

REVIEW ARTICLE

Nanoemulsion Formulation Strategies for Enhanced Drug Delivery

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Abstract: Nano emulsions are emerging as versatile drug delivery systems, offering enhanced solubility, dissolution, absorption, permeation, and bioavailability due to their nano-sized droplets and extensive interfacial area. Both high-energy and low-energy techniques are employed for nano emulsion preparation, including high-pressure homogenization, ultrasonication, phase inversion composition (PIC), and phase inversion temperature (PIT) methods. Nano emulsions demonstrate advantages in improving the stability and bioavailability of therapeutic agents, addressing common challenges such as creaming, flocculation, sedimentation, and coalescence. Stabilizers, surfactants, and process parameters play a critical role in maintaining stability and enhancing the performance of nano emulsions. Characterization methods are essential for assessing nano emulsion properties and stability. Nano emulsions show potential applications in various routes of administration, including topical, ocular, transdermal, and parenteral. The formulation, characterization, and application of nano emulsions represent a promising approach for improving therapeutic outcomes through effective and versatile drug delivery platforms. Ongoing research focuses on optimizing formulation strategies, exploring novel applications, and overcoming existing limitations to further enhance the efficacy of nano emulsion-based drug delivery systems.

Keywords: Nano emulsions; Drug delivery systems; High-energy techniques; Low-energy techniques; Formulation.

1. Introduction

Emulsions are two-phase solutions with droplets that range in size from 0.1 to 100 μm . To stabilize this instability, emulsifying agents are needed [1]. These adaptable nano emulsions are applied in various fields, like paint, agri-food sector and more, but they can become unstable because of sedimentation and creaming processes. Chemical instability can be caused by microbial infection and poor storage conditions, for example, and its properties are assessed using a variety of methods [2]. There are many different types of emulsions, such as nano, micro, double, and mixed emulsions. Nano emulsions, which contain droplets in the 10-1,000 nm size range, exhibit therapeutic potential for uses such as immune responses and anticancer treatment [1]. These colloidal particulate carriers ensure controlled and sustained drug release over an extended period by shielding drugs from degradation. Their large-scale production requires less surfactant, and they have great potential for drug delivery particularly for low-solubility medications like those used in skin treatments. There are three categories of nano emulsions: oil-in-water, water-in-oil and bi-continuous. Each type has its special qualities. They are characterized as small, transparent, and smooth emulsions, with droplet sizes usually falling between 10 - 200 nm [3]. Surfactants, co-surfactants, co-solvents, oils and aqueous phases are essential for creating stable, transparent systems with mean droplet sizes of 100 nm, which are then used to prepare nano emulsions. Nano emulsions are a promising drug delivery method because they can improve drug release, especially for low-solubility drugs used in skin treatments [4]. Through methods such as Ostwald aging and high shear homogenization uses high energy or ultrasound to prevent creaming or sedimentation, while co-surfactants such as ethanol, propanol, or propylene glycol improve stability. Although proteins and lipids can function as emulsifiers, surfactants are most frequently employed because of their electrostatic interactions and steric hindrance. The preparation of nano emulsions using high and low-energy techniques has been the subject of recent research. While high-energy processes like high-pressure homogenization and ultrasonication demand large amounts of energy, low-energy processes use characteristics of the system like the EIP & PIT to produce tiny droplets with little energy [5]. Because of their small droplet size, which influences their stability, optical properties, and release behavior, nano emulsions are highly adaptable for drug delivery through a variety of routes, including topical, ocular, transdermal, perioral, percutaneous, and parental administration [6,7,8]. By minimizing the effects of gravity during storage, the small droplet size helps to prevent flocculation and creaming. The oil-to-surfactant weight ratio provides exact control over droplet size [9,10]. The increased prominence of nano emulsions for drug delivery is attributed to the smaller droplet

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size [11]. The Differences between Macroemulsions, Microemulsions and Nanoemulsions shown in Table 1 and pictorial represented in the Figure 1.

Table 1. Differences between Macro emulsions, Micro emulsions, and Nano emulsions

Type	Macro emulsions	Micro emulsions	Nano emulsions
Size	1-100 μ m	10-100nm	20-500nm
Shape	Spherical	Spherical, lamellar	Spherical
Stability	Thermodynamically Unstable, weakly kinetically stable	Thermodynamically stable	Thermodynamically unstable, kinetically stable
Method of preparation	High and low energy methods	Low energy method	High and low energy method
Polydispersity	Often high (>40%)	Typically, low (<10%)	Typically, low (<10-30%)

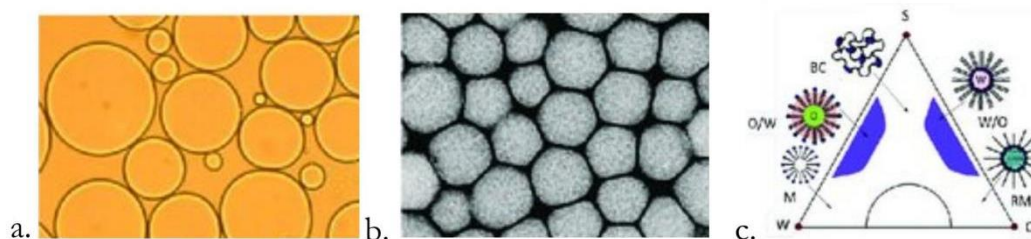


Figure 1. Schematic view of the different emulsions a. Macro emulsions, b. Micro emulsions, and c. Nano emulsions

Immediately following preparation, take 10ml (about 0.34 oz) of graduated cylinder & add 8ml (about 0.27 oz) of oil-in-water emulsion. securely sealed to prevent evaporation. For a full day, it was kept at room temperature. The thickness of the separated oil layer, or creaming layer, was measured to evaluate the emulsion's stability. The height of the top cream layer expressed as a percentage of the height of the entire emulsion sample was used to compute the creaming index (CI) [12]. Drugs are more chemically and physically stable when they are in nano emulsion form. The stability should be checked for the development of emulsions, microemulsions, and nano emulsions. Over several months, stability studies are carried out at room temperature and under refrigeration. Stability is assessed by looking for small changes in droplet size, refractive index, and viscosity during storage. In terms of stability, nano emulsions and microemulsions are very different. Microemulsions are formed by self-assembly and are thermodynamically stable, whereas nano emulsions are formed by mechanical shear and are kinetically stable. Because of their increased stability and smaller droplet size, nano emulsions don't cream or sediment [13]

2. Preparation of nanoemulsions

A nano emulsion's effective formulation depends on the choice of an appropriate constituent. Because they are less harmful, safe, or natural [GRAS-Generally Recognized as Safe] ingredients, like polysaccharides and proteins from food and surfactants (Tweens, spans), are now used in the production of nano emulsions. Based on the structural materials they employ, such as lipids, proteins, polysaccharides, or composites, edible films and coatings are typically categorized [15].

The need for innovative and effective emulsification procedures is constant because formulation of nano emulsion is an extremely cost operating problem during oil production. [16].

There are three standard methods used to increase a nano emulsion's chemical stability:

- The use of chelating agents or antioxidants
- Adjusting the interfacial properties (such as chemical reactivity, charge, and thickness)
- Regulating the ambient parameters (light, pH, temperature, oxygen concentrations) [15].

Factors affecting the preparation of nano emulsions

- The primary prerequisite for creating a nano emulsion is ultralow interfacial tension, which can only be achieved by carefully selecting the surfactant.
- To make nano emulsion, the surfactant concentration must be sufficiently high to stabilize microdroplets.
- The flexibility of the surfactant needs to be adequate to facilitate the development of the nano emulsion. Enforcing intense shear is necessary to rupture microscale droplets into nanoscale by producing stress levels that approach the Laplace pressure of the droplets, which is between 10 and 100 atm.

- The dispersed medium must be very insoluble in the dispersed medium to prevent Ostwald ripening [17]

2.1. Methods for preparation of Nano emulsions

Since they are non-equilibrium systems, nano emulsions cannot form by themselves. A substantial amount of energy is needed to make nano emulsions because of their enormous surface area, which is the result of many small-sized droplets [18]. Based on the method used to provide the system with energy that must be emulsified, nano emulsions manufacturing can be categorised into two main categories: low-energy methods and high-energy methods. The choice of an appropriate emulsification device is influenced by factors such as the volume and nature of the initial mixture, the cost of the emulsification process and the intended physicochemical characteristics of the final emulsion [19]. oil-in-water-in-oil (O/W/O) and Water-in-oil-in-water (W/O/W) are two specific forms of multiple Nano emulsion that can be produced using a two-step process. The oily phase can be produced by using various types of lipids and oils like triglycerides and essential oils to form nano emulsions of various biological and physiochemical properties [20]. Several droplets can form simultaneously by expanding the interface between two liquid phases using energy input from external equipment [21].

2.1.1. Low energy method

The development of low-energy (LE) technologies to formulate nano emulsions developed significantly later than those of high-energy techniques. These techniques involve producing nano emulsions (NEs) by spontaneous emulsification without the need for equipment or energy [22]. Emulsion droplets in the nanometric range are produced using low-energy procedures that redirect the inherent physicochemical features of the surfactants, excipients, and co-surfactants in the preparation [23]. Low-energy techniques can also be used to achieve nano emulsification, producing droplets that are smaller and more uniform in size. Nano emulsions produced with LE methods are influenced by physicochemical factors like composition, temperature, and solubility [24].

The low energy method is broadly categorized into:

- Spontaneous emulsification method (SE)
- Phase inversion temperature method (PIT)
- Phase inversion composition method (PIC)

In the pharmaceutical and cosmetic sectors, phase inversion composition (PIC) and phase inversion temperature (PIT) are the two low-energy emulsification techniques that are commonly employed.

Premix membrane emulsification was examined for the first time as a potential low-energy input process for the preparation of pharmaceutical nano emulsions and solid lipid nanoparticles, to address issues with traditional high-energy preparation methods for colloidal drug distribution systems [25].

Spontaneous emulsion (SE): This is also called self-emulsification method or solvent diffusion emulsification (ESD) and occurs through different techniques. During the emulsification process, it benefits from the release of chemical energy depending upon dilution with the continuous phase, which typically happens at constant temperature without phase transitions in the system. There is no need for specialized equipment because this technique can produce nano emulsions at room temperature. The presence of a solvent and the small amount of oil phase are the primary drawbacks of the present method [26]. Several processes lead to spontaneous emulsification, and these processes appear to be influenced by the physicochemical properties and compositions of the systems involved. Oil droplets spontaneously form when the water is mixed in an oil phase containing a water-soluble unit. The movement of a chemical which dissolves in water from the oil phase to the water phase is the mechanism that operates this method [27]. This results in interfacial disturbance and consequently, leads to the formation of spontaneous oil droplets. Figure 2 shows a schematic diagram of the spontaneous emulsion method

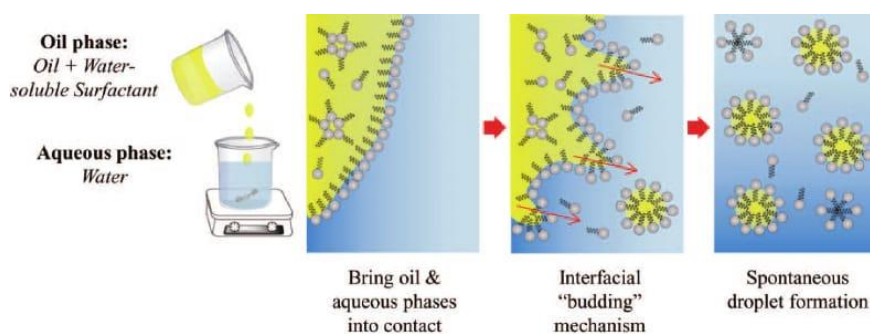


Figure 2. Schematic diagram of the spontaneous emulsion method

Emulsion phase inversion method: When the concentration of dispersed globules in the dispersion medium is relatively high, which means that the globules are packed extremely closely in the suspending fluid, phase inversion of the emulsion occurs [28]. It describes the conversion of O/W (oil-in-water) emulsions into W/O (water-in-oil) emulsions or conversely, or it describes a desirable and dynamic occurrence depending upon phase transition that occurs throughout the emulsification procedure. Salt concentration, temperature, water, oil fraction, and energy input, as well as variations in formulation parameters (salinity, temperature, etc.), may all affect the emulsion phase inversion method [26]. These techniques make use of the chemical energy released as an output the phase transformation occurs throughout the emulsification process [29]. Schematic diagram of the phase inversion method shows in Figure 3.

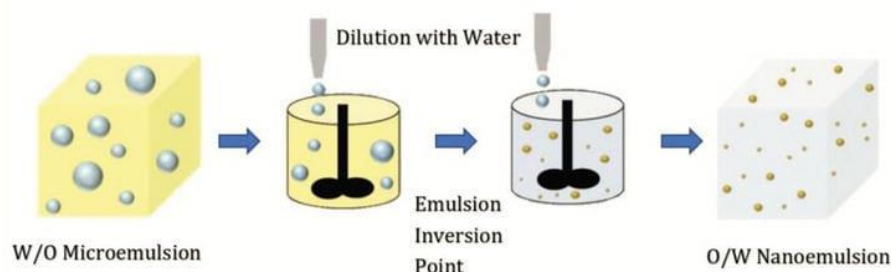


Figure 3. Schematic diagram of the phase inversion method [29].

Phase inversion composition (PIC) (Self-nano emulsification): Food-grade nano-emulsions have been produced By using this method. The process of developing nano emulsions involves gradually incorporating oil or water into the oil-surfactant or water-surfactant mixture [2]. This process is not appropriate to produce nano emulsions including surfactants such as casein, whey protein, sucrose monoesters, and quillaja saponin. This method takes longer to prepare than the spontaneous emulsion technique because it uses fewer driving forces [30]. Diagrammatic representation of Phase inversion composition shown in figure 4. This approach modifies composition while maintaining a constant temperature. This approach has received a lot of attention since it may produce nano emulsions at room temperature without the need for heat energy or organic solvents. Since adding a single substance to nano emulsion is simpler than yielding an abrupt change in temperature, the PIC [phase inversion composition] method is more suitable for manufacturing in large scale than the PIT method. It is possible to generate droplets as small as 50 nm. However, applying this technique to hydrophobic substances is difficult. It is possible to perform the reverse procedure by adding more water to dilute the mixture [30].

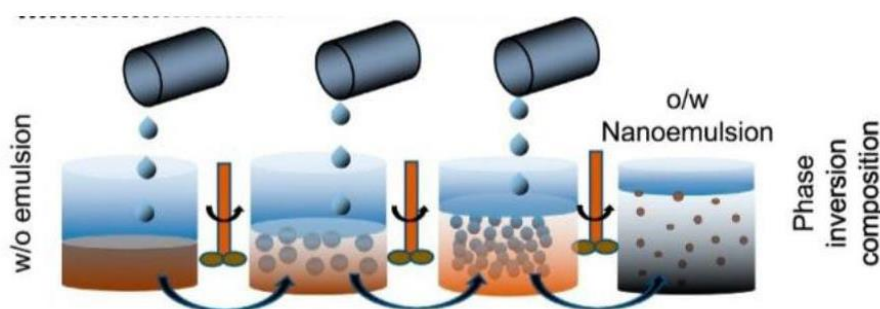


Figure 4. Diagrammatic representation of Phase inversion composition. [38]

Phase Inversion Temperature (PIT): Shinoda and his associates introduced the PIT. The phase inversion temperature method demonstrates a relationship between the complete solubilization of oil and minimum droplet size in a discontinuous phase apart from the original phase equilibrium (multiphase (or) single) [2]. The addition of co-surfactants could stabilize this system because the stability of nano emulsions created by this approach is temperature sensitive close to PIT. In this method, water, oil, and non-ionic surfactants are combined at room temperature. This process results in the formation of O/W microemulsion containing excess oil. The surfactant monolayer in this mixture displays a positive curvature [31]. Schematic representation of Phase Inversion Temperature (PIT) shows in Figure 5.

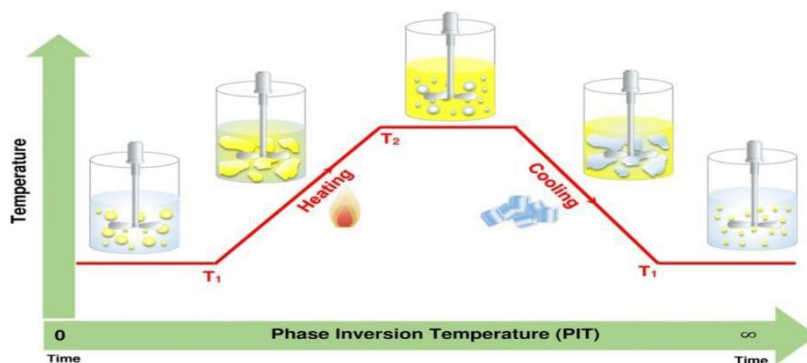


Figure 5. Schematic representation of Phase Inversion Temperature (PIT)

Water and surfactants are mixed constantly and heated gradually from room temperature to phase inversion temperature. Oil in water nano emulsions are produced by quickly chilling the solution of an ice bath. While the mixture is significantly chilled below the PIT, the molecules of surfactant in the dispersed phase is more soluble, thus encouraging formulation of oil in water nano emulsions [32]. This method is not appropriate for thermos labile drugs due to the heating of components involved. It has been noted that quickly cooling the emulsion to a temperature close to PIT can result in the production of stable, fine emulsion droplets [33].

2.1.2. High-energy methods

Since high-pressure homogenizers are suitable for carrying out this method, these are the devices more frequently employed to make nano emulsions. Because they are non-equilibrium systems, nano emulsions cannot develop on their own. Because of this, they require the input of mechanical or chemical energy to form. High-energy techniques are typically utilized in the preparation of nano emulsions [34]. While producing a nano emulsion (NE) using the high-energy method, specific equipment such as an ultrasonic generator, microfluidizer or high-pressure homogenizer, is required to supply the energy needed for emulsification, which is then assisted by the application of a suitable surfactant. In the high-energy method, the water and oil phases are broken up to yield nano-emulsions by utilizing mechanical devices that generate intense disruptive forces. [2] The system receives the necessary energy in the least amount of time to produce homogeneous, small-sized particles [35]. an outline of techniques for the preparation of Oil/Water nano emulsion shown in figure 6.

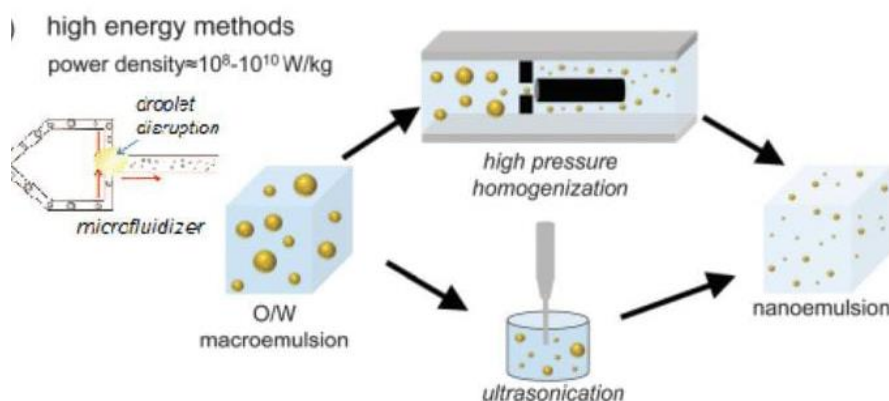


Figure 6. An outline of high-energy method for the preparation of oil in water nano emulsion

High-pressure valve homogenization method (HPVHM) : It is the more popular method to produce nano emulsions. They are sometimes referred to as piston homogenizers or dynamic high-pressure homogenization. Often, a hot-stage high-pressure (HP) homogenization process is used to produce nano-sized emulsions that maintain the appropriate stability properties even after being subjected to steam sterilization [36]. the droplet size in nanoemulsion is as compact as 1 nanometers are produced by using a high-pressure homogenizer or a piston homogenizer. These homogenizers efficiently reduce the size of a previously used coarse emulsion besides the directly generating a nano emulsion from different water and oil phases. Cavitation forces, strong turbulence, and hydraulic shear work as a group to produce tiny droplets. We could resubject the resultant product with a homogenizer until the appropriate droplet size and polydispersity index are obtained [2]. In this process, two liquids, cosurfactants & surfactants are forced using a tiny opening in a piston homogenizer at a high pressure ranges from 500 to 5000 psi to form nano emulsions [36]. However, a significant amount of energy is needed to produce tiny droplets at the submicron level. The components may deteriorate as a

result of this energy and the rising temperatures during the high-pressure homogenization process. Diagrammatic representation of high-pressure homogenization system (PandaPlus2000 homogenizer, from GEA) equipped with two valves for cellular materials disruption shown in figure 7. Nucleic acids, proteins, and enzymes are examples of thermolabile substances that might get destroyed. A large number of surfactants are incorporated to reduce coalescence [37]. However, this results in coalescence during the emulsification process. For this reason, it is preferable to utilize a surfactant to effectively reduce surface tension [2]. It is a very effective method that is used in both laboratories and industries, but it uses a lot of energy and could cause the components to deteriorate if the processing temperature rises too high.

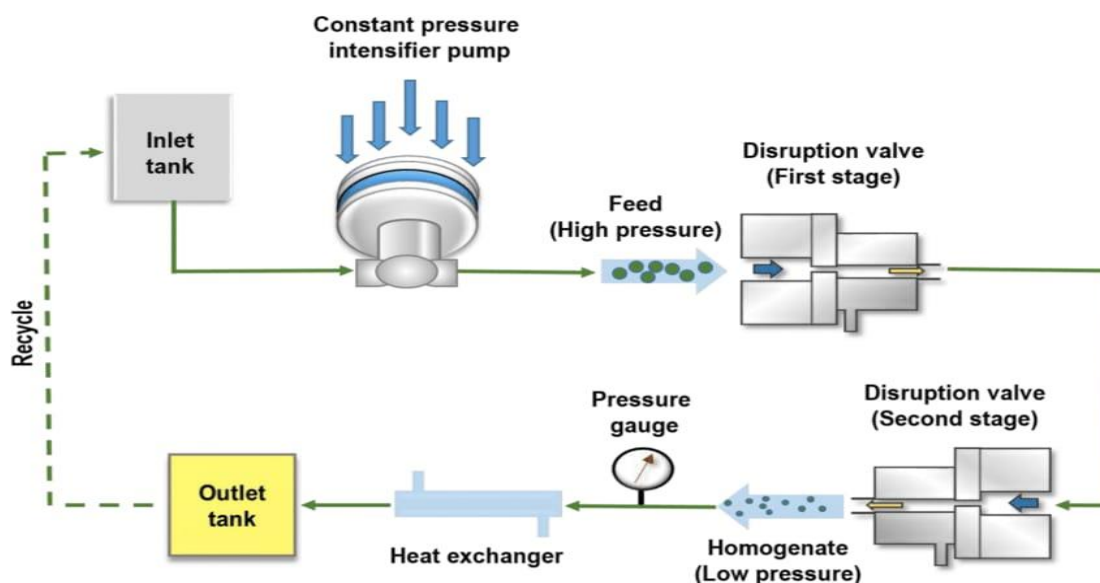


Figure 7. Schematic of high-pressure homogenization system (PandaPlus2000 homogenizer, from GEA) equipped with two valves for cellular materials disruption [40].

High-Pressure Microfluidic homogenization method (HPMH): A strong platform with a well-managed emulsification process is offered by microfluidic technology, which produces highly controllable monodisperse emulsion droplets. The pharmaceutical industries utilise this method more frequently to obtain fine emulsions. Microfluidizer is used in this technique, a device that generates high pressures. Microfluidic approaches provide flexible regulation of droplet form by allowing for dynamic adjustment of the surfactant-stabilized interface between dispersed droplets and continuous phase, with outstanding control over flow behaviors [38]. The technique is identified with the use of combination of processing methods such as high-velocity impact forces, high pressure, instantaneous pressure drop, high-frequency vibration, hydrodynamic intense and shear rate cavitation to twist. A microfluidizer contains an interaction chamber where the liquid flows as a channel or steam at a certain velocity, undergoing turbulence and high stress and categorise into 2 or more micro-streams with the significantly increased velocities because of the high reduction in pipe diameters. These high-velocity micro-streams then collide with each other and white the chamber walls, resulting in the breaking down of particles into tiny droplets, ultimately leading to the production of an emulsion. This resulting emulsion will be obtained from an outlet attached at the end of the interaction chamber. Outlet pipe is prepared with higher diameter to confirm an immediate drop of velocity or pressure results by inducing irreversible changes in the structure system of emulsion [39]. As a result of high-velocity impact, high pressure, intense shear rate and cavitation, micro fluidization can create extremely stable and homogenous aqueous media, making it one of the most promising techniques to produce nano emulsions. Therefore, high-pressure homogenization and micro fluidisation procedures could both be employed to prepare nano emulsions at the laboratory and industrial scales [40]. preparing nano delivery systems through a micro fluidization method shown in figure 8.

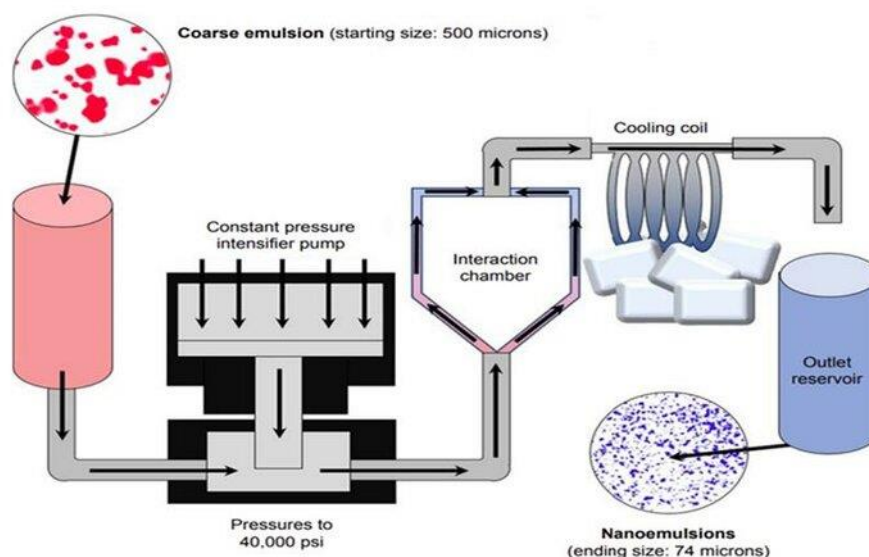


Figure 8. Preparing nano delivery systems through a micro fluidization method.

Ultrasonic homogenization method (USH): One of the most often used techniques for producing nano emulsions (NEs) is the ultrasonication method due to its energy-efficient manufacturing process, intuitive and straightforward manipulation system, affordable production costs, and ability to produce stable emulsions. For high-pressure homogenization, this method is used as an alternative [40].

Ultrasonic emulsification involves two mechanisms:

1. Interfacial waves produced by the acoustic field cause the oil phase to fragment and disseminate as droplets into the continuous phase.
2. Acoustic cavitation caused by ultrasound causes microbubbles to form and burst mostly because of pressure changes in a single sound wave.
3. The ultra-sonication procedures influence sound waves high-frequency that are 20 kHz and above. A piezo transmitter is used to produce sound waves by generating mechanical vibrations from electrical voltage [41].

High-power ultrasonic equipments such as pointed tips and focusing horns results high cavitation and sheer that leads to breaking up of droplets. However, because sonication techniques have the potential to cause lipid oxidation, protein denaturation, and polysaccharide depolymerization, there are certain issues regarding them. Ultra sonication technique is mainly used at laboratory scale. The technique is more advantageous than traditional mechanical procedures because it produces uniform Nano emulsion with less energy and surfactant concentration [42]. Nano emulsion formed by ultra-sonication method shown in the Figure 9.

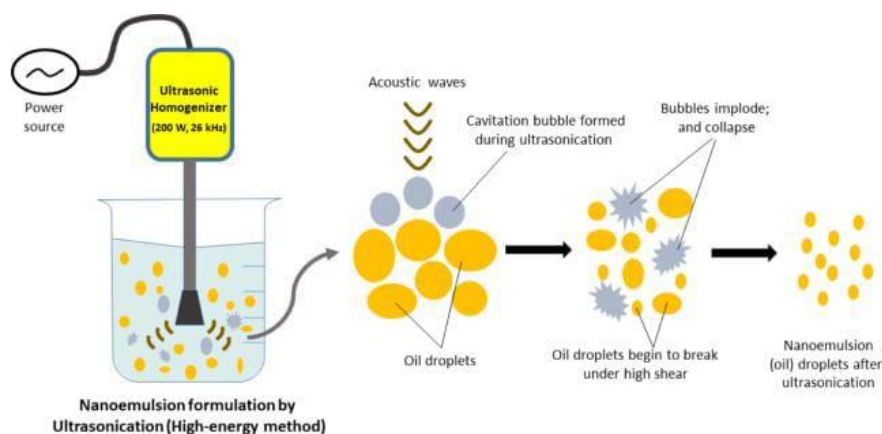


Figure 9. Nano emulsion formed by ultra-sonication method.

3. Formulation of nanoemulsions

The key components used in nanoemulsion preparation include:

3.1. Oil phase

The oil phase serves as the carrier for lipophilic drugs and influences the droplet size and stability of the nanoemulsion. Common oils used include medium-chain triglycerides, long-chain triglycerides, essential oils, and mineral oils [43]. The choice of oil depends on the drug solubility and the desired properties of the final formulation.

3.2. Aqueous phase

Water or buffer solutions form the continuous phase in oil-in-water nanoemulsions. The aqueous phase may contain hydrophilic drugs, electrolytes, or other water-soluble components [44].

3.3. Surfactants

These are crucial for reducing interfacial tension and stabilizing the nanoemulsion. Both synthetic and natural surfactants are used, including polysorbates (Tweens), sorbitan esters (Spans), phospholipids, and proteins [45]. The selection of surfactants is based on their hydrophilic-lipophilic balance (HLB) value and compatibility with other components.

3.4. Co-surfactants

These are often added to further reduce interfacial tension and improve the flexibility of the interfacial film. Common co-surfactants include short-chain alcohols, polyethylene glycol, and propylene glycol [46].

3.5. Stabilizers

Stabilizers play a crucial role in maintaining the long-term stability of nanoemulsions. These may include:

3.5.1. Texture modifiers

Such as xanthan gum or carboxymethylcellulose, which can increase viscosity and prevent gravitational separation [47].

3.5.2. Emulsifiers

Additional emulsifiers like lecithin or poloxamers can enhance the stability of the interfacial layer [48].

3.5.3. Ripening inhibitors

Compounds like long-chain triglycerides or hydrophobic compounds that can prevent Ostwald ripening [49].

3.6. Antioxidants

These are often included to prevent oxidation of the oil phase and maintain the chemical stability of the formulation. Examples include tocopherols, ascorbic acid, and butylated hydroxytoluene (BHT) [50].

3.7. pH adjusters

Buffers or pH-modifying agents may be added to optimize the pH for drug stability and physiological compatibility [51].

3.8. Osmotic agents

In some cases, osmotic agents like glycerin or sorbitol are added to adjust the osmolality of the formulation, particularly for parenteral or ocular applications [52].

The formation of solid particles, monolayer, and multilayer nanoemulsions can be achieved through careful selection and combination of these excipients. In some cases, surfactant-free emulsions can be prepared using solid particles as stabilizers, known as Pickering emulsions [53].

4. Applications of nanoemulsions

Nanoemulsions have found diverse applications across various industries, particularly in food science, pharmaceuticals, and materials engineering. Their unique properties and versatility make them ideal candidates for addressing challenges in product formulation, drug delivery, and functional materials development.

- In the food industry, nanoemulsions are increasingly used to create structured ingredients that enhance texture, flavor, appearance, and nutritional value of products [54]. Recent research has focused on developing sustainable, health-promoting, and clean-label formulations. Double emulsions, nanoemulsions, and Pickering emulsions have garnered significant attention due to their potential to improve food quality and functionality [55].
- The use of environmentally friendly ingredients, such as nanocellulose and other biopolymers, is becoming more prevalent in food-grade nanoemulsion formulations [56]. These natural materials can provide excellent stability and additional health benefits. Advanced characterization techniques, including nuclear magnetic resonance spectroscopy (NMR), are being employed to study the structure of multiple emulsions, facilitating ongoing characterization of food products [57]. Moreover, microfluidic and imaging-coupled artificial intelligence methods are being developed to simplify and accelerate the formulation and analysis processes [58].
- In the field of thermal management, nanoemulsions have shown promise for enhanced heat transfer applications. They are designed to provide improved heat transfer properties, increased pumping power, and greater storage capacities for latent heat storage in flow systems [43]. This makes them particularly useful in thermal transport and storage applications, with potential implications for energy efficiency and sustainability [59].
- The pharmaceutical industry has embraced nanoemulsions for their ability to enhance drug delivery and therapeutic efficacy. For instance, pomegranate seed oil (PSO) nanoemulsions have demonstrated significant antitumor activity in preclinical studies [44]. Treatment with PSO nanoemulsions resulted in reduced tumor weight and size, increased DNA damage in tumor tissue, and modulation of key genes involved in apoptosis and tumor suppression [60]. However, careful dose optimization is crucial to minimize potential genotoxicity to healthy tissues.
- Innovative nanoemulsion formulations are also being developed for specific therapeutic applications. For example, cinnamaldehyde-tannic acid nanoemulsions (CIN-TA-NEs) have been successfully integrated with chitosan to create composite films with enhanced functional properties [61]. These films exhibit improved water resistance, reduced oxygen and water vapor permeability, and increased compactness, making them promising candidates for food packaging and drug delivery applications.
- In the realm of pulmonary drug delivery, size-controlled nanoemulsions have shown potential as alternative medication delivery systems [45]. By optimizing process parameters, researchers have developed nanoemulsions with tailored sizes that demonstrate improved membrane permeability and favorable aerodynamic properties. These formulations show reduced toxicity in human lung fibroblast cells while maintaining efficient pulmonary transport, offering new possibilities for treating lung diseases with elevated local drug concentrations [62].
- Nanoemulsions have also shown promise in topical drug delivery, particularly for anti-psoriatic medications [46]. Their high drug-loading capacity, enhanced penetration ability, and low skin irritation make them ideal carriers for dermatological applications. The use of natural biosurfactants in nanoemulsion formulations is gaining traction due to their environmental friendliness and comparable surfactant competency to synthetic alternatives [63].
- In the field of food preservation and packaging, nanoemulsions of essential oils have demonstrated significant potential [47]. These formulations enhance the dispersibility of essential oils and facilitate their controlled delivery in food systems. Nanoemulsion-based coatings have shown effectiveness in active packaging applications, contributing to improved food safety and shelf life [64]. Additionally, essential oil nanoemulsions have been explored for their potential as bio-nanosensors and disinfectants, addressing microbiological contamination in food products [48, 65-67].

5. Importance of Nanoemulsions

Nanoemulsions have gained significant attention in various fields due to their unique properties and versatile applications. The importance of nanoemulsions can be summarized as follows:

- **Enhanced Bioavailability and Efficacy:** Nanoemulsions exhibit improved solubility, dissolution, absorption, permeation, and bioavailability due to their nano-sized droplets and extensive interfacial area [68]. This characteristic is particularly beneficial for poorly water-soluble drugs and bioactive compounds, as it can significantly enhance their therapeutic efficacy.
- **Improved Stability of Bioactive Compounds:** Encapsulation within the nanoemulsion matrix can enhance the physical stability of herbal bioactives and other sensitive compounds [69]. This protection helps preserve the integrity and activity of these substances, extending their shelf life and maintaining their efficacy over time.

- **Safety and Biocompatibility:** The oils and fats used in nanoemulsions are generally recognized as safe (GRAS) for human consumption. They are rapidly metabolized, well-tolerated by the body, and non-toxic [70]. This makes nanoemulsions suitable for various applications, including pharmaceuticals, nutraceuticals, and cosmetics.
- **Controlled and Sustained Release:** Nanoemulsions permit the deliberate and continuous transfer of active molecules [49]. This controlled release profile can lead to more consistent therapeutic effects and reduced dosing frequency, potentially improving patient compliance [71].
- **Reduced Toxicity:** Nanoemulsions can potentially reduce the required dosage while maintaining or improving therapeutic effects. This can lead to a reduction in dose-dependent side effects and overall toxicity [72].
- **Versatility in Drug Delivery:** Nanoemulsions have attracted worldwide research interest due to their capacity to solubilize and transport both hydrophilic and hydrophobic active compounds with unique physical properties [73]. This versatility makes them suitable for a wide range of applications in drug delivery and nutraceuticals.
- **Enhanced Systemic Bioavailability:** For certain routes of administration, nanoemulsions can increase the concentration of drugs in plasma by avoiding first-pass metabolism [74]. This is particularly beneficial for drugs with low oral bioavailability.
- **Value-Added Nutraceutical Products:** In the food and nutraceutical industry, nanoemulsions offer the potential to create products with added value, such as improved bioavailability of nutrients or enhanced sensory properties [75].
- **Improved Patient Compliance:** The potential for reduced dosing frequency, improved efficacy, and decreased side effects can lead to better patient compliance with treatment regimens [50].

6. Advantages and Disadvantages of Nanoemulsions

Nanoemulsions offer numerous advantages, but they also have some limitations. Following is an overview of their pros and cons:

6.1. Advantages

- Enhanced solubility and bioavailability of poorly water-soluble compounds
- Improved stability compared to conventional emulsions
- Potential for targeted drug delivery
- Controlled and sustained release of active ingredients
- Reduced dosage requirements and potentially fewer side effects
- Versatility in routes of administration (oral, topical, parenteral, etc.)
- Protection of sensitive bioactive compounds
- Potential for improved sensory attributes in food and cosmetic applications
- Increased penetration through biological membranes [76]

6.2. Disadvantages

- Potential for Ostwald ripening, leading to instability over time
- Sensitivity to environmental factors such as temperature and pH
- Possibility of drug leakage during storage
- Higher production costs compared to conventional formulations
- Potential for surfactant-induced toxicity if not properly formulated
- Limited loading capacity for some drugs
- Challenges in large-scale production and sterilization
- Potential for allergic reactions to certain components
- Regulatory challenges due to the novelty of nanoscale formulations [77]

7. Conclusion

Nanoemulsions have emerged as a promising and versatile platform in the fields of drug delivery, food science, and cosmetics. Their unique properties, including enhanced solubility, improved bioavailability, and controlled release capabilities, offer significant advantages over conventional formulations. The ability to encapsulate both hydrophilic and hydrophobic compounds, coupled with their stability and potential for targeted delivery, makes nanoemulsions particularly attractive for a wide range of applications.

Recent advancements in formulation techniques, characterization methods, and the use of novel, biocompatible materials have further expanded the potential of nanoemulsions. From improving the efficacy of pharmaceuticals to enhancing the nutritional value and shelf life of food products, nanoemulsions demonstrate remarkable versatility and efficacy.

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Anil Kumar Vadaga:

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