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An Overview on Nanoemulsion Drug Delivery System

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ABSTRACT: Nanoemulsion drug delivery systems are advanced modes for delivering and improving the bioavailability of hydrophobic drugs and the drug which have high first pass metabolism. The nanoemulsion can be prepared by both high energy and low energy methods. High energy method includes high-pressure homogenization, microfluidization, and ultrasonication where as low energy methods include the phase inversion emulsification method and the self-nanoemulsification method. Low energy methods should be preferred over high energy methods as these methods require less energy,so are more efficient and do not require any sophisticated instruments. However high energy methods are more favorable for food grade emulsion as they require lower quantities of surfactant than low energy methods. Techniques for formulation of nanoemulsion drug delivery system are overlapping in nature, especially in the case of low energy methods. In this review, we have classified different methods for formulation of nanoemulsion systems based on energy requirements, nature of phase inversion, and self-emulsification.

Keywords: nanoemulsion, drug delivery, high energy method, low energy method, phase inversion methods .

INTRODUCTION:

Nano-emulsions can be utilized in countless applications and different industries. Pharmacy and drug delivery can be mentioned as one of the most important field where nanoemulsions q'Pare utilized as nanocarriers treating a wide assortment of sicknesses. In cosmetics, nanoemulsions have also been increasingly used, especially for regulated delivery of cosmetics and active ingredients to specific skin layers. They are typically thermodynamically stable, transparent and provide hydrolysis and oxidation protection. Nanoemulsions have a major bioactive effect due to their relatively small droplet size and large surface area, enabling fast and effective penetration into the skin.

In general, cosmetic nanoemulsions do not indicate sedimentation, coalescence or flocculation. For those macroemulsions, widely reported. Compared to microemulsion, certain nanoemul-sions used in cosmetics usually require low energy and low surfactant levels. Oil-in-water (o/w) emulsions with mean droplet diameters ranging from 50 to 1000 nm can be described as nanoemulsions. The average droplet size is usually between 100 and 500 nm, as synonyms are sub-micron emulsion (SME) and mini-emulsion names. Since the first nanoemulsion was produced in the 1940s, three forms can be used, such as oil-in-water (O/W), water-in-oil (W/O) and bi-continuous. Varying the components of the emulsions will accomplish the transition between these three forms. Nanoemulsions can be made in various dosage types, such as liquid creams, sprays, gels, aerosols, foams, and can be delivered through similarly different pathways, such as topical, oral, intravenous, intranasal, pulmonary and occular. [1,2,3.]

Advantages of nanoemulsion : [2,4]

1. Increase the absorption rate.
2. Eliminates absorption variability.
3. Assists in the solubilization of lipophilic drugs.
4. Provides aqueous dosage type for medications that are water insoluble.
5. Boosts bioavailability
6. The substance can be delivered through a variety of routes, including tropical, nasal, and intravenous.
7. The drug moiety penetrates quickly and effectively.
8. It's good for masking bad tastes.
9. As a drug in the oil process in O/W, it protects against hydrolysis and oxidation. The nanoemulsion is impervious to water and air.
10. Patient compliance is improved by using a liquid dosage form.
11. There is a lower demand for energy.

12. Nanoemulsions are thermodynamically stable systems, allowing them to self-emulsify and have properties that are independent of the process used.
13. Both lipophilic and hydrophilic drugs may be carried in the same Nanoemulsion.
14. The use of Nanoemulsion as a delivery mechanism will increase a drug's effectiveness by lowering the overall dose and thereby reducing side effects.

Components of nanoemulsion: (4,2,3)

1. oil
2. surfactant/cosurfactant
3. Aqueous phase

Sr.No.	Oils	Surfactant	Co-surfactant
1.	Captex 355	Caproyl 90	Transcutol IP
2.	Captex 200	Cremophor RH 40	Glycerine
3.	Captex 8000	Gelucire 44/14,50/13	Ethylene glycol
4.	Witepsol	PEG 4000	Propylene glycol
5.	Myritol 318	Tween 80	Ethanol
6.	Isopropyl myristate	Poloxamer 124 & 188	Propanol

Formulation techniques of nanoemulsion:

- **High energy methods:**

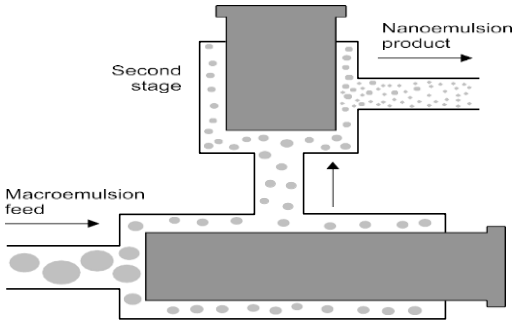
1. High pressure homogenization
2. Microfluidization
3. Ultrasonication

- **Low energy methods:**

1. Phase inversion temperature(PIT)
2. Phase inversion composition(PIC)
3. Emulsion inversion point(EPI)
4. The self-nanoemulsification method

- **High energy methods:**

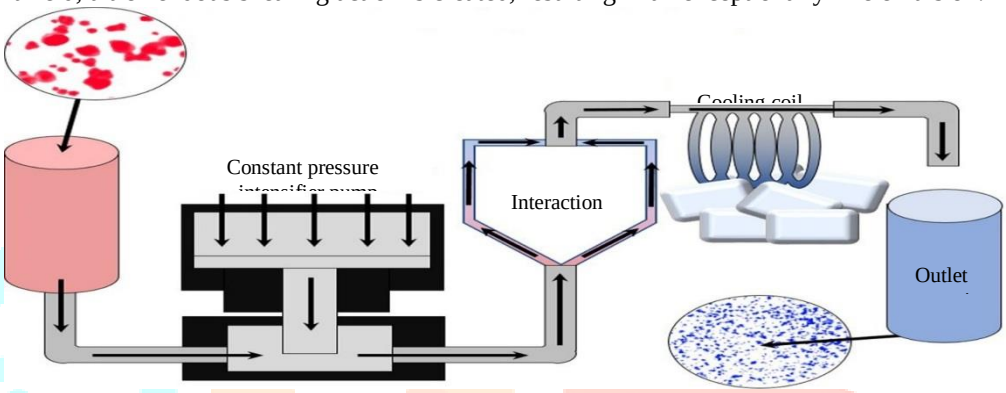
- Nanoemulsions are often generated using high-energy methods. High mechanical energy is used to create intense disruptive forces that break up large droplets into nano-sized droplets, resulting in high-kinetic-energy nanoemulsions. Mechanical devices such as ultrasonicators, microfluidizers, and high-pressure homogenizers are used to generate destructive forces. We can obtain a greater control of particle size with a choice of formulation composition by using high energy methods. High-energy methods can also be used to monitor the emulsion's stability, rheology, and colour. When it comes to food ingredients, high energy nanoemulsion formulation methods have the benefit of reducing the possibility of spoilage and inactivation of food components while maintaining food protection, nutritional, and sensory properties. The following approaches are used in high-energy methods.
- **High pressure homogenization:** It is the most widely used process for creating nanoemulsions. To make nanoemulsions with particle sizes as small as 1 nm, this process uses a high-pressure homogenizer or a piston homogenizer. During the procedure, the macroemulsion is pushed through a narrow orifice at a pressure ranging from 500 to 5000 psi. Since many forces work together during the process, such as hydraulic shear, heavy turbulence, and cavitation, extremely small droplet sized nanoemulsions are achieved. Because of the interaction of many forces such as hydraulic shear, strong turbulence, and cavitation during the process, extremely small droplet sized nanoemulsions are achieved. This process can be repeated until the desired droplet size and polydispersity index are achieved (PDI). PDI specifies the droplet size uniformity in nanoemulsions. In nanoemulsions, a higher
  PDI implies less droplet size uniformity. PDI less than 0.08 indicates monodisperse samples, PDI between 0.08 and 0.3 indicates a narrow size distribution, and PDI greater than 0.3 indicates a wider size distribution. Obtaining tiny submicron droplets, on the other hand, necessitates a significant amount of energy. During the high-pressure homogenization process, this amount of energy and rising temperatures can cause the components to deteriorate. Proteins, enzymes, and nucleic acids are examples of thermolabile compounds that can be affected.



High-pressure homogenization techniques

- **Microfluidization:** Two jets of crude emulsion from two opposite channels collide in the nozzle of the microfludizer, which is the core of this system (the interaction chamber), to create emulsion at far higher pressures up to approximately 700 Mpa. A pneumatically operated pump delivers the process stream, which can pressurise the in-house compressed air (150/650 Mpa) to around 150 Mpa. By forcing the flow stream through microchannels at high pressure toward an impingement field, a tremendous shearing action is created, resulting in an exceptionally fine emulsion.

The



microfluidization process is a high-energy process that deals with the dynamics of microchannels that have been specially developed. The lipid carrier overcomes its barrier due to the created turbulence and momentum. The lipids and active compounds are mixed at very high velocities in the engineered microchannels by a pump powered by compressed air, resulting in stable nano-delivery systems. Two forms of microfluidization are currently used in the construction of nanodelivery systems. Two types of microfluidization exist: two-step single-channel microfluidization and single-step dual-channel microfluidization, each with its own set of benefits and drawbacks. In the case of a nanoemulsion-based delivery method, microfluidization-based nanoemulsions produced using a two-step single channel have a number of drawbacks, including additional energy and more costly lipid and oil wastage in the initial preparation of coarse emulsion to be fed into the microfluidizer. Single-step dual-channel microfluidization, on the other hand, overcomes the aforementioned drawbacks and produces a robust nanoemulsion with higher loading abilities, which has a wider application in the medical, food, and nutraceutical industries.

- **Ultrasonication:** In terms of operation and washing, ultrasonication outperforms other high-energy methods. Ultrasonic waves create cavitation forces in ultrasonic emulsions, which split the macroemulsion into nanoemulsions. Ultrasonicators, which consist of a probe that emits ultrasonic waves, are used in this process. We can achieve the desired particle size and stability of the nanoemulsion by varying the ultrasonic energy input and time. Physical shear is primarily generated by the acoustic cavitation process in ultrasonic emulsification. Cavitation is the phenomenon of microbubble formation and development, followed by microbubble collapse, caused by acoustic wave pressure fluctuations. Microbubbles collapsing create a lot of turbulence, which leads to the creation of nano-sized droplets. Ultrasound irradiation of an oil-water system induces cavitation forces, which provide excess energy for new interface formations, resulting in nano-sized emulsion droplets. Nanoemulsions can be made without the use of surfactants using ultrasonication. The efficiency of ultrasonic emulsification is based on ultrasonication speed, time, and the nature of the surfactant, according to a recent report. Ultrasonication has been widely used to create drug and food product nanoemulsions. Food-grade ultrasonication nanoemulsions are more stable and have smaller droplet sizes than other high-energy methods, and they require less energy input;
- **Low energy methods:** The development of nanoemulsion systems using these methods requires very little energy. Low-energy emulsifitation methods are more energy efficient because they make use of the systems internal chemical energy and only involve gentle stirring to produce nanoemulsions. Emulsification of low energy Phase inversion emulsification and self-emulsification are popular methods. Low energy methods are generally not considered for the formulation of food-grade nanoemulsions because they require a high concentration of surfactant, which can affect the taste and protection of the food formulation.
- **Phase Inversion methods:** During the emulsification process, the spontaneous curvature of the surfactant causes phase transition in this system. Changes in parameters such as temperature, composition, and so on cause changes in the surfactant's spontaneous curvature. TPI methods, which include PIT and PIC, and CPI methods, which include EIP, are the two forms of phase inversion emulsification methods. Transitional phase inversion occurs as a result of changes in the surfactant's spontaneous curvature or affinity as a result of changes in parameters such as temperature and composition. CPI, on the other hand, occurs when dispersed phase is continuously added before the dispersed phase drops accumulate and form bi-continuous/lamellar structural phases. A catastrophe is a drastic change in a system's actions as a result of changing circumstances. For catastrophic phase inversion to occur, the surfactant must be primarily present in the dispersed phase, resulting in a high rate of coalescence and rapid phase inversion. During transitional phase inversion, spontaneous curvature or surfactant affinity changes, while spontaneous curvature or surfactant affinity does not alter during catastrophic phase inversion.
- **Phase inversion Temperature (PIT):** Surfactant spontaneous curvature is inversed in the PIT method by changing temperature. Nonionic surfactants, such as polyethoxylated surfactants, have their POE groups dehydrated, making them more lipophilic and causing changes in surfactant curvature. As a result, phase inversion occurs, resulting in the formation of nanoemulsion.

  Oil, water, and nonionic surfactants are combined at room temperature to create oil-in-water (O/W) emulsions in this process. The dehydration of surfactant POE groups occurs as the temperature rises, making the surfactant more lipophilic and causing it to have a stronger preference for the oily process. Via intermediate liquid crystalline or bi-continuous structures, phase inversion from the original O/W emulsion to a water-in-oil (W/O) nanoemulsion occurs (e.g. lamellar phase). The non-ionic surfactant has zero curvature and has a similar affinity to the aqueous and oily phases at hydrophile-lipophile balance (HLB) temperatures (an intermediate temperature). Rapid cooling or heating of HLB (to obtain O/W or W/O emulsions, respectively) is needed for efficient phase inversion. Nanoemulsions that are rapidly cooled or heated become kinetically stable.
- **Phase inversion Composition (PIC):** The phase inversion composition, or PIC, process is similar to the PIT method, except that phase inversion is accomplished by adjusting the system composition rather than the system temperature in PIC. PIC involves adding one of the ingredients, such as water, to a mixture, and then adding oil-surfactant or oil to the water-surfactant mixture. While other types of nonionic surfactants may be used, POE type nonionic surfactants are commonly used in the PIC process to formulate Nanoemulsions. Surfactant POE chain hydration occurs as water is steadily applied to the oil process and the amount of the water fraction increases. The water phase's surfactant hydrophilic-lipophilic properties will be balanced, and the surfactant's spontaneous curvature will change to zero, close to the HLB temperature in the PIT process. A bi-continuous or lamellar structure is formed during this transition. As more water is applied, the transition composition is surpassed, and the zero-curvature structures of the surfactant layer become high-positive curvature structures. This change in curvature induces phase inversion and the creation of nano-sized droplets. As a result, adjusting the system's com-position induces phase inversion. Transitional phase inversion is also responsible for nano-size emulsion droplets when other composition parameters, such as salt addition and pH changes, are modified.
- **Emulsion inversion point (EIP):** Phase inversion occurs in the EIP method through CPI mechanisms, which are induced by changing the fractioned volume of the dispersed phase rather than the surfactant properties. When water is added to the oil-surfactant mixture, the system begins to behave like a W/O nanoemulsion. Water droplets combine with each other and the phase inversion stage is reached as growing volumes of water are applied above a critical water content with constant stirring; this results in the formation of bi-continuous or lamellar structures. Via an intermediate bi-continuous microemulsion, further dilution with water induces phase inversion from a W/O to an O/W device. The size of the nanoemulsion droplets produced is determined by process variables including water addition rate and stirring speed. The surfactant must be mainly present in the distributed process for catastrophic phase inversion to occur, resulting in a high degree of coalescence and rapid phase inversion. In disastrous step inversion, small molecule surfactants may be used. Both W/O and O/W emulsions can be stabilised with these surfactants. Since the surfactant is mostly present in the dispersed phase during catastrophic phase inversion, it acts as an irregular

emulsion (unstable emulsion) that defies Bancroft's law. According to Bancroft's law, the emulsifier should be primarily present in the continuous process for a stable emulsion (normal emulsion). As a result, the irregular emulsion undergoes disastrous phase inversion, resulting in the formation of a more stable natural emulsion

- **Self nanoemulsification method:** Nanoemulsion formation is performed using the self-emulsification process without altering the surfactant's spontaneous curvature. Surfactant and/or co-solvent molecules diffuse quickly from the scattered to the continuous phases, causing agitation and the formation of nano-sized emulsion droplets. The spontaneous emulsification approach is another name for the self-emulsification method. SNEDDS are based on the self-emulsification phenomenon and have a lower lipid content, as well as more hydrophilic surfactants or co-surfactants (co-solvents). An isotropic combination of an oil, surfactant, co-surfactant, and drug is known as SNEDDS. When this mixture is mixed with aqueous fluids in vivo, it forms a fine and optically transparent O/W nanoemulsion, which is assisted by gentle agitation produced by the stomach and intestine's digestive motility. The diffusion of the hydrophilic co-solvent or co-surfactant from the organic phase into the aqueous phase is one of the two most widely described processes of nanoemulsion production from SNEDDS. at transient negative or ultra-low interfacial tensions, and creation of nanoemulsion negative free energy SNEDDS are also the most common and promising method for delivering low-bioavailability hydrophobic drugs. Bioactive food ingredients have also been delivered using SNEDDS.[5,6,7,8,9,24,25,26,27,28,40,41,42,29,43,44,30,13,12,32,14,15,10,45,11,16,17,18,19,20,21)]

Characterization and Evaluation of Nanoemulsion:

1. **Nanoemulsion Droplet Size Analysis:** One of the relevant physicochemical characteristics of a nano-emulsion is droplet size distribution, which was determined using a diffusion process and a light-scattering particle size analyzer Coulter LS-230. It uses the absorption of laser light by particles to determine the size distribution. Polarization intensity differential scattering (PIDS) is a system that includes an incandescent light source, polarising filters, a PIDS sample chamber, and seven more photodiode detectors. It's used to calculate the droplet size distribution, such as when 0.5 ml of emulsion is added to the measure compartment (125 ml of water). The volume distribution was used to present the data. Many other techniques for measuring droplet size of nanoemulsions have been developed, but two are of particular interest in this article: laser light scattering (LLS) and energy filtering transmission electron microscopy (EFTEM). They have intrinsic resilience against creaming, sedimentation, flocculation, and coalescence due to their limited droplet size. It also facilitates the delivery of active ingredients to the skin.
2. **Viscosity measurement:** Using a Brookfield style rotary viscometer, the viscosity of Nanoemulsions of various compositions can be determined at various shear rates and temperatures. A thermobath must be used to keep the instrument's sample room at 370.2°C, and the instruments for measurement must be submerged in it before processing.
3. **Polydispersity Index:** Polydispersity is defined as the ratio of standard deviation to mean droplet size, and it indicates droplet size uniformity within the formulation. The smaller the uniformity of the droplet size in the formulation, the higher the polydispersity. Malvern Zetasizer is a polydispersity measurement system focused on complex light scattering.
4. **Zeta Potential:** As electrons are submerged in liquid, the zeta potential is used to determine their surface charge. The zeta potential is a physicochemical property of a drug, substance, or vehicle that is used to predict dispersion stability. Its value is determined by the absorption of electrolytes and their adsorption. The Malvern Zetasizer instrument is used to calculate it. Nanoemulsion is diluted to determine zeta potential, which is calculated based on the electrophoretic mobility of oil droplets. A zeta potential of 30 mV is thought to be adequate for maintaining nanoemulsion physical stability.
5. **pH:** The pH of nanoemulsion can be determined by pH meter.
6. **Drug Content:** Preweighed nanoemulsion is removed by dissolving in an appropriate solvent, and the extract is compared to a drug quality solution using a spectrophotometer or HPLC.
7. **Transmission electron microscopy:** Transmission electron microscopy was used to examine the nanoemulsion's morphology and composition. The form and size of nanoemulsion droplets were shown using a combination of bright field imaging at increasing magnification and diffraction modes. The experiments were carried out by putting a drop of nanoemulsion directly on the holey film grid and watching it dry.
8. **In-vitro drug release:** By the use of a semipermeable membrane in a dissolution apparatus, in vitro release tests of nanoemulsions containing drugs can be examined. a glass cylindrical tube with a diameter of 2.5 cm and a length of 10 cm

   Instead of the basket, a 6 cm long piece of semipermeable membrane should be attached and securely wrapped. The drug-loaded nanoemulsion is mounted on the semipermeable membrane surface in the cylindrical tube. To allow the sink conditions to be established and to ensure permanent solubilization, the cylindrical tube should be dipped in 100 ml buffer while retaining the pH. At 32 degrees Celsius, the release analysis can be carried out for 24 hours. The stirring shaft can spin at a rate of 100 revolutions per minute. At fixed intervals of time (1, 2, 4, 6, 8, 12, 20, 24 hrs.) To retain a constant volume, aliquots of one millilitre of the release medium are drained and dissolved, then purified for examination and supplemented with an equivalent volume of the buffer solution. A UV spectrometer can be used to determine the absorbance of the collected samples.
9. **Stability Studies:** Stability tests are carried out to determine the medication substance's stability in the presence of different environmental conditions such as temperature, humidity, and light. Nanoemulsion stability tests are carried out after storing the formulation for 24 months in a dispersed and freeze/dried environment, following the recommendations of the International Conference on Harmonisation. The following storage conditions were used: atmospheric (252°/605% RH), refrigeration (53°), and freeze (–205°). The required amount of nanoemulsion is held in glass bottles that are tightly sealed. Samples are taken at predetermined intervals and analysed for particle size, packing, and EE, as well as the in vitro drug release profile. When the formulation was processed for 3 months at 25°/60 percent RH and 30°/65 percent RH, no difference in viscosity, drug composition, or particle size was observed.[2,4,6,36,37,38,31,46,24,48,47,35).]

Application of nanoemulsion:

1. Nanoemulsions are commonly used to transport active pharmaceutical ingredients through a variety of routes, including nasal, parentral, topical, ocular, and transdermal.
2. Nanoemulsions can be used extensively in cosmetics due to their small particle size, which allows for easier absorption and, as a result, improved results. As a luxurious substance, they can be used as moisturisers and creams.
3. Because of the small particle size, nanoemulsions can be used to improve the oral bioavailability of drugs that are poorly water soluble.
4. Because of their high permeability across the skin and lack of irritation, these may be used in transdermal drug delivery.
5. These can induce antimicrobial activity on the skin that was previously only possible with systemic antibiotics.
6. To maintain the drug's pharmacological effects, these may be used in an ocular drug delivery system.
7. Nanoemulsion formulations should be taken orally because they boost absorption, therapeutic potency, and opioid toxicity as compared to traditional formulations.
8. Direct delivery and target ability of drug to effected area of skin in topical administration
9. Nanoemulsions can be used in cancer therapy for target drug delivery. (Gupta P.K, Devarajan V., Chouksey R. K,jyostna,bhatt,patel)
10. Nanoemulsion is also used in Biotechnology. [2,4,31,32,34,33,39]

REFERANCES:

1. Seyed Mohammad Mohsen Modarres-Gheisaria., Roghayeh Gavagsaz-Ghoachani(2019). Ultrasonic nano-emulsification–A review, Ultrasonics-Sonochemistry, 88-105.
2. P. Bhatt and S. Madhav. (2011). a detailed review on nanoemulsion drug delivery system. International journal of pharmaceutical sciences and research, 2(10), 2482-2489.
3. Yuvraj Singh, Jaya Gopal Meher, Kavit Raval (2017).Nanoemulsion: Concepts, development and application in drug delivery. Journal of control release, 28-49.
4. Ronak P. Patel., Jay R. Joshi. (2012). an overview on nanoemulsion: a novel approach. International journal of pharmaceutical sciences and research, 3(12), 4640-4650.
5. Manish Kumar, Ram Singh Bishnoi, Chandra Prakash Jain (2019). Techniques for Formulation of Nanoemulsion Drug Delivery System:A Review. Preventive Nutrition And Food Science, 24(3), 225-234.
6. Vaibhav Changediya., Rupalben Jani·, Pradip Kakde(2019).A Review on nanoemulsion : A recent drug delivery tool. Journal of drug delivery and therapeutics, 9(5), 185-191.
7. Palanivel Ganesan, Govindarajan K, shin young park, (2018). Microfluidization trends in the development of nanodelivery systems and applications in chronic disease treatments. International journal of nanomedicine, 13, 6109-6121.
8. Solans C., Sole I. (2012).Nanoemulsions: formation by low-energy methods.Current Opinion in Colloid Interface Science., 17(5), 246-254.
9. Komaiko J.S., McClements D.J.,(2016). Formation of food-grade nanoemulsion using low energy preparation methods: a review of available methods. Comprehensive Review in Food Science and Food Safety, 15, 331-352.
10. Izquierdo P, Feng J., Tadros T F., (2005).The influence of surfactant mixing ratio on nanoemulsion formation by the pit method. Journal of Colloid Interface Science. 285, 388-394.
11. Izquierdo P, Esquena J, Tadros T. F. (2002) Formation and Stability of nano-emuilsions prepared using the phase inversion temperature method. Langmuir. 18, 26-30.
12. Sole I, Pey C. M., Maestro A.L, (2010). Nanoemulsion prepared by the phase inversion method: preparation variables and scale up. Journal of colloid interfeace Science. 344, 417-423.
13. Ishak K. A., Annur MSM., (2016). Phase inversion of medium-chain-length poly-3-hydroxyalkanoates (mcl-PHA)-incorporated nanoemulsion: sffects of mcl-PHA molecular weight and amount on its mechanism. Colloids Polymer Science. 294, 1969-1981.
14. Armanet L, Hunkeler D., (2007). Phase inversion of polyacrylamide-based inverse-emulsion: influence of inverting-surfactant type and concentration. Journal of Applied polymer Science,103, 3567-3584.
15. Moreira de Morais J.,dos Santos O.D.H., Delicato T., Gonçalves R.A., (2006). Physicochemical characterization of canola oil/water nano-emulsions obtained by determination of required HLB number and emulsion phase inversion methods. Journal of Dispersion Science and Technology,27,109-115.
16. Sokolov Y.V., (2014). Nanoemulsion formation by low-energy methods a review. Technology of medicines, 3(79),16-19.
17. Vandamme T.F., Anton N. (2010). Low-energy nanoemulsification to design veterinary controlled drug delivery devices. International Journal of Nanomedicine,5,867-873.
18. Maestro A., Solè I., González C.,(2008). Influence of the phase behavior on the properties of ionic nanoemulsions prepared by the phase inversion composition method. journal of cooloid interface science,327(2), 433-439.
19. McClements D.J., Rao J., (2011). Food-grade nanoemulsions: formulation, fabrication, properties, performance, biological fate, and potential toxicity.Critical Review Food Science and Nutrition, 51(4), 285-330.
20. Fernandez P, André V, Rieger J., (2004). Nano-emulsion formation by emulsion phase inversion. Colloids and Surface A: Physicochemical and Engineering Aspects, 251(1-3), 53-58.
21. Perazzo A., Preziosi V., Guido S., (2015). Phase inversion emulsification:current understanding and applications. Advance in Colloid and Interface Science, 222,581-599.

22. Solans C., Morales D., Homs M., (2016). Spontaneous emulsification. Current Opinion in Colloid and Interface Science, 22,88-93.
23. Solans C, Solé I., (2012).Nano-emulsions: formation by low-energy methods. Current Opinion Colloid and Interface Science, 17(5), 246-254.
24. Solè I., Solans C., Maestro A., (2012).Study of nano-emulsion formation by dilution of microemulsions. Journal of Colloid and Interface Science, 376(1), 133-139.
25. Agrawal S., Giri T.K., Tripathi D.K., Ajazuddin,(2012). A review on novel therapeutic strategies for the enhancement of solubility for hydrophobic drugs through lipid and surfactant based self micro emulsifying drug delivery system: a novel approach. American Journal of Drug Discovery Development, 2(4), 143-183.
26. Bandyopadhyay S., Beg S., Katare O.P.,(2015). QbD-Oriented development of self-nanoemulsifying drug delivery systems (SNEDDS) of valsartan with improved biopharmaceutical performance. Current Drug Delivery, 12((5),544-563.
27. Khan A.W., Kotta S., Ansari S.H., (2015).Self-nanoemulsifying drug delivery system (SNEDDS) of the poorly water-soluble grapefruit flavonoid naringenin: design, characterization, in vitro and in vivo evaluation. Drug Delivery, 22(4),552-561.
28. Pouton C.W., (2000).Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and 'self-microemulsifying' drug delivery systems. European Journal of Pharmaceutical Science, 11(2),S93-S98.
29. Patel A.R, Vavia P.R., (2007). Preparation and in vivo evaluation of SMEDDS (self-microemulsifying drug delivery system) containing fenofibrate. The AAPS Journal, 9(3), E344-E352.
30. Kheawfu K., Pikulkaew S., Rades T.,(2018).Development and characterization of clove oil nanoemulsions and self-microemulsifying drug delivery systems. Journal of Drug Delivery Science and Technology, 46,330-338.
31. Jyotsna Suyal (2017). Nanoemulsion: A novel approach in various Pharmaceutical Appications. Journal of Pharmaceutical science and bioscientific research, 7(1), 153-157.
32. Kumar S. L. H and Singh V., (2012). Nanoemulsification: A novel targeted drug delivery tool. Journal of Drug Delivery and Therapeutics, 2(4), 40-45.
33. Gupta P.K, Pandit J. K, Kumar A., (2010). Pharmaceutical nanotechnology novel nanoemulsion high energy emulsification preparation, evaluation and application. The Pharma Research, 3, 117138.
34. Devarajan V. and Ravichandran V., (2011).Nanoemulsion as modified drug delivery tool. International Journal of Comprehensive Pharmacy, 4(1), 1-6.
35. Ghada H. E. (2012). Formulation and in-vitro evaluation of nystatin nanoemulsion based gel for topical delivery. Journal of American Science,8(12).
36. Bouchemal K., Briancon S., Fessi H., (2004).Nanoemulsion formulation using spontaneous emulsification: solvent, oil and surfactant optimization .International Journal of Pharmaceutics 280-243.
37. Ali Javed, Ahuja Alka, Baboota S., (2007).Design development and evaluation of novel nanoemulsion formulations for transdermal potential of Celecoxib. Acta Pharm; 57, 315–33210.2478/v10007007-0025-5.
38. Farhan Ahmad J., mushir ali, faiyaz shakel.(2008).Investigation of Nanoemulsion System for Transdermal Delivery of Domperidone: Ex-vivo and in vivo Studies382.Current Nanoscience,382.
39. Nitin Sharma, Mayank Bansal, Sharad Visht1, (2010).Nanoemulsion: A new concept of delivery system. Chronicles of Young Scientists, 1(2), 2-6.
40. Gurram A. K., Deshpande P.B., Kar S. S. (2015).Role of components in the formation of self-microemulsifying drug delivery systems. Indian Journal of Pharmaceutical Science, 77(3), 249- 257.
41. Kohli K., Chopra S., Dhar D., (2010). Self-emulsifying drug delivery systems: an approach to enhance oral bioavailability, Drug Discovery Today. 15(21-22), 958-965.
42. Meena A. K., Sharma K., Kandaswamy M., (2012). Formulation development of an albendazole self-emulsifying drug delivery system (SEDDS) with enhanced systemic exposure. Acta Pharmaceutical, 62(4), 563-580.
43. Patel G., Shelat P., Lalwani A. (2016). Statistical modeling, optimization and characterization of solid self-nanoemulsifying drug delivery system of lopinavir using design of experiment. Drug Delivery. 23(8), 3027-3042.
44. Suryawanshi MR, Kondawar MS. (2014). Formulation and evaluation of solid self micro emulsifying drug delivery system for Clarithromycin. Der Pharmacia Sinica. 5(5), 27-35.
45. Izquierdo P., Esquena J., Tadros T. F., (2004).Phase behavior and nano-emulsion formation by the phase inversion temperature method. Langmuir. 20(16), 6594-6598.
46. Jaiswal M., Dudhe R and Sharma P. K., (2015). Nanoemulsion: an advanced mode of drug delivery system. Biotech Springer, 5, 123-127.
47. Chen H, Du D., Mao D. (2008) Hydrogelthickened nanoemulsion system for topical delivery of lipophilic drugs. International Journal of Pharmaceutics, 353(1-2), 270-276.
48. Singh K.K., Vingkar S.K. (2008) Formulation, antimalarial activity and biodistribution of oral lipid nanoemulsion of primaquine. International Journal of Pharmaceutics, 347(1-2), 136-143.