

Nanoemulsions as medicinal components in insoluble medicines

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Abstract

Background: Medicine's success relies on solubility, which is the process of dissolving a solid substance in a fluid phase to create a uniform molecular dispersion. However, hydrophobic active medicinal components exhibit poor solubility in water, limiting their effectiveness and incorporation into medications.

Aim: This review explores the potential of nanoemulsions as a solution for delivering hydrophobic medicinal components with low solubility. The study investigates the benefits of nanoemulsions, including enhanced absorption, effective targeting, controlled release, and protection of encapsulated bioactive ingredients.

Materials and methods: Nanoemulsions are formulated by combining two immiscible liquids with emulsifying agents within a thermodynamically stable colloidal dispersion system. The review categorizes various preparation techniques into high-energy and low-energy spontaneous emulsification methods. The choice of preparation procedures and materials used significantly affects the stability of nanoemulsions over time. Evaluation of nanoemulsions includes studying medication release in vitro, in vitro permeation, stability and thermodynamic stability, shelf life, viscosity, interfacial tension, pH, and osmolarity.

Results: Nanoemulsions, such as Celecoxib (Phase Inversion), acetylsalicylic acid (Ultrasonication), and Flurbiprofen (Homogenization and Ultrasonication), offer distinct advantages for medications with low solubility compared to conventional emulsions. These nanoemulsions comprise small droplets with a larger surface area, promoting enhanced absorption. They demonstrate effective targeting, controlled release, and protection of encapsulated bioactive ingredients. Moreover, the diminutive droplet sizes of nanoemulsions contribute to their reduced susceptibility to issues like flocculation, coalescence, sedimentation, or creaming.

Conclusion: Nanoemulsions hold great promise in overcoming the solubility limitations of hydrophobic medicinal components. They provide enhanced absorption, effective targeting, controlled release, and protection of bioactive ingredients. The choice of preparation techniques and materials plays a crucial role in ensuring the stability of nanoemulsions over time. Further studies are warranted to optimize their use and explore their potential applications in drug delivery systems.

Keywords

solubility, hydrophobic medicinal components, nanoemulsions, formulation techniques, stability

Introduction

Drug product solubility can be described both quantitatively and qualitatively. Quantitative solubility refers to the amount of solute particles required to form a saturated solution (Albetawi et al. 2021). Some drugs exhibit limited solubility, commonly known as poor soluble drugs; however, there are several techniques available to improve solubility. Qualitative solubility refers to the ability of two phases to dissolve and form a homogeneous solution (Popova et al. 2020). The limited bioavailability of oral dosage forms poses a significant challenge in drug design.

Pharmacokinetic properties are influenced by variables such as aqueous solubility, dissolution rate, drug permeability, first-pass metabolism, and sensitivity to efflux mechanisms. Poor solubility and inadequate permeability are the two main factors contributing to low oral bioavailability (Abuzar et al. 2018). Converting poorly water-soluble drugs into usable pharmaceuticals remains an ongoing issue. A complex interplay of physical-chemical, pharmacological, physiological, and anatomical factors acts individually and collectively to limit medication bioavailability, hindering their effective oral administration (Ding et al. 2023).

Solubility has emerged as a critical aspect of drug discovery and development, encompassing both physicochemical and biological considerations. Poor solubility ranks among the top undesirable biopharmaceutical characteristics. Unfortunately, poor water solubility has frequently resulted in failures in therapeutic development, as evidenced by the increasing number of compounds classified as BCS class II and class IV. Accurately and biopharmaceutically assessing a substance's solubility poses difficulties.

Solubility is categorized by the United States Pharmacopeia (USP) and British Pharmacopoeia (BP), employing specific criteria listed in Table 1 for quantification purposes only. The requirement for efficient formulations of BCS class II and class IV pharmaceuticals has driven the development of diverse technological solutions to address inadequate biopharmaceutical qualities and advancements in the field of drug delivery systems for oral administration (Ding et al. 2023). The Biopharmaceutics Classification System (BCS) was established in the mid-1990s to classify pharmacological compounds based on their membrane permeability and dissolution rate, as illustrated in Table 2.

Table 1. Solubility criteria (Popova et al. 2020).

Description	Parts of solvent required for one part of solute
Very soluble	Less than 1
Freely soluble	1–10
Soluble	10–30
Sparingly soluble	30–100
Slightly soluble	100–1000
Very slightly soluble	1000–10000
Insoluble	More than 10000

Table 2. Drugs are classified as BCS-I to BCS-V (Ding et al. 2023).

Classification	Property
BCS-I	Highly Soluble, Highly Permeable
BCS-II	Low Soluble, Highly Permeable
BCS-III	Highly Soluble, Low Permeable
BCS-IV	Low Soluble, Low Permeable

Poor solubility

In the process of developing new drugs, a significant number of Active Pharmaceutical Ingredients (APIs) exhibit low solubilities. Poorly soluble medications pose challenges in terms of synthesis using traditional techniques and often have low bioavailability. In recent years, attention has been directed towards the utilization of nanosizing techniques to create nanocrystals for poorly water-soluble pharmaceuticals. Nanosizing involves reducing the size of a drug to the sub-micron range, aiming to enhance its surface area, dissolution rate, and ultimately its bioavailability (Al-Kassas et al. 201).

Dissolving and solubility are fundamental concepts in the physical and chemical sciences and in the biopharmaceutical and pharmacokinetic aspects of drug treatment.

Techniques for solubility enhancement (Al-Kassas et al. 201)

Various methods have been employed to improve the solubility and dissolution rates of poorly water-soluble drugs:

- a) Particle Size Reduction:** This method involves crushing the drug to achieve the desired particle size. Hammer mills and roller mills are commonly used in the feed industry. Factors such as the type of ingredient, energy usage, and grinding capacity are considered when selecting a mill. Multi-stage grinding combining different mills can be employed to achieve optimal particle size reduction at a reasonable cost (Lyu et al. 2020).
- b) Nanonization:** Nanonization refers to using a drug in the form of nanoparticles, which are particles smaller than one micron. Various definitions of nanomaterial have been put forth by regulatory organizations, with a general consensus that the average size should fall between 1 and 100 nm. Nanonization techniques offer the potential for improved solubility and bioavailability of drugs (Da Silva et al. 2020).
- c) Cosolvency:** Cosolvency is a commonly used technique to enhance solubility. It involves using aqueous-organic solvent combinations during the manufacturing of liquid dosage forms, solution preparation, or crystallization processes. The cosolvency approach can also be applied to generate medicinal nanosuspensions by utilizing solubility data in cosolvent-water mixtures (Jouyban 2019).
- d) Hydrotropy:** Hydrotropy involves the addition of a significant amount of a second solute to enhance the

dissolution of a third solute in water. Hydrotropic solutions, such as sodium benzoate and salicylate, have been reported to increase the aqueous solubility of poorly water-soluble drugs (ALZobaidy et al. 2021).

- e) **pH Adjustment:** Adjusting the pH can potentially increase the water solubility of drugs. The choice of buffer capacity and the tolerability of the selected pH are crucial considerations in this method. Acidic drugs may exhibit increased solubility when excipients soluble in higher pH environments are added, while alkalizing agents can enhance the solubility of basic drugs (Jagtap et al. 2018).
- f) **Sonocrystallization:** Sonocrystallization involves the application of ultrasound (US) during the crystallization process. Research has shown that sonocrystallization offers advantages such as increased product homogeneity, favored polymorph formation, faster crystallization times, and higher crystal purity (Nalesso et al. 2019).
- g) **Supercritical Fluid (SCF) Process:** The supercritical fluid process utilizes carbon dioxide gas under pressure and heat. When carbon dioxide reaches the supercritical point, it transitions from a liquid to a supercritical phase. In this process, carbon dioxide is used to dissolve the intended chemical to be converted into nanoparticles. The mixture is then rapidly expanded by spraying it through a nozzle, causing carbon dioxide to evaporate and resulting in the production of nanoparticles (Hussein et al. 2018).
- h) **Solid Dispersion:** Solid dispersion involves the creation of a mixture by melting, using a solvent, or melting a solvent technique, of one or more hydrophobic active components in an inert hydrophilic carrier. The final product consists of a hydrophilic matrix and a hydrophobic drug (Abbas et al. 2016).
- i) **Self-Emulsifying (SE) or Self-Micro Emulsifying Systems (SEMS):** Self-Emulsifying Drug Delivery Systems (SEDDS) have been developed to enhance drug solubility. SEDDS are characterized as isotropic mixtures of hydrophilic solvents and cosolvents, solid or liquid surfactants, and natural or synthetic oils. Simple binary systems, such as the lipophilic phase and drug or the lipophilic phase, surfactant, and drug, can be employed in SEDDS formulations. Co-surfactants are used to create microemulsions in SEDDS formulations. In vitro lipid droplet sizes of 200 nm to 5 μm and a cloudy appearance of the dispersion distinguish SEDDS formulations (Kanjani et al. 2016).

Nanoemulsion nanoemulsions and sub-micron emulsions (SMEs)

Nanoemulsion Nanoemulsions and sub-micron emulsions (SMEs) are thermodynamically unstable but can be stabilized by surfactant and co-surfactant molecules coating the interface, as illustrated in Fig. 1. Nanoemulsions have gained popularity in the administration of vaccines, DNA-encod-

ed drugs, antibiotics, cosmetics, and topical preparations. These substances can be administered through various routes, including oral, pulmonary, intranasal, ophthalmic, and transdermal (Savardekar and Bajaj 2016).

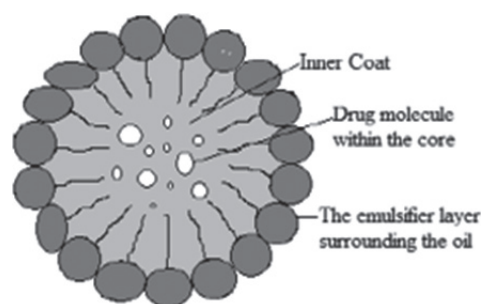


Figure 1. Structure of nanoemulsion (Mushtaq et al. 2023).

The order of mixing the various components during formulation is crucial when creating nanoemulsions. Combining the oily phase with surfactants as the initial step promotes favorable conditions for nanoemulsion development. Conversely, preparing surfactants and water as the initial step would favor the formation of “macroscopic” emulsions (Che Marzuki et al. 2019).

Since an emulsifier reduces the surface energy per unit area between the oil and water phases of the emulsion, it is essential for the production of fine droplets. Through repellent electrostatic interactions and steric hindrance, the emulsifier also contributes to the stabilization of nanoemulsions (Mushtaq et al. 2023).

Surfactants are often the emulsifier employed, but proteins and lipids have also been successful in the creation of NEs. The preparation of NEs using diverse techniques, broadly categorized into two main categories: high-energy and low-energy procedures, has been the focus of research over the past ten years. Ultrasonication and high-pressure homogenization (HPH) are high-energy processes that use a lot of energy ($\sim 10^8$ – 10^{10} W kg⁻¹) to create tiny drops. On the other hand, low-energy techniques take advantage of particular system characteristics to create tiny droplets without expending a lot of energy ($\sim 10^3$ W kg⁻¹) (Mushtaq et al. 2023).

Partitioning from oil into the surfactant layer and ultimately into the aqueous phase is how drugs are released from NEs. Nanoprecipitation occurs when the drug’s solubilized moiety contacts nearby water while diffusing out of oil. This significantly increases the drug’s surface area, hastening the drug’s disintegration in accordance with Noyes-equation. Whitney’s Thus, to create a sustained/controlled release device, the dynamics of drug release can be changed at each of these steps by subtly changing the composition of NEs (Dave et al. 2017).

Types and contents of nanoemulsions

Types of nanoemulsions

When characterizing emulsions, both morphological and compositional characteristics are taken into account. Three

different forms of NEs are more likely to occur depending on the composition, as shown demonstrated in (Fig. 2):

- Nanoemulsions of oil in water (O/W), in which the oil droplets are scattered throughout the continuous aqueous phase.
- Water-in-oil nanoemulsions (W/O), in which water puddles are scattered throughout a continuous oil phase.
- Bi-continuous nanoemulsions: These come in two varieties: Oil in water in oil (O/W/O) - In this case, oil serves as a dissolution medium while water acts as a dispersed phase. The second type is water in oil in water (O/W/O), in which water serves as a dispersion medium and W/O oil acts as a dispersed phase (Sarkeret al. 2015).

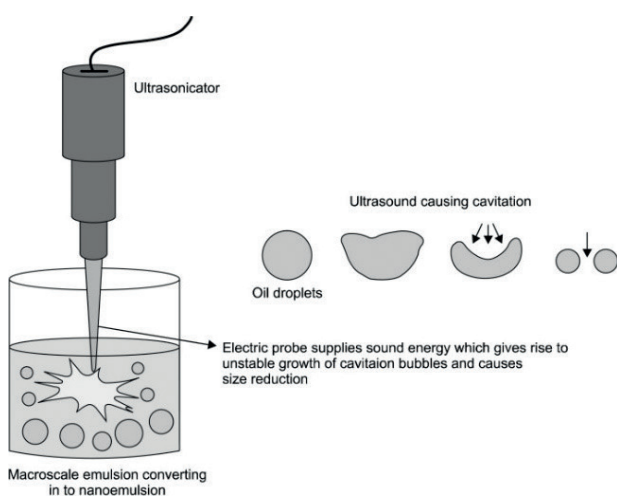


Figure 2. Ultrasonication techniques (Vaibhav et al. 2019).

Contents of nanoemulsions

(a) Aqueous phase

The characteristics of the aqueous phase, such as pH, ionic concentration of the aqueous phase, and electrolytes, has an impact on the droplet size and stability of NEs. Ringer's solution, simulated stomach fluid (pH 1.2), simulated intestinal fluid (pH 6.8), phosphate buffered saline, and plain water can all be employed as the aqueous phase when evaluating spontaneous Nano emulsification of NEs. Among the aqueous phase's other characteristics, pH can significantly impact how NEs behave in phases when a medication with a pH-dependent solubility is added to the system (Sarkeret al. 2015).

(b) Oil phase

The second most important transport medium after water due to its capacity to solubilize lipophilic drug molecules and improve absorption through the body's lipid layer. Oil is incredibly useful for administering medications with lipophilic active ingredients because of its extraordinary capacity to penetrate cell membranes. The oil phase also affects the swelling of the surfactant's tail group region (Kaleet al. 2017). The preparation of NEs uses a variety of oils (Table 3).

Table 3. Types of oils used in nanoemulsions (Kaleet al. 2017).

S.No.	Oils	Chemical Name
1.	Capmul MCM	Glycerol monocaprylate
2.	Capryol90	Propylene glycol monocaprylate
3.	Captex 200	Propylene Dicaprylate
4.	Captex 355	Glyceryl Tricaorylate/Capratae
5.	Captex 8000	Glyceryl Tricaprylate
6.	Carbitol	Glycerol Triacetate
7.	Isopropyl Myristate	Myristic acid isopropyl ester
8.	Labrafac	Medium chain triglyceride
9.	Maisine 35-1	1-Monolinolein
10.	Myritol318	c8/c10 triglyceride
11.	Peceol	Glyceryl Oleate
12.	Sefsol 218	Caprylic/ capric triglyceride
13.	Witepsol	90:10% w/w c-12 glyceride tri:diesters

The selection of a suitable surfactant is critical for the formulation of nanoemulsions. The surfactant should possess a strong solubilizing capacity for hydrophobic drug molecules and be capable of micro-emulsifying the oily phase (c). In nanoemulsion (NE) formulations, the choice of surfactant plays a vital role. A hydrophilic surfactant that forms an oil-in-water (O/W) nanoemulsion with a hydrophilic-lipophilic balance (HLB) value of 10 is preferred. The hydrophobic core of the surfactant improves drug entrapment and enhances solubility. When the oil concentration is high, the surfactant concentrates at the oil-water interface, resulting in emulsions where the drug is solubilized in the internal oil phase. Conversely, when the oil level is low, tiny oil-entrapped surfactant globules, known as NEs, are formed (Savardekar and Bajaj 2016).

Ionic or non-ionic surfactants can be used in NE production; however, ionic surfactants are not recommended due to potential toxicological effects. It is essential to accurately determine the surfactant concentration since high levels of surfactants can cause irritation in the gastrointestinal (GI) tract. Therefore, there is a relationship between the surfactant concentration and the size of the droplets. In some cases, increasing the surfactant content, such as with a mixture of saturated C8–C10 polyglycolized glycerides, may result in smaller droplets. However, in certain situations, increasing surfactant concentrations may lead to an increase in the mean droplet size (Ee et al. 2008). Common forms of surfactants are listed in Table 4.

Some of the desirable properties of a surfactant are:

- 1) It must be capable of lowering surface tension to less than 10 dynes/cm.
- 2) To avoid coalescence, it must be quickly adsorbed around the dispersed phase globule to form a complete and coherent film.
- 3) It should contribute to the system's development of an acceptable zeta potential and viscosity in order to bestow stability.
- 4) It ought to work well at relatively low concentrations. Surfactants enclose the dispersed globules in monomolecular, multimolecular, or particulate films (Islam et al. 2023).

Table 4. Types of Surfactants used in nanoemulsions (Ee et al. 2008).

Sl.No	Surfactants
01	Capryol 90
02	Gelucire 44/14, 50/13
03	Cremophor RH 40
04	Imwitor 191, 308(1), 380, 742, 780 K, 928, 988
05	Labrafil M 1944 CS, M 2125 CS
06	Lauroslycol 90
07	PEG MW > 4000
08	Phuol Oleique CC 497
09	Poloxamer 124 and 188
10	Softiaen 701, 767
11	TagatTO
12	Tween 80
13	Labrasol
14	Poloxamer 407
15	Polaxmer 188
16	Emulphor-620

(d) Co-surfactants

These substances are added to surfactants to strengthen the interfacial film because they fit well between structurally weaker locations (Mushtaq et al. 2023). Co-surfactants are utilized when surfactant fails to reduce the interfacial tension between oil and water to produce a stable NE. Co-surfactant disrupts the liquid crystalline phase by permeating the surfactant monolayer and additionally adds fluidity. (Wilson et al. 2022) Several varieties of co-surfactants are utilized, such as (Table 5).

Table 5. Types of co-surfactants used in nanoemulsions (Wilson et al. 2022).

Name	Chemical name
Transcutol P	Diethylene glycol monoethyl ether
Ethylene glycol	Ethane 1.2 diol
Propylene glycol	1.2 propanediol

Advantages and disadvantages of nanoemulsions

Advantages (Wilson et al. 2022)

The advantages of the NEs are as follows:

- 1) Because they have a larger surface area and more free energy than macro emulsions, NEs are an efficient delivery mechanism.
- 2) NEs are safe for skin and mucosal membranes because they are neither poisonous nor irritating.
- 3) The formulation is administered orally using bio-compatible surfactants.
- 4) It can be used to treat both humans and animals.
- 5) It aids in the solubilization of lipophilic medications.
- 6) Increases bioavailability by increasing the rate of absorption.
- 7) It must transport substances that are both lipophilic and hydrophilic.
- 8) Reduces adverse effects due to a lower overall dose.

Disadvantages (Wiket al. 2020)

There's several disadvantage:

- 1) Stability issues.
- 2) Thermodynamic not stable.
- 3) Possibility of Ostwald ripening.
- 4) Flocculation.
- 5) Coalescence.
- 6) Creaming/Sedimentation.
- 7) Expensive and tedious preparations hinder the scale-up of operation.

Methods of preparation of nanoemulsions

NEs can be made using either a high energy dissipation approach or a low energy dissipation method. The energy requirements of these two approaches vary. In the high energy approach, powerful disruptive forces are produced mechanically. In contrast, low energy methods change the system's physiochemical characteristics to produce nanoparticles (Safaya and Rotliwala 2020).

High energy method

Uses mechanical tools that may produce powerful disruptive forces that combine and disturb the phases of oil and water, causing the creation of the small oil droplets. Intense energies are needed to generate disruptive forces greater than the restoring forces to keep the droplets in spherical shapes (Karthik et al. 2015).

Any type of oil can be used to manufacture NEs using high energy methods; however these techniques are most commonly preferred for highly viscous and high molecular weight oils. By using this strategy, fewer surfactants are used, and choosing a surfactant is simpler. Due to heat-sensitive components, this approach appears to be problematic for drug delivery systems (Safaya and Rotliwala 2020).

High/shear stirring

In this technique, NEs are prepared using high-energy mixers and rotor/stator devices. By intensifying the mixing in these devices, the internal phase droplet sizes can be greatly reduced. However, it can be challenging to create emulsions with an average droplet size of less than 200/300 nm (Aswathanarayan and Vittal 2019). A multipass regime must be used to solve this shortcoming because the single-pass regime cannot achieve the system's maximal degree of dispersion and the efficacy drops when high-viscosity systems are employed (Safaya and Rotliwala 2020). High shear stirring involves using mechanical force to separate bigger droplets into smaller droplets. It is typically employed in conjunction with other techniques (Çinar 2017).

Ultrasonication

This technique is based on the idea that as external pressure and coarse emulsion are subjected to an ultrasonic

field, the cavitation threshold will likewise rise, limiting the formation of fine nanoparticles. The fundamental principle of ultrasound is the implosion of the droplets through a succession of mechanical depressions and compressions that produce cavitation stresses. Cavitation is a phenomena that results from the pressure changes of the acoustic wave and is characterized by the production, expansion, and subsequent collapse of microbubbles. Nano-sized droplets occur as a result of the extreme turbulence brought on by the collapse of microbubbles. When ultrasonic waves are used to irradiate an oil and water mixture, cavitation forces are created. This extra energy leads to the creation of nanoscale emulsion droplets at the interfaces. NEs can be created via ultrasonication without the need for surfactants (Vaibhav et al. 2019).

High pressure homogenization

Using pressure, a liquid is forced through a homogenization valve that has been designed to produce suspended particles with a homogeneous size distribution. Modern homogenizers are capable of applying pressures of 20 to 100 MPa, which can reduce particle size and improve NE stability by preventing destabilizing processes such as creaming and coalescence (Yukuyamaa et al. 2017).

This procedure uses a combination of factors, including cavitation, hydraulic shear, and severe turbulence, to produce lipid emulsions that are nanoscale in size. Preferably, a high volume fraction of the dispersion lipid phase is used to create the emulsion, which can then be diluted. High phase volume ratios, however, run the risk of instability through coalescence during emulsification or storage. If at all possible, dissolve the surfactant in the disperse phase as opposed to the continuous phase; this frequently results in smaller drops (Kumar et al. 2019).

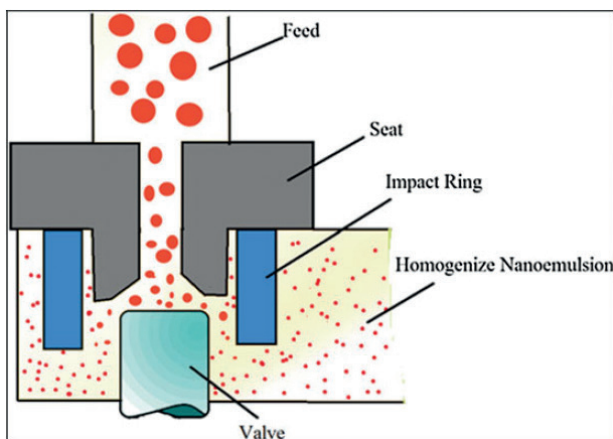


Figure 3. Production of nano emulsions using high pressure homogenization (Kumar et al. 2019).

Microfluidization method

Micro fluidization is a technique that produces high pressures of 500 to 20000 psi using a small-scale fluidizer, a device that has been expressly built for the purpose. Initially, a coarse emulsion is created by combining oil and water. This coarse emulsion is then driven down smaller-scale

channels into an impingement zone to create fine particles that are nanoscale, followed by filtration to obtain homogeneous particles (Al-Hussaniy et al. 2022).

Micro fluidization is a two-step technique, and depending on the formulation, it can produce emulsions with droplet sizes smaller than 600 nm. In general, synthetic surfactants tend to have smaller mean particle sizes than natural ones (Talegaonkar and Negi 2015).

Low energy methods

The low-energy techniques create dispersions by utilizing the chemical potential of the system's internal parts. Phase transitions that happen in reaction to changes in temperature and composition are used in low-energy emulsification and condensation techniques (Basha et al. 2020).

Techniques for low-energy emulsification result in thermodynamically stable NE. Because they utilise the system's stored energy to generate tiny droplets, low-energy technologies are becoming increasingly popular. Since they are "soft," enclosed molecules are supposed to be unharmed by them. These techniques also use less energy, making them more desirable for large-scale production (Sheth et al. 2020).

Phase inversion temperature method

In order for NEs to form spontaneously, the temperature-time profiles of the constituent parts must be altered, and abrupt temperature fluctuations prevent coalescence and the creation of stable NEs. The mixture of oil, water, and nonionic surfactant exhibits a positive curvature at room temperature (Tayeb and Sainsbury 2018).

However, it is experimentally challenging to generate a quick change in temperature when employing the PIT method to prepare a significant volume of NEs on an industrial scale. Polydisperse emulsions are created when coalescence predominates and the cooling or heating process does not proceed quickly enough. As a result, it is anticipated that a reasonable and simple approach will be created (Rai et al. 2018).

Phase Inversion Composition method

The Phase Inversion Composition method (PIC) entails obtaining O/W NEs from their W/O analogs by changing the volume proportion of the water at a specific temperature, which results in a shift in the natural emulsifier curvature. The water phase is gradually added to the oil phase during the PIC nano-emulsification process, which causes the water volume fraction to steadily rise. At a certain level, a phase inversion may occur, causing a bicontinuous phase to appear. This bicontinuous phase may then capture oil phases into water phases to produce O/W NEs. The PIC method has various benefits, including minimal cost and the requirement for straightforward equipment.

Due to the weaker driving pressures of the PIC approach, the preparation time was longer than that of the SE technique.

With a mean particle diameter of 40 nm, food-grade NEs enhanced with vitamin E acetate have been created us-

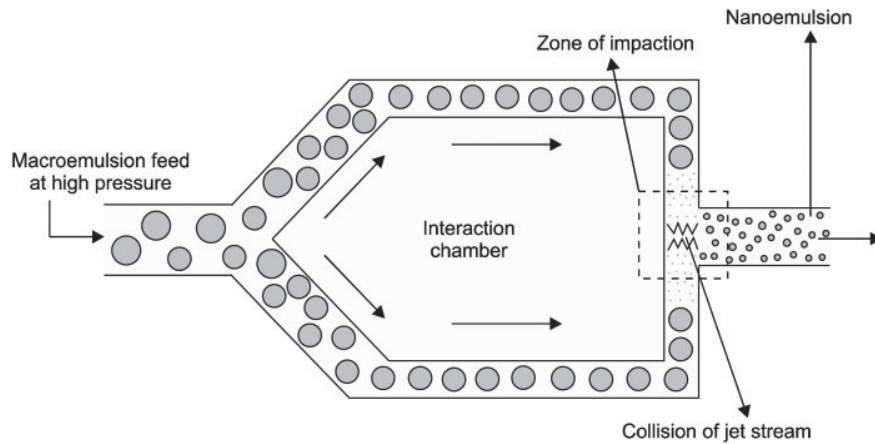


Figure 4. Micro fluidization method for the manufacture of nano emulsions (Talegaonkar and Negi 2015).

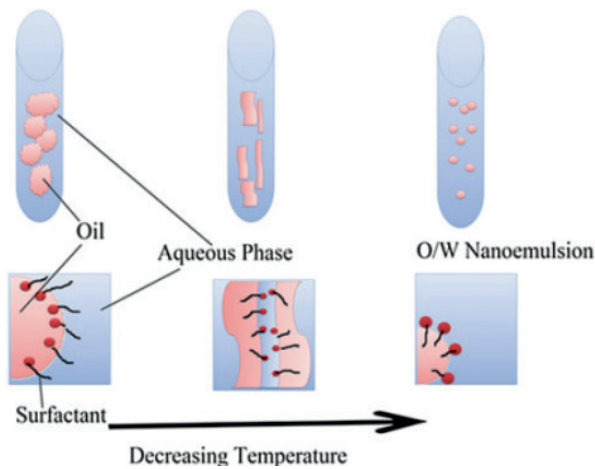


Figure 5. Phase inversion temperature method for the manufacture of nanoemulsions (Rai et al. 2018).

ing this technique. In comparison to the microfluidization technique, this method was more successful at producing NEs at high surfactant concentrations. For NEs compositions with label-friendly surfactants, such as Quillaja Saponin, whey protein, casein, and sucrose monoesters, the approach was not ideal (Al-hussaniy et al. 2022).

Spontaneous emulsification

This technique calls for 3 steps of preparing NE. The production of an biological solution containing oil, a lipophilic surfactant, a water-miscible solvent, and a hydrophilic surfactant was part of the first stage. The second stage involved insertion the organic phase into the aqueous phase stirring to generate the O/W emulsion. In the third stage, the organic solvent was subsequently eliminated using evaporation. The mean droplet size was determined to be between 50 and 100 nm when Sugumar et al. used spon-

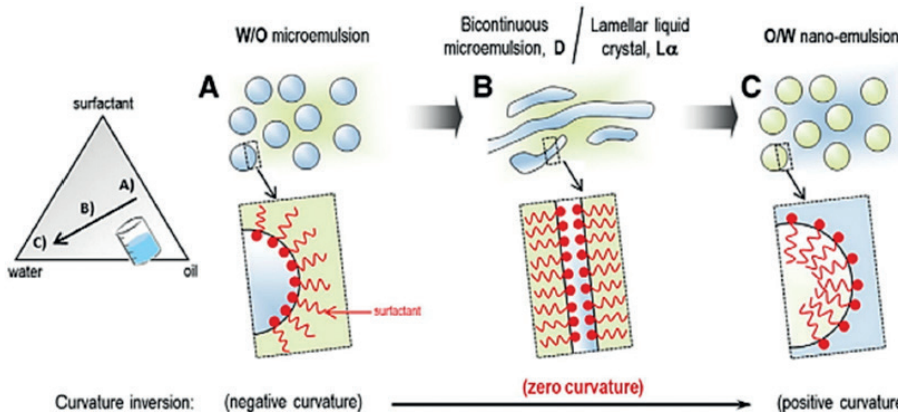


Figure 6. A schematic illustration of the Phase Inversion Composition (PIC) method’s NE creation (Al-hussaniy et al. 2022).

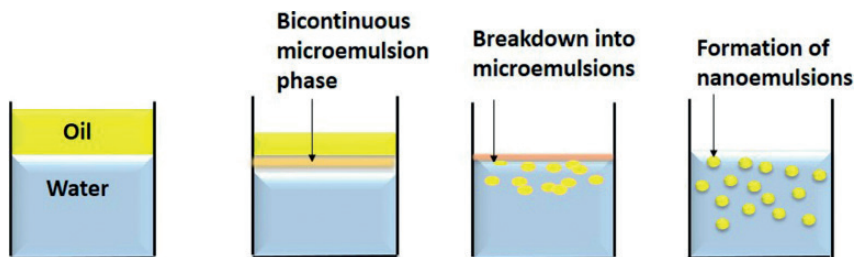


Figure 7. Spontaneous emulsification preparation method (Echeverría and Duarte Galhardo de Albuquerque 2019).

taneous emulsification to create stable eucalyptus oil NE (Ali et al. 2017).

Because it is primarily a diffusion-driven process, spontaneous emulsification—also referred to as self-emulsification or emulsification by solvent diffusion (ESD)—can be either delayed due to kinetic barriers or rapid due to the Ouzo effect. Although it is still in the early stages of development, this technique has been identified as a potentially efficient one that might produce droplets as thin as 10 nm (Echeverría and Duarte Galhardo de Albuquerque 2019).

Evaluation of nanoemulsions

Drug content

Utilizing a UV visible spectroscopic technique, the drug content of the drug NE formulation was determined. The NE formulation was used to prepare the 2 g/ml aliquot, which was then diluted with a solvent. The samples were examined using a UV/VIS spectroscopic technique at 278.2 nm. Results were evaluated in triplicate, with the average being taken into account (Hammodi and Abd Alhammid 2020).

Viscosity

The viscosity of NEs was determined using the Brookfield viscometer (Spindle LV-1, Model DV-E; Brookfield Engineering Laboratories, Inc., Middleborough, MA). For NE-1 and NE-2, the NE samples were sheared at a rate of 30 and 50 rpm, respectively. When the reading was stable, measurements (n 14 3) were made (Hamed and Abd Alhammid 2021).

Interfacial tension

By measuring the interfacial tension, it is possible to study the genesis and characteristics of NEs. When the presence of a surfactant phase or middle phase NEs is in equilibrium with an aqueous or an oil phase, ultra-low values of interfacial tension are connected with phase behavior. It is possible to test the extremely low interfacial tension of NEs using a spinning-drop technique (Rashid and Abd-Alhammid 2019).

pH and Osmolarity measurements

Using a pH meter, the pH of the formulation was determined (Eutech instrument, Landsmeer, the Netherlands). A micro-osmometer autocal type 13 based on the freezing-point method (Roebeling, Berlin, Germany) was used to measure the osmolarity of the emulsions. Measurements were taken after 100 mL of each native NE was added to a microtube (Jasim et al. 2020).

Thermodynamic stability studies

- **Heating Cooling Cycle**
- **Centrifugation:** at 3500 RPM

- **Freeze Thaw Cycle:** In this experiment, the formulation underwent three freeze-thaw cycles among twenty-one °C and +25 °C held under typical laboratory conditions.

Three months were spent doing these studies. At ambient humidity and accelerated temperatures of 30 °C, 40 °C, 50 °C, and 60 °C, three batches of formulations were maintained. The samples were taken out on a regular basis at intervals of 0, 1, 2, and 3 months, and the drug content was determined using an HPLC method that indicates stability (Hamed and Hussein 2020).

In vitro drug release

Semipermeable membrane utilized in a dissolution equipment can be used to evaluate the in vitro release studies of drugs containing NE. Instead of the basket, a glass tube with a cylindrical shape and a length of 6 cm is added. This tube must be tightly covered in the semi-permeable membrane. The cylindrical tube containing the drug-loaded NE is positioned at the semi-permeable membrane surface. To produce sink conditions and maintain permanent solubilization, the cylindrical tube should be submerged in 100 ml of buffer while preserving pH. At 32C, the release study can be performed for 24 hours. The speed of the stirring shaft should be 100 revolutions per minute. The UV spectrometer can be used to determine the samples' absorbance (Chaudhari and Kuchekar 2018).

In vitro permeation studies

Using a Keshary Chien diffusion cell, in vitro skin permeation investigations are performed on abdomen skins taken from male rats weighing (25010 g). The vertical diffusion cell's donor and receptor chambers are separated by skin. A 20% ethanol solution of fresh water is used to fill the receptor chamber. The solution in the receiver chamber is constantly agitated at 30RPM while the receiver chamber's temperature is set at 37 °C. The formulations are put in the donor chamber, and the solution in the receiver chamber is taken out for Glass Chromatography (GC) analysis at various times and promptly replaced with a fresh solution of the same volume. The same sample is used three times. To determine the overall amounts of medicines penetrated at each time interval, cumulative adjustments are made. Plotted as a function of time are the total amounts of medication that have passed through the skin of rats. The slope of the linear component of the cumulative amount of drug permeated through the rat skins per unit area vs time plot is used to compute the steady-state drug permeation rates through rat skins (Chaudhari and Kuchekar 2018).

Shelf-life determination

To ascertain a NE's shelf life, accelerated stability studies are carried out. The formulations are kept at three different temperatures and humidity levels (30 °, 40 °, and 50 0.5 °) for

almost three months. After a predetermined amount of time (0, 30, 60, and 90d), samples are taken out and examined using HPLC at max to determine how much medication is still there. For samples withdrawn at zero time, checks are used. Following the calculation of the reaction rate constant (K) for the degradation from the line slope using the equation $\text{slope} = K/2.303$ at each elevated temperature, this establishes the order of the reaction. The logarithm values of K are then plotted against the reciprocal of absolute temperature at various elevated temperatures (Arrhenius plot).

This plot value for K at 25 °C is used to determine it, and the value is then used to predict shelf life by entering the value into the following equation: $t(0.9) = 0.1052/K25$. Where t 0.9 is the amount of time needed for a medicine to lose 10% of its effectiveness, also known as shelf life (Chaudhari and Kuchekar 2018; Hamed and Hussein 2020; Jasim et al. 2020).

Further research

The research on nanoemulsions for the delivery of insoluble medicines is still in its early stages, but there are a number of areas where further research is needed. These include:

The development of more stable nanoemulsions. As mentioned earlier, nanoemulsions can be unstable due to factors such as coalescence, Ostwald ripening, and aggregation. Further research is needed to develop more stable nanoemulsions that are less likely to break down over time (Al Turki 2015; Al-otaibi 2021).

The identification of less toxic surfactants. Some surfactants used in nanoemulsions can be toxic. Further research is needed to identify less toxic surfactants that can be used to stabilize nanoemulsions.

The development of methods for targeting nanoemulsions to specific tissues or cells. This could be done by using targeting ligands or by developing new methods for controlling the release of drugs from nanoemulsions.

The evaluation of the efficacy and safety of nanoemulsions in clinical trials. This is essential to determine the optimal formulation and dosage of nanoemulsions for specific diseases.

Despite the challenges, the potential benefits of nanoemulsions for the delivery of insoluble medicines are

significant. Nanoemulsions have the potential to improve the solubility, bioavailability, stability, and targeting of poorly soluble drugs. This could lead to new and improved treatments for a wide range of diseases.

Conclusion

Nanoemulsions are distinctive nanocarriers for the transport of lipophilic components due to their ability to provide a more stable, bioavailable, easily manufactured, and tolerable formulation. By entrapping bioactive molecules in nanosized micelles, they offer effective protection against external impacts. Moreover, their traits, such as large surface area, stability, and variable rheology, can enhance drug absorption and mitigate the invasiveness and hazards of various therapies.

Recently, there has been growing interest in utilizing natural oils due to their proven intriguing qualities, including antibacterial, antioxidant, and anti-inflammatory capabilities. Both high-energy and low-energy emulsification techniques can produce nanoemulsions with small droplet sizes and stability.

However, there is still a considerable need for further research to scale up these processes and gain a comprehensive understanding of their impact on the size and stability of nanoemulsions. This reality explains the scarcity of commercial nanoemulsion-based products relative to the extensive research published in this field. There are still obstacles to be addressed before nanoemulsions can be widely adopted in the pharmaceutical industry.

In conclusion, the recent research in nanoemulsions has demonstrated significant advancements in formulation strategies, characterization techniques, targeted delivery, and enhanced bioavailability of poorly soluble drugs. Nanoemulsions offer great potential for overcoming the challenges associated with drug solubility and delivery, leading to improved therapeutic outcomes. Continued research and development in this field will pave the way for the translation of nanoemulsion-based drug delivery systems into clinical applications, benefiting patients by providing more efficient and patient-friendly treatment options.

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