion point (Fig. 2).

RECENT ADVANCEMENTS IN NOSE-TO-BRAIN NANOEMULSION DRUG DELIVERY SYSTEM

Nanoemulsions have recently become increasingly important as potential vehicles for the targeting drugs to the brain via the nasal route. There is a lot of research going on in this particular area of interest due to its wide applicability (Semwal et al., 2017).

The nanoemulsion and mucoadhesive nanoemulsion of risperidone to accomplish the nose-to-brain delivery of drug to the rat revealed the biodistribution in the brain and blood following intranasal and intravenous administration using optimized technetium-labelled risperidone formulations (Kumar et al., 2008a). Gamma scintigraphy imaging of rat brain showed the higher drug transport efficiency and direct nose-to-brain drug transport for mucoadhesive nanoemulsions which stated that it is more effective and best brain targeting of risperidone amongst the prepared nanoemulsions, although, the globules size was not constant in the study. Another study by Kumar et al. (2008b) on tramadol demonstrated the rapid and larger extent of transport of intranasal nanoemulsion when compared with an intranasal solution, intranasal mucoadhesive nanoemulsion and intravenous nanoemulsion. However, the study did not correlate the time duration for the effectiveness of nanoemulsion when compared with mucoadhesive nanoemulsion.

Sarwar (2012) also found excellent results for the nanoemulsion and mucoadhesive nanoemulsion of risperidone for nose-to-brain targeting. The study was, however, found limited to the multi-dimensions. The nanoemulsion of tramadol as compared to the microemulsion was found to be safe with respect to the multiple dosing via nasal route after performing biodistribution, pharmacokinetic and pharmacodynamic studies in mice (Lalani et al., 2015). This study significantly compared microemulsion and nanoemulsion of tramadol to achieve maximum therapeutic efficacy in the treatment of episodic and emergency pain.

Mahajan et al. (2014) developed an intranasal nanoemulsion for enhanced bioavailability and CNS targeting of saquinavir mesylate which is a protease inhibitor and widely used as an anti-retroviral drug. It is having poor water solubility and poor oral bioavailability that is about 4%. The study showed a significant increase in the drug permeation rate as compared to the plain drug

suspension. The results of *in vivo* biodistribution studies showed the higher drug concentration in the brain using intranasal administration of nanoemulsion than intravenous delivered plain drug suspension. However, the size optimization and retention time of formulation in the nasal mucosa was not determined in the study.

A separate study based on intranasal nanoemulsion and nanogel formulations for rizatriptan benzoate for the nose-to-brain targeting by Bhanushali et al. (2009) revealed that that the nanoemulsions have greater efficiency for brain targeting as compare to the nanogels, although, the retention time has been found to 15 min which tends to poor bioavailability. Thus to increase the bioavailability of nanoemulsions for the nose-to-brain delivery is the biggest opportunity for future research. A nanoemulsion loaded with selegiline for direct nose-to-brain delivery was developed by Kumar et al. (2016) which revealed the effect of shape in drug permeation where the spherical shape of nanoemulsion showed 3.7 times higher in the drug permeation as compared to a drug suspension. Although the shape is an important parameter in drug permeation, this study does not show the comparison between nanoemulsion and a drug suspension. Hence, the comparison of globules size within the same formulation is still waiting for future research.

Ahmad et al. (2016) studied the nose to brain targeting using nanoemulsion as a model carrier. The nanoemulsion was detected in the biological tissues based on the on-off signal switching of the embedded dyes. The study found that nanoemulsion with a particle size of ~100 nm has longer retention time in nostrils and slower mucociliary clearance than a large one (900 nm). However, the extent of the nose to brain delivery required to be optimized in future research.

CONCLUSION

Nanoemulsions have gained popularity over the past decade because of their exceptional applicability. Nanoemulsions have been used in clinics for more than four decades as total parenteral nutrition fluids. There are so many formulations available in the market and some are patented. Nose-to-brain targeting of nanoemulsions are reported in a number of reports but optimization and validation of globule size range, globule shape, retention time extension, dosing and factors affecting permeation are still the matter of future research. Hence, further findings and developments in this field of nanoemulsions could lead this drug delivery system as flagship drug delivery in near future.

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest.

ACKNOWLEDGMENT

Declared none.

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How to cite this article?

Semwal R (2017). Nanoemulsion - An ideal drug delivery for nose-to-brain targeting. Current Medical and Drug Research, 1 (1), Article ID 175.

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