Review article

Rapports De Pharmacie Vol.2 (3), 2016, 279-283
ISSN: 2455-0507

HYPOTHESIS REVIEW: NANOEMULSIONS

Shirley Wong Jing Wen

Research student of pharmacy, Asian Institute of Medicine, Science and Technology (AIMST) University, Bedong 08100, Kedah, Malaysia

ABSTRACT

Nanoemulsions are recognized as essentially thermodynamically unstable colloidal systems, transparent, monodisperse, and kinetically stable. Currently, they have aroused particular attention of different industrial fields. With a structure constituted by nano droplets with a size between 20 and 200 nm surrounded by surfactant, forming a w/o or o/w, these systems have many advantages compared to conventional emulsions for practical applications in the chemical, pharmaceutical and cosmetic industries.Currently, there is a need to determine the optimum conditions in which these systems are formed. Such factors should be considered when choosing the type of surfactant, oil, and phases concentrations, in order to achieve their application as drug delivery systems.

Keywords: Ultrasonic Agitation,Cosmetic Industry,Mucosal Vaccines

INTRODUCTION

Nanoemulsion is emulsion comprising of small droplets in the size range of 20-200nm, which are also known as mini-emulsion, ultrafine emulsion, or submicron emulsion [1-6]. It is a heterogeneous mixture, consisting of two immiscible phase which are oil phase and aqueous phase [7].Recently, nanoemulsions, a form of emulsion based drug delivery systems have been commonly used due to their easy production, high physical stability and better bioavailability [8].There are three types of nanoemulsions which vary with its composition: oil in water, water in oil, multiple emulsions. The differences between nanoemulsion and emulsion are listed below [9].

With oil, surfactants and aqueous phase, nanoemulsion can be formulated. The surfactants used for formulation of nanoemulsion are tween 80, poloxamer, PEG (>4000) etc [11]. Nanoemulsion is frequently used lately because of the benefits it brings in various aspects such as antibiotics, DNA encoded drug, delivery of vaccine, cosmetic and topical preparation. It can be administered through different routes of administration like oral, ocular, transdermal, pulmonary, parenteral etc [12,13]. The merits and demerits of nanoemulsion are shown as following.

Address for correspondence:
Shirley Wong Jing Wen,
UG Research student,
AIMST University,
Semeling, Bedong,
Malaysia.
Email: shirlev.280795@gmail.com

Nanoemulsion:

- Thermodynamically and kinetically stable
- Clear and translucent
- Higher free energy
- Larger surface area to volume
- Required less surfactant
- Required/Does not required high energy input

Microemulsion:

- Unstable
- Cloudy
- Less free energy
- Smaller surface area to volume
- Required more surfactant
- Required high energy input

Merits:

- It is thermodynamically and kinetically stable. Thus, no flocculation, aggregation, creaming and coalescence.
- No toxicity and irritation.
- It has various routes of administration.
- It is able to deliver both polar and non-polar drugs.
- Nanoemulsion has nano sized droplets, so surface area is larger. Hence, the rate of absorption is increased and better bioavailability.
- It does not cause damage to the human or animal cell. Therefore, it is proper for human and animal uses.
- It prevents the drug from being hydrolyzed and oxidized because of encapsulation. It also masks the taste of the drug.

- It improves the permeability of drug through the skin barrier.

Demerits:

- Temperature and pH will affect its stability.
- Instability occurs due to Ostwald ripening.
- Large amount of surfactants is required to improve the stability.

FORMULATION TECHNIQUES OF NANOEMULSION

Nanoemulsions can be prepared by two types of methods: high-energy and low-energy methods. In high-energy methods, specialized mechanical devices are used to fragment droplets into fine particles, for example, high pressure valve homogenizers, sonicators, microfluidizers etc. [8, 14, and 15]. On the other hand, low-energy method can form very fine particles spontaneously due to controlled changes in the solution settings or environment. [14,16]. Low-energy method, for instance, spontaneous emulsification is more commonly used as compared to high-energy methods because of their cheaper preparation expenses, ability to form smaller sized particles and simple production techniques [14].

Spontaneous emulsification:

It is one of the simplest low-energy methods used for production of nanoemulsion. This method only involves the addition of one phase into another phase with nonstop stirring in order to form a nanoemulsion spontaneously. The oil phase containing oil and surfactant is added to the aueous phase with slight stirring [16-19].

High Pressure Homogenizer:

In this method, heated and filtered oil phase is added to the aqueous phase which is previously heated and pH adjusted. Suitable concentrations of emulsifiers are added to stabilize the mixture which is then undergoes rapid cooling. The cooled mixture is inserted into the high pressure homogenizer with the pressure of 500-2000 psi to subject the product to intense turbulence and hydraulic shear resulting in the formation of nano sized particles [9,19,20].

Microfluidization:

A quickly flowing stream of premixed emulsion are passed through stainless steel micro channels to form strong dimensional flow by using a pump of 500-20,000psi. Therefore, very fine particles with submicron size are produced. The premixed emulsion is circulated through the microfluidizer continuously until the desired particle size is obtained [7,13,19].

Ultrasonic Agitation:

The premixed emulsion is break down into nano particles when it was agitated at ultrasonic frequency of 20kHz. In order to form even particle size distribution, the emulsion is recirculated through high shear region. The water jacket is used in this method to regulate and maintain the temperature. Ultrasonic frequency is practiced because of its ability to fragment the particle size into very fine particles [19,21,22].

Phase Inversion:

Phase inversion can produce nanoemulsion as a result of changing the composition and maintaining the constant temperature or vice versa [19].

EVALUATION OF NANOEMULSION

Particle size:

Particle size can be determined by photon correlation spectroscopy. The nanoemulsion is diluted with appropriate amount of 0.2µm double filtered distilled water before applying to the photon correlation spectrometer. In addition, dynamic light scattering spectrophotometer can also determine the particle size and particle distribution. This technique is carried out at 90^0 with a neon laser of wavelength 632nm [23,9].

Zeta potential:

Malvern Zetasizer Nano Range can measured the zeta potential of the product. Zeta potential determines the surface charge of nanoemulsion using a mini electrode [24].

Turbidity:

By measuring the absorbance of undiluted nanoemulsion at wavelength 600nm using Hitachi U-2000 spectrophotometer, the turbidity of the nanoemulsion can be determined [25].

Refractive index:

The refractive index of nanoemulsion can be measured with refractometer, for example, Milton Roy Abbe-type refractometer [25].

Viscosity:

Rotary viscometer is used to measure the viscosity of the nanoemulsion. They possess very low viscosity [9,26, 27].

Drug content:

Quantity of drug contained in the nanoemulsion can be estimated by Western Blot technique [11, 28].

SIGNIFICANCE OF NANOEMULSION

In food industry:

Nanoemulsions are used to encapsulate active therapeutic ingredients for food and beverage products supplementation to improve and uniform the bioavailability of the active therapeutic molecules. They are able to protect the food or beverage supplement from the alteration of its organoleptic properties and shield the content until its discharge at the desired site of action. Moreover, they can maintain the nutritional characteristics of the active molecules from degradation during the preparation and storage stages [29-31].

In cosmetic industry:

Nanoemulsions are beneficial system for use in the cosmetics because the active molecules are easily absorbed to produce efficient effect as a result of the submicron sized particles and minimize the loss of water from the skin. Flocculation and creaming are not taking place resulting in production of a more attractive and stable formulation. They are frequently used as creams and moisturizer [7,13,32,33].

Oral delivery system of drug:

As a result of its submicron particle size, the bioavailability of poor soluble drug administered via oral route is increased. Nanoemulsion is also able to integrate non-polar drug in oil phase [13,34].

Transdermal delivery system of drug:

Active drug molecules can be introduce into the nanoemulsion and crossed the cell membrane [35]. Nanoemulsion acts as a carrier for the delivery of drug molecules across the stratum corneum of skin due to its rapid permeation through the skin and stability [36].

In chemotherapy:

One of the targeted-drug delivery methods is depended on the point that tumor cells required high amount of cholesterol for targeted- drug delivery to cancer cells [37-39]. Nanoemulsions consisting high cholesterol are able to target the anticancer drug to cancerous cells [40-42].

As anti-microbial drug

Oil in water (O/W) nanoemulsion with a broad spectrum activity against bacteria, enveloped viruses, spores and fungi are used as antimicrobial agent. They are droplets attached with organisms consisting of lipid and discharge part of the energy within the emulsion. The lipid membrane of pathogen is destabilized by active therapeutics molecule and energy released from the emulsion, resulting to the lysis of the pathogen cell [43,44].

In cell culture:

Due to their ability to improve uptake of oil soluble substance in cell culture and increase the growth of culture cell, nanoemulsion are used in cell culture technology.

As mucosal vaccines:

Nanoemulsion can deliver inactivated organism and recombinant protein to a mucosal surface via needle free injection because of its ability to cause the protein surface to be adjuvanted and therefore assists uptake by antigen-presenting cells [13,34].

CONCLUSION

Nanoemulsions are extensively used in pharmaceutical formulations. Nanoemulsion formulation deals numerous advantages such as delivery of drugs, biological or diagnostic agents. The most significant application of nanoemulsion is for masking the unpleasant taste of oily liquids. Nanoemulsion may also protect the drugs, which are susceptible to hydrolysis and oxidation. Nanoemulsions are lipophilic drug carrier. As a result of good permeation through the skin barrier and low irritancy, it is suitable for transdermal drug delivery systems. Nowadays, they are widely used in various industry such as cosmetic, food and beverage, pharmaceutical and etc. because of their submicron particle size and many other advantages. More research work and development should be done to explore their uses in other fields.

REFERENCES

[1] C Solans, P Izquierdo, J Nolla, N Azemar, MJ Garcia-Celma. Nano-emulsions. *Curr. Opin. Colloid Interface Sci.* 10, 102–110 (2005).

[2] TG Mason, JN Wilking, K Meleson, CB Chang, SM Graves. Nanoemulsions: formation, structure, and physical properties, *J. Phys.:Condens.Matter*, 18: R635–R666 (2006).

[3] MY Koroleva, EV Yurtov. Nanoemulsions: the properties, methods of preparation and promising applications, *Russ. Chem. Rev.* 81, 21–43 (2012).

[4] R Pons, I Carrera, J Caelles, J Rouch, P Panizza. Formation and properties of

miniemulsions formed by microemulsions dilution, *Adv. Colloid Interface Sci*. 106, 129–146 (2003).

[5] S Sajjadi. Effect of mixing protocolon formation of fine emulsions, *Chem.Eng. Sci*. 61, 3009–3017 (2006).

[6] DJ McClements. Nanoemulsions versus microemulsions: terminology, differences, and similarities, *Soft Matter8*, 1719–1729 (2012).

[7] P Shah and D Bhalodia. Nanoemulsion a pharmaceutical review, *Sys Rev. Pharm.*, 1(1):24-31 (2011).

[8] DJ McClements. Edible nanoemulsions: fabrication, properties, and functional performance. *Soft Matter7* (6), 2297–2316 (2011).

[9] V Devarajan and V Ravichandran. Nanoemulsion: As Modified Drug Delivery Tool. *Pharmacie Globale International Journal of Comprehensive Pharmacy*, 4(2):1-6 (2011).

[10] T Hamouda, MM Hayes, Z Cao, R Tonda, K Johnson, DC Wright, J Brisker and JR Baker Jr. A novel surfactant nanoemulsion with broad-spectrum sporicidal activity against *Bacillus* species., *J. Infect. Dis.*, 180(6):1939-1949 (1999).

[11] Jiajia, R and David Julian Mcclaments. Formation of Flavor Oil Micro emulsions, Nanoemulsions and Emulsions: Influence of Composition and Preparation Method. *Journal of Agriculture and Food Chemistry*, 59(9): 5026-5035 (2011).

[12] U Ravi Theaj Prakash and P Thiagaraja. Nanoemulsions for drug delivery through different routes. *Research in Biotechnology*, 2(3): 01-13 (2011).

[13] N Sharma, M Bansal and S Visht. Nanoemulsion: A new concept of delivery system. *Chron Young Sci*, 1(2): 2-6 (2010).

[14] DJ McClements, J Rao. Food-grade nanoemulsions: formulation, fabrication, properties, performance, biological fate, and potential toxicity. *Crit. Rev. Food Sci. Nutr.* 51 (4), 285–330 (2011).

[15] T Tadros, P Izquierdo, J Esquena, C Solans. Formation and stability of nano-emulsions. *Adv. Colloid Interface Sci*. 108–109, 303–318 (2004).

[16] C Solans, I Sole. Nano-emulsions: formation by low-energy methods. *Curr. Opin. Colloid Interface Sci.* 17 (5), 246–254 (2012).

[17] SM Jafari, Y He, B Bhandari. Optimization of nano-emulsions production by microfluidization. *Eur. Food Res. Technol. Zeitschrift für Lebensmitteluntersuchung und -Forschung.* A 225 (5-6), 733–741 (2007).

[18] SM Jafari, E Assadpoor, Y He, B Bhandari. Re-coalescence of emulsion droplets during high-energy emulsification. *Food Hydrocolloids* 22 (7), 1191–1202 (2008).

[19] Reza, Kh Hussan. Nanoemulsion as a novel transdermal Drug Delivery System. *International Journal Pharmacy Science Research*, 2(8):1938-1946 (2011).

[20] NK Jain. Targeted and controlled drug delivery, *CBS publisher and distributors*, pp: 283 (2011).

[21] TG Mason, JN Wilking, K Meleson, CB Chang and SM Graves. Nanoemulsions: formation, structure and physical properties. *Journal of Physics: condensed matter*, 18: R635-R666 (2006).

[22] S Kentish, T Wooster, M Ashok Kumar, S Balachandran, R Mawson and L Simons. The use of ultrasonics for nanoemulsion preparation. *Elservier Ltd*., 9(2):170-175 (2008).

[23] L Wang, R Tabor, J Eastoe, X Li, K Richard, *et al*. Formation and stability of nanoemulsion with mixed ionic-nonionic surfactants. *Advance in Colloid and Interface Science*, 108: 303-318 (2004).

[24] P Bhatt and S Madhav. A detailed review on nanoemulsion drug delivery system. *International Journal Pharmacy Science and Research*, 2(9): 2292-2298 (2011).

[25] V Ghosh, A Mukherjee, & N Chandrasekaran. Ultrasonic emulsification of food-grade nanoemulsion formulation and evaluation of its bactericidal activity. *Ultrasonics Sonochemistry*, 20(1), 338–344 (2013).

[26] Qian Chang and David Julian Mc Clements. Formation of nanoemulsions stabilized by model food-grade emulsifiers using high-pressure homogenization: Factors affecting particle size, *Elsevier B.V.*, 25(5): 1000-1008 (2011).

[27] PK Gupta, JK Pandit, A Kumar, P Swaroop and S Gupta. Pharmaceutical nanotechnology novel nanoemulsion high energy

emulsification preparation, evaluation and application. *The Pharma Research*, 3: 117-138 (2010).

[28] S Debnath, Satayanarayan and KG Vijay. Nanoemulsion-a method to improve the solubility of lipophilic drugs, 2(2-3): 72-82 (2011).

[29] EJ Acosta. Association colloids as delivery systems: principles and applications in the food and nutraceutical industries. In: Huang, Q. (Ed.), *Nanotechnology in the Food, Beverage and Nutraceutical Industries. Woodhead Publishing*, Amsterdam (2012).

[30] DJ McClements, H Xiao. Potential biological fate of ingested nanoemulsions: influence of particle characteristics. *Food Funct*. 3, 202–220 (2012).

[31] CJH Porter, NL Trevaskis, WN Charman. Lipids and lipid-based formulations: optimizing the oral delivery of lipophilic drugs. *Nat. Rev. Drug Discov.* 6, 231–248 (2007).

[32] Aubrun, O Sonneville, JT Simonnet and FL Alloret. Nanoemulsions: a new vehicle for skincare products, *Advances in Colloid and Interface Science*, 108-109: 145-149 (2004).

[33] http://ec.europa.eu/health/ph_risk/risk_en. html: accessed on 22/11/2016.

[34] PD Patel, GJ Patel, PD Bharadia, VM Pandya and DA Modi. Nanoemulsion: An advanced concept of dosage form. *Journal and Cosmetology*, 5(1): 122-133 (2011).

[35] Q Huang, H Yu, Q Ru. Bioavailability and delivery of nutraceuticals using nanotechnology. *J. Food Sci.* 75, R50–R57 (2010).

[36] A Soottitantawata, F Bigeardb, H Yoshiia, T Furutaa, M Ohkawarac, P Linkod. Influence of emulsion and powder size on the stability of encapsulated d-limonene by spray drying. *Innov. Food Sci. Emerg. Technol.* 6, 107–114 (2005).

[37] S Vitols. Uptake of low-density lipoprotein by malignant cells-possible therapeutic applications. *Cancer Cells* 3, 488–495 (1991).

[38] L Polo, G Valduga, G Jori, E Reddi. Density lipoprotein receptors in the uptake of tumor photosensitizer by human and rat transformed fibroblasts. *Int. J. Biochem. Cell Biol.* 34, 10–23 (2002).

[39] RA Firestone. Low density lipoprotein as a vehicle for targeting antitumor compounds to cancer cells. *Bioconjug. Chem.* 5, 105–113 (1994).

[40] JA Moura, CJ Valduga, ER Tavares, IF Kretzer, DA Maria, RC Maranhão. Novel formulation of a methotrexate derivative with a lipid nanoemulsion. *Int. J. Nanomedicine* 6, 2285–2295 (2011).

[41] RC Maranhão, TB César, SR Pedroso-Mariani, MH Hirata, CH Mesquita. Metabolic behavior in rats of a non-protein microemulsion resembling low density lipoprotein. *Lipids* 28, 691–696 (1993).

[42] ML Dias, JP Carvalho, DG Rodrigues, SR Graziani, RC Maranhão. Pharmacokinetics and tumor uptake of a derivatized form of paclitaxel associated to a cholesterol-rich nanoemulsion (LDE) in patients with gynecologic cancers. *Cancer Chemother. Pharmacol.* 59, 105–111 (2007).

[43] K Ziani, Y Chang, L Mc, LS Borough and J McClements David. Physiocochemical Properties and Antimicrobial Efficacy of Electrostatic Complexes Based on Cationic ε-Polylysine and Anionic Pectin. *J. Agric. Food Chem.*, 59(11): 6247-6255 (2011).

[44] T Hamoud, A Myc, B Dono van, AY Shih, JD Reuter and JR Baker. A novel surfactant nanoemulsion with a unique non-irritant topical antimicrobial activity against bacteria, enveloped viruses and fungi. *Microbiological Research*, 156(1):1-7 (2001).