



Submicron Emulsion - A Novel and Versatile Paradigm for Delivery of Therapeutics for Bioavailability Enhancement

Birkaran Singh, Tanya Sehgal, Satwinder Kaur, Jasjeet Kaur Narang*

Department of Pharmaceutics, Khalsa College of Pharmacy, Amritsar, Punjab, India

*Corresponding author's E-mail: jasjeet2975@yahoo.com

Received: 24-01-2022; Revised: 28-03-2022; Accepted: 06-04-2022; Published on: 15-04-2022.

ABSTRACT

Submicron emulsions are the small atomic sized granular systems which enhance the bioavailability of certain drug products. They are isotropic system in which emulsifying agents are mixed with immiscible liquids to form single phase. This review article focuses on classification, advantages, disadvantages, method of preparation of submicron emulsion, its evaluation parameters and pharmaceutical applications of submicron emulsions.

Keywords: Submicron emulsions, delivery, bioavailability, emulsifying agents.

QUICK RESPONSE CODE →

DOI:

10.47583/ijpsrr.2022.v73i02.022



DOI link: <http://dx.doi.org/10.47583/ijpsrr.2022.v73i02.022>

INTRODUCTION

Submicron emulsions are tiny granular systems in the atomic size range which act as a carrier for drug molecules for enhancing the bioavailability of therapeutics. The size of submicron emulsion range within 10-1000nm. They are thermodynamically unstable isotropic systems in which emulsifying agents (surfactant and cosurfactant) are mixed along with two immiscible liquids to form a single phase. Submicron emulsions consist of oil, water, surfactant and cosurfactant. They are spherical in shape. They are classified as: o/w emulsion, w/o emulsion and bi-continuous emulsion¹.

Classification of submicron emulsions

The submicron emulsions are classified into the following three types:

1. Oil in water submicron emulsion
2. Water in oil submicron emulsion
3. Bi-continuous submicron emulsion²

Advantages of submicron emulsions

The submicron emulsions have been widely used by researchers over the past few years due to the advantages they possess. A few advantages of submicron emulsions are:

- Due to their greater surface area and free energy submicron emulsions are effective carrier system for drugs.

- They do not show the problem of creaming, flocculation and sedimentation because they are kinetically stable.
- Submicron emulsions are easily applicable to skin or mucous membranes.
- They are non-toxic and non-irritant.
- They improve the solubility of lipophilic drugs due to their small size.
- Another inherent advantage invested in submicron emulsions is their ability to easily penetrate through the "rough" skin surface/mucous membrane due to their very small size and lipophilic nature, which makes them a suitable dosage form for the topical delivery of drugs.
- They possess enhanced rate of absorption.
- They are easy to make at the lab scale³.

Disadvantages of submicron emulsions

The submicron emulsions have a few disadvantages, which are given below:

- They may cause toxicity if the quantity of surfactants/cosurfactants added is high.
- Change in temperature and pH decreases the stability of submicron emulsions.
- Surfactant used must be non-toxic and non-irritant for utilization in pharmaceutical applications.
- The manufacturing of submicron emulsion is an expensive process at a commercial scale^{4,5}.

Methods for the formulation of ultrafine emulsions

The following methods are commonly used for the formulation of submicron emulsions:



- High –Energy methods (for lab and industrial preparation)
 1. High pressure homogenization
 2. Microfluidization
- Low-Energy methods (for lab preparation)
 1. Solvent evaporation
 2. Phase inversion

High pressure homogenization method

The method is used for the preparation of submicron emulsions. In this method, high energy homogenizer is used to make ultrafine emulsions of atomic size ranged up to 1nm. A dispersion of aqueous phase and oily phase is achieved by passing the mixture through a small inlet orifice at very high pressure (500 to 5000 psi) and then the product/formulation is subjected to processes like intense turbulence and hydraulic shear. This results in the formation of submicron emulsions of very low particle size⁶. Figure 1 represents the high pressure homogenization method.

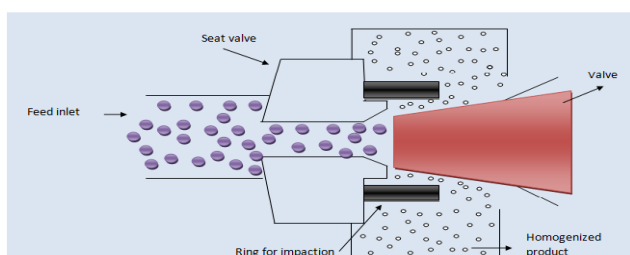


Figure 1: High pressure Homogenisor

Microfluidization

It is a mixing technique, in which microfluidizer is used. High-pressure positive displacement pump (500 to 20000psi), is used in this device and this pump subjects the product/formulation to pass through the patented interaction chamber, which consists of 'microchannels', which results in sub- micron emulsion⁷. Figure 2 represents a microfluidizer.

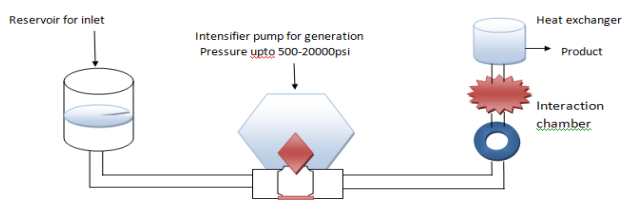


Figure 2: Microfluidizer

Solvent evaporation process

In this technique, a drug is taken and mixed with lipophilic surfactant. Then the drug surfactant mixture is dissolved in a water immiscible solvent. After this aqueous surfactant is added and continuous stirring is done for some time. Then the formulation is subjected to high pressure homogenization for the formation of submicron emulsions. At the last evaporation of solvent

is done and submicron emulsions are formed⁵. A schematic representation of the process is given in the figure 3.

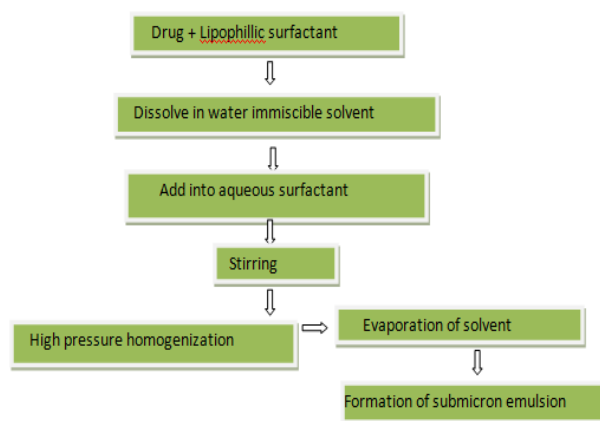


Figure 3: A schematic representation of Solvent evaporation process

Phase inversion process

It is a phenomenon in which o/w type emulsion changes to w/o type due to phase inversion. It is the physical process. This change in a phase can be brought about by shifting the emulsifier affinity from one phase to another, by varying the phase volume ratio, by adding electrolytes and by changing the temperature¹. The phase inversion method is given in figure 4.

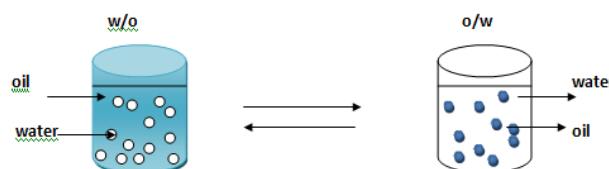


Figure 4: Phase inversion method

Evaluation parameters for Submicron emulsions

Evaluation is a very important aspect of formulation development. The following parameters are used for the evaluation of submicron emulsions:

- **Droplet size analysis-** Diffusion method by light-scattering particle size analyzer_Coulter LS 230 is used to measure the droplet size. Another method for the determination of particle size is Dynamic Light scattering technique³.
- **Viscosity Determination-** Viscosity determination is an important parameter for the evaluation of submicron emulsion. It can be done with the help of Brookfield viscometer or a rheometer. Viscosity determination confirms that the system is o/w or w/o emulsion¹.
- **Morphology and structure-** Transmission electron microscopy (TEM) is used to study the morphology and structure of the submicron emulsion. Bright field imaging at increasing magnification in combination with diffraction modes can also be used to disclose the size and form of submicron emulsion droplets.

- **Zeta potential**- It is used to measure the charge on the surface as well as the stability of submicron emulsions. In this technique Zetasizer is used for the determination of surface charge properties. The zeta potential between -30mV to +30mV is desirable⁸.
- **Percentage Transmittance**- UV-Vis spectrophotometer is used to determine the percentage transmittance of prepared submicron emulsion. A clear transparent ultrafine emulsion will have a percentage transmittance value of approximately 100%⁹.
- **Polydispersity** - The uniformity of droplet size in submicron emulsion is measured as polydispersity. There exists non-uniformity in droplet size of submicron emulsions, if the value of polydispersity is high. The polydispersity value which ranges from 0-1, signifies monodisperse system and 1 signifies polydisperse system. Zetasizer is used to measure its value¹.
- **Dye Test**- In this a water- soluble dye is used and when this dye is added to o/w submicron emulsion, the colour of the whole emulsion changes as the dispersion medium is water. On the other side, if the emulsion is w/o type, then the change in colour takes place only in dispersed phase i.e water and there is no change in colour of whole emulsion. Microscopic examination of this can be done to see the changes that takes place in emulsions¹.

Applications of submicron emulsions

Submicron size emulsions have been widely used by researchers for their antimicrobial property, as mucosal vaccines, for targeted delivery of drugs which is very important in treatment of diseases like cancer, for the protection of drugs against degradation, for the delivery of cosmetics etc^{10,11}.

Table I represents a few applications of submicron emulsions.

Table 1: Examples of some submicron emulsion are given in table below:

CLASS	Name of Drug	Type of submicron emulsion	Uses	Reference no.
Antimalarial	Primaquine	Oral submicron emulsion	Used to prevent and treat malaria	12
ACE Inhibitors	Ramipril	Submicron emulsion	Treat heart failure and high blood pressure	13
NSAIDS	Aceclofenac	o/w submicron emulsion	Treat pain and inflammation in osteoarthritis and rheumatoid arthritis.	14
Progestins (Female Hormone)	Progesterone	Lecithin- based submicron emulsion	It works as part of hormone replacement therapy by decreasing the amount of estrogen in the uterus.	15
Antiviral	Acyclovir	Multiple w/o/w submicron emulsion	Decrease pain and speed the healing of sores or blisters in people who have varicella, herpes zoster.	16
NSAIDS	Ibuprofen	Lipid submicron emulsion	Painkiller for backpain, period pain, toothache.	17
Antiretroviral	Lopinavir	Nanoparticle	Help to control HIV infection	18
Bioactive compound (antioxidant)	Curcumin	Nanocapsule	Antioxidant	19
Anticancer	Polymethoxy flavone	Nanocapsule	Used to treat cancer	20
Antibiotic	Amoxicillin	w/o submicron emulsion	Antibacterial	21
Cardiovascular	Ramipril	o/w submicron emulsion	Used to treat hypertension, CHF, stroke and heart attack	22
Antiemetic	Granisetron	Lipid submicron emulsion	Used to treat nausea and vomiting in anticancer therapy	23

CONCLUSION

Sub micron emulsions have gained importance for the delivery of BCS Class II. However, inspite of several advantages, a few of which include sustained and targeted drug release, protection of unstable drugs, enhancement of drug solubility with a consequent improvement in drug bioavailability, and improved patient convenience and compliance, steps have to be taken to improve its commercial viability.

REFERENCES

- Ahuja A, Ali J, Baboota S, Faisal MS, Shakeell F, Shafiq S. Stability evaluation of Celecoxib nanoemulsion containing Tween 80. *Thai J Pharm Sci.* 2008;32:4–9.
- Garti, N., and Benichou, A. Recent developments in double emulsions for food applications. *Food Emuls.* 2004;132: 353–412. doi: 10.1201/9780203913222.ch10.
- Bouchemal K, Briancon S, Fessi H, Perrier E :Nano-emulsion formulation using spontaneous emulsification: solvent, oil and surfactant optimization, *Int J Pharmaceutics* 2004;280:242
- 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.
- Kh. Hussan R: Nanoemulsion as a Novel Transdermal Drug Delivery System. *International Journal of Pharmaceutical Sciences and Research* 2011; Vol. 2(8):1938-1946.
- Lachman L, Lieberman HA, Kanig JL: *The Theory and Practice of Industrial Pharmacy*, Edition 2018;3: 510-11.
- Devarajan V and Ravichandran V: Nanoemulsions: As Modified Drug Delivery Tool. *International Journal of Comprehensive Pharmacy* 2011;4(01):1-6.
- Erol Yilmaz, Hans-Hubert Borchert: Design of a phytosphingosine-containing, positively-charged nanoemulsion as a colloidal carrier system. *European Journal of Pharmaceutics and Biopharmaceutics* 2005;60:93.
- Ali Mushir, Ali Javed and Bali Vikas: Study of surfactant combinations and development of a novel nanoemulsion for minimising variations in bioavailability of ezetimibe. *Colloid and Surfaces B:Biointerfaces*, 2010;76:412
- [Ruktanonchai U, Sakulku U, Nuchuchua o, et.al: Characterization and mosquito repellent activity of citronella oil nanoemulsion *Int. J Pharm.* 2009;112: 256-282.
- Junyaprasert B.V, Muller H.R, Souto B.E et al.: Q10 loaded NLC versus nanoemulsions; stability, rheology and in vitro skin permeation. *Int. J Pharm.* 2009; 377:207-214.
- Singh KK, Vingkar SK. Formulation, antimalarial activity and biodistribution of oral lipid nanoemulsion of primaquine. *Int J Pharm* 2008;347:136-43.
- Shafiq S, Shakeel F, Talegaonkar S, Ahmad FJ, Khar RK, Ali M. Development and bioavailability assessment of ramipril nanoemulsion formulation. *Eur J Pharm Biopharm* 2007;66:227-43.
- Shakeel F, Baboota S, Ahuja A, Ali J, Aqil M, Shafiq S. Nanoemulsions as vehicles for transdermal delivery of aceclofenac. *AAPS PharmSciTech* 2007;8:E104.
- Klang V, Matsko N, Zimmermann AM, Vojnikovic E, Valenta C. Enhancement of stability and skin permeation by sucrose stearate and cyclodextrins in progesterone nanoemulsions. *Int J Pharm* 2010;393:152-60.
- Schwarz JC, Klangv, Karall S, Mahrhauser D, Resch GP, Valenta C. Optimisation of multiple W/O/W nanoemulsions for dermal delivery of acyclovir. *Int J Pharm* 2012;435:69-75.
- Mottaleb MM, Neumann D, Lamprecht A. In vitro drug release mechanism from lipid nanocapsules (LNC). *Int J Pharm* 2010;390:208 – 13.
- Destache CJ, Belgum T, Christensen K, Shibata A, Sharma A, Dash A. Combination antiretroviral drugs in PLGA nanoparticle for HIV-1. *BMC Infect Dis* 2009;198:01 – 08.
- Dons i F, Sessa M, Mediouni H, Mgaidi A, Ferrari G. Encapsulation of bioactive compounds in nanoemulsionbased delivery systems. *Procedia Food Science* 2011;1:1666 – 71.
- Li Y, Zheng J, Xiao H, McClements Dj. Nanoemulsion-based delivery systems for poorly water-soluble bioactive compounds: influence of formulation parameters on polymethoxyflavone crystallization. *Food Hydrocolloid* 2012;27:517 – 28.
- Mason TG. New fundamental concepts in emulsion rheology. *Curr Opin Coll Interface Sci* 1999;4:231– 8.
- Shafiq S, Shakeel F, Talegaonkar S, Ahmad FJ, Khar RK, Ali M. Development and bioavailability assessment of ramipril nanoemulsion formulation. *Eur J Pharm Biopharm* 2006; 66:228 – 9.
- Doh HJ, Jung Y, Balakrishnan P, Cho HJ, Kim DD. A novel lipid nanoemulsion system for improved permeation of granisetron. *Colloid Surface B* 2012;101:475– 80.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

For any question relates to this article, please reach us at: globalresearchonline@rediffmail.com

New manuscripts for publication can be submitted at: submit@globalresearchonline.net and submit_ijpsrr@rediffmail.com

