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Review on: Methodology of Nanoemulsion Formulation

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Abstract- Nanoemulsions are thermodynamically stable systems consisting of two immiscible liquids combined with emulsifying agents, such as co- surfactants and surfactants, to create a single phase. Nanoemulsion represents an innovative drug delivery system that facilitates controlled or sustained release of medications. It is characterized as a dispersion comprising a surfactant, oil, and a clear aqueous phase, exhibiting kinetic or thermodynamic stability with droplet sizes ranging from 10 to 100 nanometers. The application of nanoemulsions enhances the solubility and bioavailability of lipophilic drugs, offering numerous advantages for drug delivery. Various methods exist for the preparation of nanoemulsions, including high-energy emulsification, spontaneous nanoemulsion formation, and phase inversion temperature (PIT) techniques. This system is applicable across multiple delivery routes, thereby demonstrating significant potential in diverse fields such as cosmetics, therapeutics, and biotechnology.

Index Terms- Preparation of nono-emulsion, Formulation techniques, Characteristics, Nanoemulsion, Tyes, Applications.

I. INTRODUCTION

The preparation of nanoemulsions represents an advanced delivery system for drugs, biologically active compounds, and genetic materials that encounter challenges related to release. Approximately 40% of chemical substances are inherently water-insoluble, making the delivery of these hydrophobic compounds particularly difficult. A nanoemulsion can be characterized as a colloidal dispersion that comprises a suitable ratio of oil emulsified within an aqueous phase, along with surfactants and co-surfactants. Nanoemulsions are noted for their clarity, as well as their thermodynamic and kinetic stability. Their application in the pharmaceutical industry is significant, as they enhance the solubility of lipophilic drugs, thereby improving the bioavailability of these substances through the reduction of particle size and the formation of nano-sized droplets ranging from 10 to 100 nm. It is important to distinguish between emulsions and nanoemulsions; emulsions typically demonstrate good kinetic stability but are thermodynamically unstable and appear cloudy, whereas nanoemulsions are translucent or clear. Additionally, the preparation of emulsions necessitates a substantial energy input, whereas nanoemulsions do not require such energy expenditure.

Advantages of Nanoemulsion

- Nanoemulsions enhance the bioavailability of pharmaceuticals.
- Safe and non-irritating: Nanoemulsions are characterized by their non-toxic and non-irritating properties.
- Taste concealment: Nanoemulsions are effective in masking unpleasant tastes.
- Economical: Nanoemulsions can minimize the quantity of colorant required to achieve the desired hue, thus proving to be cost-effective.
- Energy-saving: The production of nanoemulsions requires less energy compared to conventional mixing methods.
- Multifunctional: Nanoemulsions can be formulated in various forms, such as foams, creams, liquids, and sprays.
- Enhanced absorption of oil-soluble supplements: Nanoemulsions facilitate improved cellular absorption of oil-soluble supplements.
- Solubilization of lipophilic medications: Nanoemulsions assist in the solubilization of lipophilic drugs.

Disadvantages of Nanoemulsion

- Nanoemulsions exhibit limited solubility for substances characterized by elevated melting points.
- A significant quantity of surfactants and co-surfactants is necessary to ensure the stability of the nano-droplets in nanoemulsion.
- The stability of nanoemulsions is influenced by various environmental conditions, including temperature and pH levels.
- Low solubility capacity for high melting materials.

Nanoemulsion Types

- Oil-in-water (O/W) refers to a system where oil droplets are suspended within a continuous water phase.
- Water-in-oil (W/O) describes a scenario in which water droplets are distributed throughout a continuous oil phase.
- In a bicontinuous system, both oil and water microdomains are interspersed throughout the entire medium.

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Component of Nanoemulsion

- Oil
- Surfactant
- Co-surfactant
- Aqueous phase.

Characteristics of Nanoemulsion

- **Stability:** Nanoemulsions exhibit kinetic stability and possess commendable physical stability.
- **Transparency:** Typically, nanoemulsions are either optically transparent or semi-transparent.
- **Rheology:** The rheological properties of nanoemulsions can be adjusted as needed.
- **Viscosity:** The viscosity of nanoemulsions is a critical characteristic, influencing both their stability and the release of drugs.
- **Droplet Size:** A reduction in droplet size contributes to a more uniform structure.
- **Bioavailability:** Nanoemulsions have the potential to improve the bioavailability of the substances they encapsulate.
- **Preparation:** The method of preparation is contingent upon the specific formulation requirements.
- **Lipophilic components:** Nanoemulsions consist of lipophilic components that are uniformly dispersed within the oil phase.
- **Thermodynamic Stability:** The thermodynamic stability of nanoemulsions is assessed through tests for phase separation, creaming, cracking, coalescence, or phase inversion.
- **Zeta potential;** Zeta potential is a measure of particle charge which is important which is important characteristic to determine stability of nanoemulsion.

II. METHODS OF PREPARATION

1. High–Energy Emulsification Method

The high-energy method is employed to prepare nanoemulsions, utilizing mechanical energy through devices such as ultrasound generators, high-pressure homogenizers, and high shear stirrers. These mechanical instruments generate significant forces that disrupt the oil and water phases, facilitating the formation of nanoemulsions. High-pressure homogenizers deliver energy rapidly, resulting in uniformly small-sized droplets, which makes them widely utilized in the preparation of nanoemulsions. In contrast, ultrasound generators are more cost-effective, as they require less surfactant. Additionally, alterations in formulation, such as reductions in droplet size and changes in pH, can lead to flocculation within the formulation.

2. Low–Energy Emulsification Method

This approach yielded droplets that were more uniform and smaller by utilizing the physicochemical characteristics of the system. However, there are certain limitations associated with this method regarding the types of oils and emulsifiers that can be employed, particularly polysaccharides and proteins. To address this issue, synthetic surfactants are utilized at elevated concentrations in conjunction with low-energy techniques; however, this restricts its applicability, particularly in the context of food processing.

3. Spontanous Nanoemulsion

It employs the chemical energy that is released during dilution processes with a continuous phase, occurring at a constant temperature throughout the emulsification procedure, without any phase transition within the system. This approach yields.

4. Nanoemulsion Without Special Device at Room Temperature

In this system, an oil phase with a hydrophilic substance mixed with water, oil droplet immediately formed, this mechanism depends on water-dispersible material movement from oil to water phase as red arrows which lead to spontaneous oil droplet formation.

III. FORMULATION TECHNIQUES OF NANOEMULSION

- . High-Pressure Homogenization (HPH)
- Ultrasonication
- Microfluidization
- Solvent Displacement Techniques
- Solvent evaporation Technique
- Phase inversion Technique

1. High-Pressure Homogenization – Nanoemulsions are often produced in high-pressure homogenizers

Construction

- A pump used in high-pressure homogenizers increases the dispersion's pressure by 500–5000 psi.
- The homogenizing valve's opening through which fluids are forced

Process

Coarse emulsion is initially created using a high shear mixer and subsequently processed in a high-pressure homogenizer, which leads to the formation of a fine emulsion. Various forces, including turbulence, shear, cavitation, shock, shear stress, pressure gradient, and expansion shear, contribute to the fragmentation of droplets. The homogenizer utilizes different types of nozzles to facilitate droplet disruption, resulting in a Nanoemulsion characterized by a lipophilic core encased in a monomolecular phospholipid layer. The final product is subjected to hydraulic shear and turbulence, which effectively reduces the size of coarse emulsions by separately mixing oil and water.

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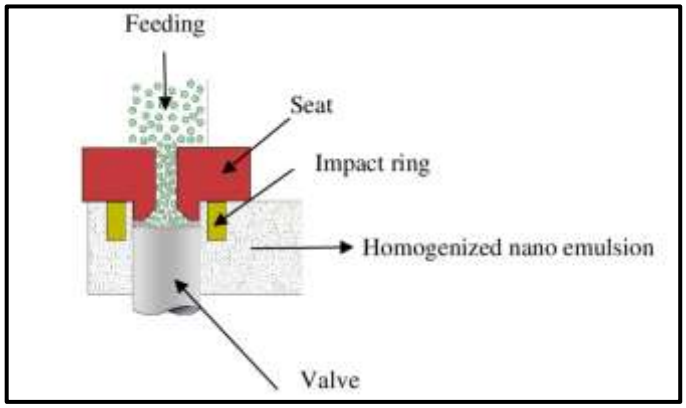

Fig 1 : High pressure homogenization for Nanoemulsion

Merits

High Efficiency

The homogenizer achieves reduced particle sizes by applying energy in the briefest duration while ensuring the most uniform flow, reaching sizes as small as 1 nm

Demerits

- Significant dependence on energy consumption.
- Elevated emulsion temperatures during processing.

2] Ultrasonication- Ultrasonication is an energy-intensive technique employed to reduce droplet size in emulsions through the generation of sinusoidal pressure fluctuations resulting from mechanical vibrations exceeding 2 kHz.

Construction

This process utilizes a piezoelectric probe, which generates a significant disruptive force via its tip.

Process

The procedure entails the incorporation of a uniform oil phase into a water phase, resulting in a coarse emulsion. This emulsion is subsequently treated with ultrasonication to generate nanoemulsions. The process produces bubbles via cavitation, which leads to the condensation of droplets.

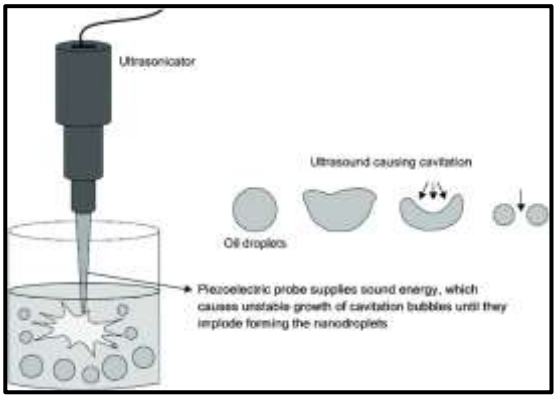

Fig 2: Ultrasonication technique.

Merits : Less energy expenditure,
Demerits : Contamination caused by probes.

3. Micro Fluidization - The size of the droplets in the previously created coarse emulsion is diminished through the application of microfluidizers. The process of size reduction operates through various mechanisms, including hydraulic shear, impact, attrition, impingement, intense turbulence, and cavitation.

Construction

- A Fluidizer consist of
- An Inlet feed;
- A pressure intensifier pump;
- An interaction chambers;
- Cooling coil;
- Outlet.

Process -

The pre-emulsion feed is separated into two pathways by a stainless-steel block located within the apparatus. The dimensions of the block's channel decrease until reaching approximately 75 µm in width. The two feeds are directed to collide head-on, thereby creating an extremely high shear force that facilitates the formation of Nanoemulsion.

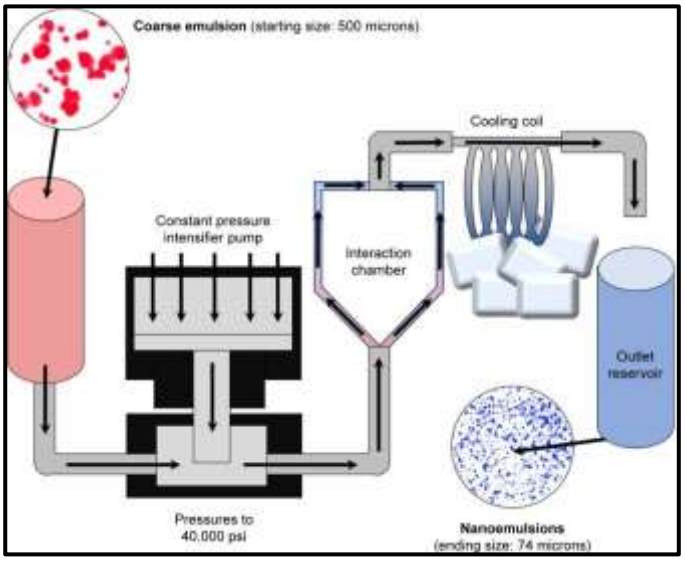

Fig 3 : Micro fluidization technique.

Merits :

- There is no contamination of the feed material.
- The continuous mass production of substantial quantities of products and formulations is achievable.

Demerits :

- The rapid onset of emulsification prevents the biopolymers employed in this technique from effectively

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stabilizing droplets that have been recently disrupted within such a brief timeframe.
- High energy density that is produced during the procedure.

4] Solvent Displacement Method - This method involves combining the organic phase—which contains the oil dispersed in a solvent such as ethanol or acetone—with the aqueous phase, which contains the surfactants.

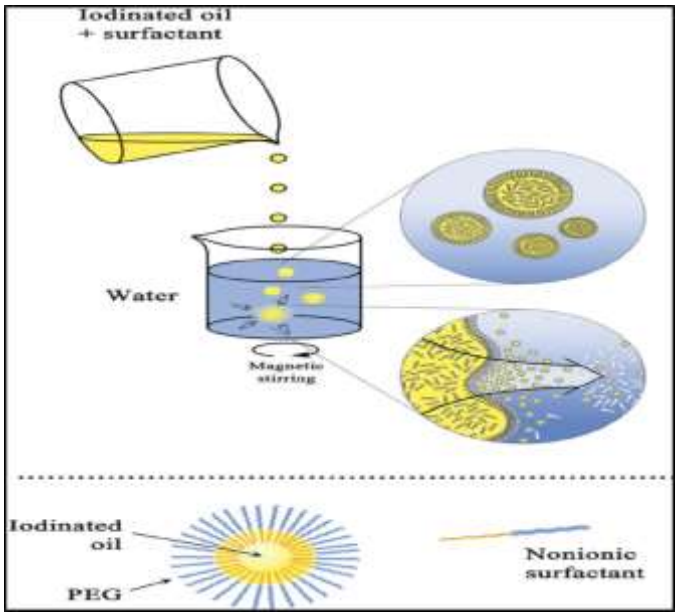

Fig 4: Solvent displacement technique.

Process –
The solvent displacement technique involves the precipitation of polymers from an organic solution. Initially, the polymers are dissolved in a semipolar solvent, which is subsequently introduced into an aqueous solution containing a stabilizer, resulting in the immediate formation of nanoparticles.

Merit : Required no heating
Demrit : The need of large ratio of solvent and oil for the production of small sized droplets of disperse phase.

5 Solvent Evaporation Technique
Process:
The solvent evaporation technique, also known as the hydrogel method, involves the preparation of a drug solution that is subsequently emulsified into a different liquid, which serves as a non-solvent for the drug. Following this, the solvent is evaporated, resulting in the precipitation of the drug. A high-speed stirrer may be utilized to control the growth of crystals and prevent particle aggregation. The hydrogel method closely resembles the solvent evaporation technique, with the primary distinction being that in this method, the drug solution is miscible with the drug antisolvent.

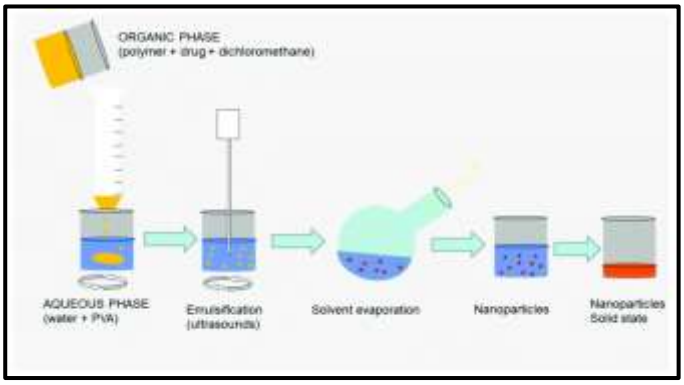

Fig 5 : Solvent evaporation technique.

6 Phase inversion technique:
In the phase inversion method, fine dispersion is achieved through the chemical energy generated by phase transitions that occur during the emulsification process. This phase transition is induced by altering the composition of the emulsion while maintaining a constant temperature. The concept of phase inversion temperature was initially explored, revealing that an increase in temperature leads to chemical alterations in polyoxyethylene surfactants, primarily through the degradation of the polymer chain. This method is particularly effective for the formulation of oil-in-water (o/w) nanoemulsions. A significant advantage of this approach lies in its reliance on the phase transitions that occur throughout the emulsification process. By modifying the composition of the components, the hydrophilic-lipophilic characteristics of the emulsifier can be adjusted accordingly.

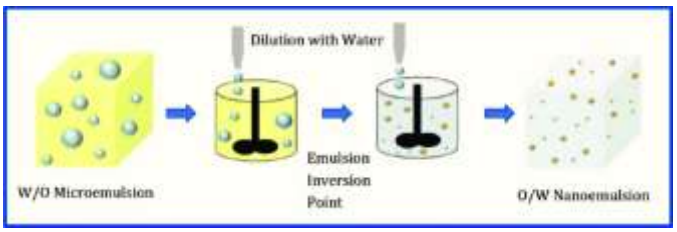

Fig 6: Phase Invasion Technique.

Factors Influencing the Formulation of Nano-emulsion :
- A suitable composition is essential to prevent Ostwald ripening; the dispersed phase must exhibit high insolubility in the continuous medium.
- Surfactants play a crucial role in the formulation of nanoemulsions. It is important that they do not lead to the formation of lyotropic liquid crystalline "microemulsion" phases. Typically, systems comprising short-chain alkanes, alcohols, water, and surfactants are utilized alongside co-surfactants.

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- The presence of an excess of surfactants facilitates the rapid coating of newly created nanoscale surface areas during the emulsification process, thereby reducing the likelihood of induced coalescence.
- Significant shear forces must be applied to break down microscale droplets into nanoscale droplets, necessitating stress levels that exceed the Laplace pressure of the droplets, typically ranging from 10 to 100 atm. Among various techniques, ultrasonication is the most commonly employed method in laboratory settings.

Applications of Nano-emulsion :

Nanoemulsion for Oral Administration

Poorly water-soluble drugs often exhibit low bioavailability due to their limited dissolution rates.

The use of oil-in-water (o/w) nanoemulsions for these drugs enhances their solubility, absorption, and overall bioavailability following oral administration.

Nanoemulsion for Ocular Delivery

To enhance the delivery of lipophilic drugs to the eye, o/w nanoemulsions are employed, including compounds such as pilocarpine and erythromycin.

Nanoemulsion for Nasal Delivery

The nasal route offers several advantages over oral and parenteral routes, including the ability to bypass first-pass metabolism in the liver. Additionally, the increased contact time between the nasal mucosa and nanoemulsion droplets contributes to improved drug absorption.

Nanoemulsion for Transdermal Delivery

Chemical substances can penetrate the skin through three primary pathways: hair follicles, sweat ducts, or directly through the stratum corneum, which can limit drug absorption and reduce bioavailability.

Nanoemulsions enhance drug targeting and control redistribution throughout the blood and lymphatic systems. Their nano-sized droplets can effectively penetrate skin pores, facilitating systemic delivery. Furthermore, nanoemulsions are recognized as a promising technique due to their low preparation costs, high stability during storage, absence of organic solvents, and thermodynamic stability.

Nanoemulsion in Cosmetics

Nanoemulsions serve as effective vehicles for controlled delivery in cosmetic applications, aiding in the dispersion of active ingredients within the skin layers.

Their use in cosmetics is advantageous as they do not experience sedimentation, creaming, or flocculation, which are common issues associated with microemulsions.

IV. CONCLUSION

This study explores various Nanoemulsion formulating techniques, preparation, characterization, release studies,and kinetic modelling. This document discusses various high- and low-energy techniques such as high-pressure homogenization, ultrasonication, microfluidization, phase inversion by temperature, solvent displacement method,and self-emulsifying Nanoemulsion, respectively, that are considered the best methods for formulating Nanoemulsion. The techniques employed in the formulation of nanoemulsions are straightforward, reliable, and precise. Nanoemulsion drug delivery systems successfully address the challenge of low bioavailability commonly associated with hydrophobic drugs and food components that undergo significant first-pass metabolism. The formulation methods for nanoemulsion drug delivery systems can be systematically categorized based on the energy input required, the characteristics of phase inversion, and the process of self-emulsification. Nanoemulsions offer advantages in drug delivery, masking oily liquids' unpleasant taste, and protecting drugs from hydrolysis and oxidation, making them popular for targeted anticancer, photosensitivity, and therapeutic agents.

REFERENCES

1. Manjit Jaiswal, Rupesh Dudhe (2015), Nanoemulsion an advanced mode of drug delivery system. Biotech journal. 5(2): 123–127.
2. Amine N, Das B (2019), Review on formulation and characterization of Nanoemulsion. Int J. Curr pharm Res, vol 11(4), 1-5.
3. Sarardekar P., Bajaj A. (2016), Nanoemulasion A Review. IJRPC6(2), 312-322.
4. Weiss J, Takhistov P, McClements DJ. Functional materials in food nanotechnology. Journal of Food Science. 2006;71: 107–116.
5. Komaiko JS, McClements DJ. Formation of food-grade nanoemulsions using low-energy preparation methods: are view of available methods. Comprehensive Reviews in Food Science and Food Safety. 2016; 15: 331–352.
6. Karthik P, Ezhilarasi PN, Anandharamakrishnan C. Challenges associated in stability of food grade nanoemulsions. Critical Reviews in Food Science and Nutrition. 2017; 57: 1435-1450.
7. Qian C, Mc Clements DJ. Formation of nanoemulsions stabilized by model food-grade emulsifiers using highpressure homogenization: factors affecting particle size. Food Hydrocolloids. 2011; 25: 1
8. Kumar S. Role of nano-emulsion in pharmaceutical sciences-a review. AJRPSB 2014;2:1-15.3.

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9. Bhosale RR, Osmani RA, Ghodake PP, Shaikh SM, Chavan SR. Nanoemulsion: A Review on novel profusion in advanced drug delivery. Indian J Pharm Biol Res 2014;2:122-7. 4.
10. Jaiswal M, Dudhe R, Sharma PK. Nanoemulsion: an advanced mode of drug delivery system. 3 Biotech 2015;5:123-7.5.
11. Singh KK, Vingkar SK. Formulation, antimalarial activity and biodistribution of oral lipid nanoemulsion of primaquine. Int J Pharm 2008;347:136-43.6.
12. Bhatt, P., & Madhav, S. (2011). A detailed review on Nanoemulsion drug delivery system. International Journal of Pharmaceutical Sciences and Research, 2(10): 2482. doi: http://dx.doi.org/10.13040/IJPSR.0975-8232.2(10). 2482-89.
13. Silva, H.D., Cerqueira, M.A., & Vicente, A.A. (2012). Nanoemulsions for food applications: development and characterization. Food and Bioprocess Technology, 5: 854–867. doi: 10.1007/s11947-011-0683-7.
14. Pathan, I., Mangle, M., & Bairagi, S. (2016). Design and characterization of Nanoemulsion for transdermal delivery of meloxicam. Analytical Chemistry Letters, 6(3): 286–295. doi: 10.1080/22297928.2016.1209126.
15. [15] Martins, J.T., et al. (2018). Protein-based structures for food applications: From macro to nanoscale. Frontiers in Sustainable Food Systems, 2: 77. doi: https://doi.org/10.3389/fsufs.2018.00077.
16. Gurpreet, K., & Singh, S. (2018). Review of Nanoemulsion formulation and characterization techniques. Indian Journal of Pharmaceutical Sciences, 80(5). doi: 10.4172/pharmaceutical-sciences.1000422.
17. "Nanoemulsion Formation by High-Pressure Homogenization" (Journal of Pharmaceutical Sciences)
18. "Ultrasonication-Assisted Nanoemulsion Formation" (International Journal of Nanomedicine)
19. "Microfluidization: A Novel Technique for Nanoemulsion Formation" (European Journal of Pharmaceutics and Biopharmaceutics)
20. Akbas E, Soyler B, Oztop MH. Formation of capsaicin loaded nanoemulsions with high pressure homogenization and ultrasonication. LWT. 2018;96:266–273. doi: 10.1016/j.lwt.2018.05.043. [CrossRef] [Google Scholar]
21. Alshamsan A, Kazi M, Badran MM, Alanazi FK. Role of alternative lipid excipients in the design of self-nanoemulsifying formulations for fenofibrate: characterization, in vitro dispersion, digestion and ex vivo gut permeation studies. Front Pharmacol. 2018;9:1219. doi: 10.3389/fphar.2018.01219. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
22. Armanet L, Hunkeler D. Phase inversion of polyacrylamide-based inverse-emulsions: influence of inverting-surfactant type and concentration. J Appl Polym Sci. 2007;103:3567–3584. doi: 10.1002/app.25062. [CrossRef] [Google Scholar]
23. Azeem A, Rizwan M, Ahmad FJ, Iqbal Z, Khar RK, Aqil M, et al. Nanoemulsion components screening and selection: a technical note. AAPS PharmSciTech. 2009a;10:69–76. doi: 10.1208/s12249-008-9178-x. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
24. Azeem A, Rizwan M, Ahmad FJ, Khar RK, Iqbal Z, Talegaonkar S. Components screening and influence of surfactant and co-surfactant on nanoemulsion formation. Curr Nanosci. 2009b;5:220–226. doi: 10.2174/157341309788185505. [CrossRef] [Google Scholar]
25. Y. Singh et al. Nanoemulsion: Concepts, development and applications in drug delivery J. Control. Release.(2017)
26. Fernandez, P., Andre, V., Rieger, J. and Kühnle A., 2004 Nano-emulsion formation by emulsion phase inversion, Colloids and Surfaces A: Physicochem. Eng. Aspects, 251, 53– 58.
27. Floury, J., Desrumaux, A., and Lardieres, J., 2000 Effect of high-pressure homogenization on droplet size distributions and rheological properties of model oil-in-water emulsions, Innovative Food Science & Emerging Technologies, 1(2), 127-134.
28. Ghosh V, Mukherjee A, Chandrasekaran N. 2013 Ultrasonic emulsification of food-grade nanoemulsion formulation and evaluation of its bactericidal activity. UltrasonSonochem;20:338-44.
29. Klang, V, Matsko, N, Valenta, C. & Hofer F,Electron microscopy of nanoemulsions: An essential tool for characterisation and stability assessment, Micron, 43, 85–103, 2012.
30. Koroleva, M.Y., and Yurtov, E.V.,Nanoemulsions: the properties, methods of preparation and promising applications, Russian Chemical Reviews, 81(1), 21-43, 2012.
31. Leong, T.S.H., Wooster, T.J., Kentish, S.E., and Ashokkumar, M., Minimising oil droplet size using ultrasonic emulsification, Ultrasonics Sonochemistry, 16(6), 721-727, 2009.
32. Sadurní N, Solans C, Azemar N, Garcia Celma MJ. Studies on the formation of o/w nano-emulsions, by low energy methods, suitable for pharmaceutical applications. Eur J Pharm Appl 2005;26:438-45.
33. Sukanya G, Mantry S, Anjum S. Review on nanoemulsions. Int J Innovative Pharm Sci Res 2013;1:192-205.
34. Bhatt P, Madhav S. A detailed review on nanoemulsion drug delivery system. Int J Pharm Sci Res 2011;2:2482-9.

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