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Review

Nanoemulsions: Factory for Food, Pharmaceutical and Cosmetics

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Abstract: Nanotechnology, particularly nanoemulsions (NEs), have gained increasing interest from researchers throughout the years. The small-sized droplet with a high surface area makes NEs important in many industries. In this review article, the components, properties, formation, and applications are summarized. The advantages and disadvantages are also described in this article. The formation of the nanosized emulsion can be divided into two types: high and low energy methods. In high energy methods, high-pressure homogenization, microfluidization, and ultrasonic emulsification are described thoroughly. Spontaneous emulsification, phase inversion temperature (PIT), phase inversion composition (PIC), and the less known D-phase emulsification (DPE) methods are emphasized in low energy methods. The applications of NEs are described in three main areas which are food, cosmetics, and drug delivery.

Keywords: nanoemulsions (NEs); oil-in-water; ultrasonication; homogenization; cosmetics; pharmaceutical

1. Introduction

A few decades back, nanotechnology has raised interest in many industries, mainly those related to food and pharmaceutical, to deliver drug and lipophilic substances such as flavors, colors, and fatty acids [1]. Nanoemulsions (NEs) have been extensively investigated throughout the years. NEs are systems that are not at equilibrium, either oil-in-water (O/W) or water-in-oil (W/O) emulsions that are nano-sized and have droplet diameters around 50 to 1000 nm [2]. However, another definition, more specifically, refers NEs only to disperse systems with less than 100 nm droplets [3]. To consider NEs as a stable isotropic system thermodynamically, two liquids that are not miscible are combined and a single phase is formed with the help of an emulsifying agent such as surfactants and cosurfactants as well as energy input either mechanically or physiochemically. The size and shape of the particles dispersed in a continuous phase are what differentiate the emulsion (1–20 μm) and NE size (10–200 nm) [4]. The long term stability can also show a clear distinction between emulsion and NEs. NEs can be prepared in three ways: (1) oil-in-water (O/W) NEs where oil is disseminated in a continuous aqueous phase; (2) water-in-oil (W/O) NEs where water is dispersed in a continuous oil phase; and (3) the bicontinuous phase. NEs have a variety of shapes as they can be seen as spherical swollen micelles or bicontinuous structures [5]. As the preparation of NEs plays an important role, this review will focus on how NEs are formed and the applications of NEs in the food, pharmaceutical, and cosmetics industries. This review will also cover their components and properties as well as the advantages and disadvantages of NEs.

2. Components of NEs (NEs)

NEs are colloidal dispersions made up of two phases, an oil phase and an aqueous phase, with the help of surfactant and cosurfactants at accurate proportions. The properties of the phases and surfactant contribute significantly to the performance of NEs.

2.1. Oil and Aqueous Phase

Variety of nonpolar molecules such as mineral and essential oils, free fatty acids (FFA), and other lipophilic nutraceuticals can be utilized as the oil phase for formulating NEs [5]. The formation, stability, and characteristics of NEs are dependent on the physical and chemical properties of the oil phase such as viscosity, water solubility, density, polarity, refractive index, and interfacial tension as well as chemical stability [6]. Table 1 shows successful NEs obtained using different oil and aqueous phases in the presence of surfactant(s).

Table 1. Nanoemulsions (NEs) formulation using different oil phases, aqueous phases and surfactants.

Nanoemulsions	Aqueous Phase	Surfactant/Co-Solvent	Ref.
NEs incorporating citral essential oil	Deionized water	Sorbitane trioleate Polyoxyethylene (10) Oleyl ether Ethylene glycol	[7]
Mangosteen extract in virgin coconut oil based NEs	Water	Tween 80 Span 80	[8]
NEs with *C. guianensis* Aublet (*Meliaceae*) oil	Water	Polysorbate 80 Sorbitan monooleate	[9]
NEs based vitamin E delivery systems	Water	Quillaja saponin Lecithin	[10]
Vitamin E-enriched NEs	Water	Tween 80	[11]
NEs based delivery systems for curcumin long, medium, short chain triglycerides	Deionized water	Lipase Bile extract	[12]
Neem oil (*Azadirachta indica*) NEs	Water	Tween 20	[13]

To formulate the aqueous phase, water can be mixed with a wide array of polar molecules, carbohydrates, proteins, and others. The formulation, stability, and physicochemical qualities of NEs are determined by the pH, ionic strength, polarity, density, rheology, refractive index, interfacial tension, and phase behavior of the aqueous phase, which depend on the concentration of the components used and their type [5].

2.2. Surfactants/Emulsifiers

Unlike emulsions micronized with external energy, thermodynamically stable NEs are formed by adding surfactants as it will promote low interfacial tension. When oil and water are mixed, a temporary emulsion will be formed. However, because of the coalescence of the dispersed globules, the mixture will be segregated into two different phases when left to stand [5]. Significant concentrations of emulsifiers and surfactants from generally regarded as safe (GRAS) agent components are incorporated into NEs. Examples of emulsifiers include phospholipids, small molecule surfactants, polysaccharides, and proteins. Destabilization processes like Oswald ripening could be avoided in NEs if surfactants are put together with oil and other components in a suitable ratio [14]. Typically, steric interactions increase the repulsive maximum due to the adsorbed layer of emulsifier on the droplet, which in turn stabilizes the emulsions against flocculation and coalescence. The steric stabilization is stronger in nanoemulsions and therefore, enables a stable system [15]. As time passes, coalescence in the droplets can follow varied behavior and may show homogenous growth where the average size of the droplet

increases with time, or more often result in early phase separation (heterogeneous growth). Coalescence is more common in microemulsions than nanoemulsions. Since the droplet size of nanoemulsions is very small, reversible aggregation of droplets does not take place. In deciding which surfactant is to be used in the NE formations, the hydrophile–lipophile balance (HLB) system can be utilized. In over five decades, the HLB system has been proven to determine the optimum surfactant needed to produce emulsions with desired characteristics (O/W or W/O) [16]. According to the system, high HLB values of above 10 indicate hydrophilic surfactants, while lipophilic surfactants have lower HLB values ranging from one to ten [17].

3. Properties

Many fascinating physical properties of NEs make them distinct from those larger microscale emulsions [18]. One of them is the transparent appearance of NEs, which is classified based on the droplet size. NEs are transparent in the range of 50 to 200 nm. However, they appear milky and cloudy at droplet sizes above 500 nm [18]. By adjusting the dispersed phase, volume fraction, and size of the droplet as well as the incorporation of salt and depletion agents, the rheological properties of NEs can be controlled. Another distinct quality of NEs when compared to macroemulsions is that they possess stronger elasticity, and this makes NEs stand out from a rheological point of view [7]. Droplet size and its distribution play important roles in the stability of the emulsions. Smaller droplet size and narrower size distributions of NEs might be the main reason contributing to its stability [19]. Emulsions might show exceptional stability in term of kinetics, but eventually, phase separation will occur in emulsions as they are not stable thermodynamically [20]. Among the measurements used to measure stability is viscosity. To evaluate the stability of NEs formulations, the change in viscosity can be observed and monitored. A Brookfield type rotary viscometer can be used to determine the viscosity of NEs of different compositions at different shear rates at several temperatures [20]. Owing to their small droplet size, NEs are stable against sedimentation or creaming. However, as there is electrostatic and steric stabilization, flocculation will occur, and in order to stabilize against this phenomenon, ionic and non-ionic ethoxylated surfactants are usually used [21].

4. Formation of NEs

As stated in the preceding section, NEs are very small in size, and by using equipment with high pressure, the tiny particles can be obtained. Currently, high and low energy emulsification methods can be utilized to fabricate NEs. Depending on the methods exploited, many types of emulsion systems comprising functional compounds have been prepared and investigated.

4.1. High Energy Emulsification Methods

Different mechanical methods such as high-pressure homogenization (HPH) or microfluidizers and ultrasonication have been applied in high energy emulsification to form intensive disruptive forces like collision, compression, and cavitation, which allows one phase to be dispersed into another as tiny droplets [22]. In high energy emulsification methods, the emulsion is produced by using mechanical equipment. Despite the efficacy of these high energy methods in decreasing the size of particles, they are very unlikely for thermolabile drugs and macromolecules such as proteins, enzymes, retinoids, peptides, and nucleic acids [23]. This is because high energy methods deal with high temperature and pressure, which could potentially damage thermolabile or sensitive drugs as well as proteins.

4.1.1. High-Pressure Homogenization

All in all, conventional high-pressure homogenizers employ pressures between 50 and 100 MPa. Nevertheless, with new technologies, an instrument utilizing pressures as high as 350 MPa has been developed recently [24]. In HPH, a small gap—usually with a gap height around 1 to 10 nm—causes the sudden pressure drop across HPH to reach a few thousand bars; the different phases composed of oil, water, and surfactant are forced into droplets and experience extreme shear and elongational

stress, leading the droplets to be disrupted into finer droplets. The mixture is typically passed many times through the homogenizer until the droplet size is approximately constant [25–27]. Due to many different factors, for example, turbulence, and elongational and shear stress as well as cavitation, the fluid-dynamic stresses in HPH become higher. These factors are superior than the others, depending on the equipment used, process fluid properties, droplet composition, and operating conditions [28]. The droplet size will keep reducing as the difference in pressure heightens, unless in the case of the occurrence of coalescence. In HPH, increasing the pressure difference or increasing the energy density will decrease the droplet diameter unless coalescence occurs. However, the disruption unit also gives impact to the droplet sizes as they influence the flow pattern, which will specify droplet breakup [29]. In the homogenization chamber, three flow patterns of disruption units can be found, as seen in Figure 1.

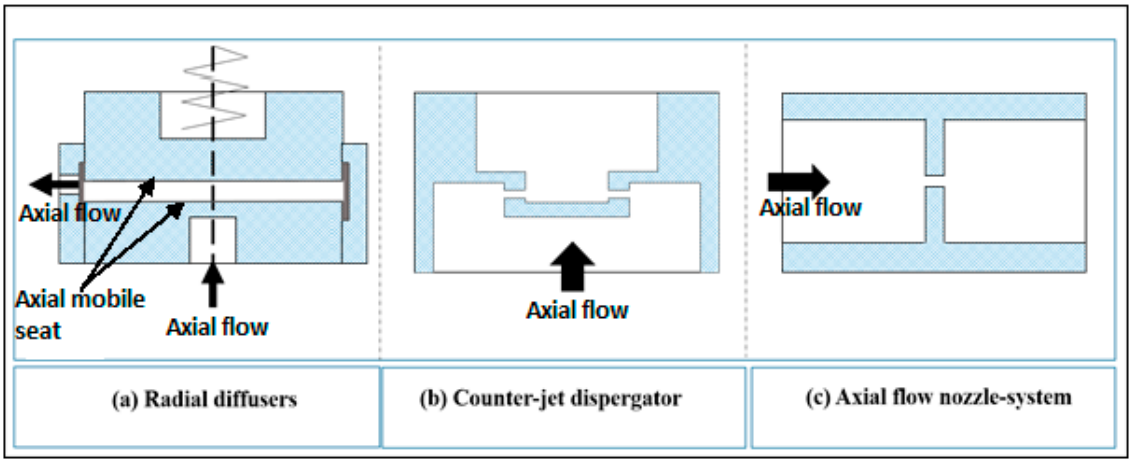

Figure 1. High-pressure homogenization (HPH) disruption units in (**a**) radial-diffusers; (**b**) counter-jet-dispergator: jet-dispergator; and (**c**) axial flow nozzle-system. Reproduced with permission from Gall et al. Processes; published by MDPI, 2016 [28].

Radial diffusers are comprised of an axially mobile seat that allows for variation in the flow rate by changing the slit width [26]. The counter-jet dispergator includes a collision area of two or more opposed jets of the emulsion. There are no movable parts for counter-jet dispergators or the axial flow-nozzle systems, which makes them suitable for very high pressures. Nozzle aggregates can be distinct by their axial flow direction. Simple orifices are normally made up of 0.1–2 mm diameter round holes. It has been proven that when the same energy density is used, different disruption units produce different droplet sizes. The most important advantages of HPH for industrial production is that it is scalable, easy to operate, efficient, and has high reproducibility [27]. In HPH, an emulsion is formed by controlling the variation of the emulsifier and how fast the rate of coating the newly produced interface in the homogenizer is. Hydrodynamic conditions within the break-up zone, the rate of energy dissipation, the viscosity of the two phases, and the residence time in the break-up zone determine the formation rate of the new interface [30]. There are two methods that can be used in HPH, which are the hot or cold HPH technique. Both techniques have their own advantages, but the cold HPH technique is used for extremely temperature-sensitive compounds [31]. In both techniques, the active compound is dissolved or dispersed in the melted lipid phase, but in the hot HPH technique, the mixture is dispersed into a hot surfactant solution above the melting point by high-speed stirring, whereas in the cold HPH technique, the combination of the active compound and lipid phase is cooled down, ground, and then dissolved into a cold surfactant solution so that a cold pre-suspension of micronized phase is formed [32]. Next, for both approaches, the pre-emulsion goes through HPH at high temperatures for the hot HPH technique or room temperature for the cold HPH technique to acquire the NEs. In order to obtain narrow size distribution of NEs, an additional factor can be taken into consideration. The higher the number of cycles of the emulsion in HPH, the droplets will encounter the peak shear rate generated

by a flow-producing device during emulsification to obtain low polydispersity NEs at some point [33]. Nevertheless, poor productivity and component deterioration due to the generation of much heat is the main disadvantage of HPH. Sharma et al. [34] stated that with this method, only O/W NEs with less than a 20% oil phase can be successfully obtained, while NEs with a high viscosity with sizes smaller than 200 nm cannot be prepared. The summary of the method is shown in Figure 2.

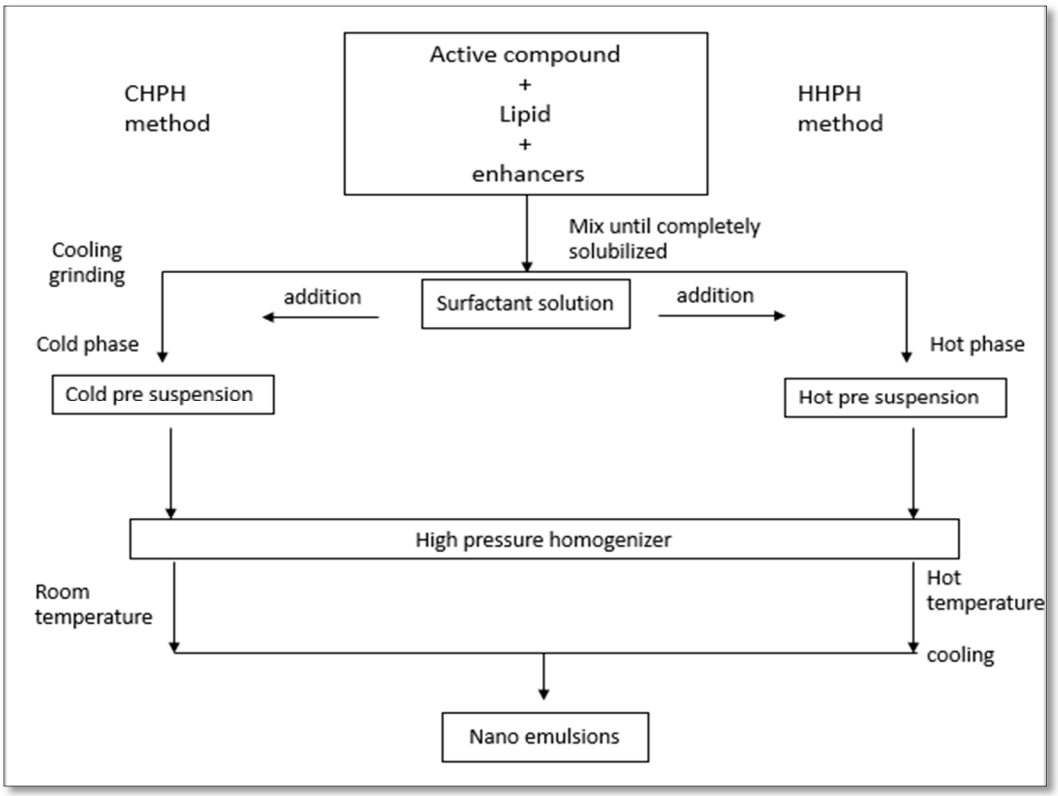

Figure 2. Summary of the NE production process using the cold and hot HPH techniques. This figure is modified & reproduced with permission from Pardeike et al. International Journal of Pharmaceutics; published by Elsevier, 2009, [32]. CHPH = cold high pressure homogenization method; HHPH = hot high pressure homogenization method.

4.1.2. Microfluidization

The microfluidization technique is a technology that utilizes a device called a 'microfluidizer', which also uses high pressure. This method forces the product through the interaction chamber with small channels called microchannels inside using a high-pressure positive displacement pump (500–200 psi). Then, the process follows on through the microchannels to an impingement area that forms tiny particles of the submicron range. The aqueous phase and oily phase are mixed and processed in an inline homogenizer to obtain coarse emulsion. Finally, to obtain stable, small-sized NEs, the coarse emulsion is further processed in the microfluidizer. This technique does not require pre-emulsification as the dispersed phase is injected directly into the continuous phase through micro channels and is known as the 'direct' emulsification technique. This is considered to be a big advantage over the HPH method [35]. From the mechanical point of view, the microfluidizer is a high-velocity version of a static mixer that has no moving parts [36]. The advantage of this method is that it can be applied at both a laboratory and industrial scale. The schematic of the microfluidizer is presented in Figure 3.

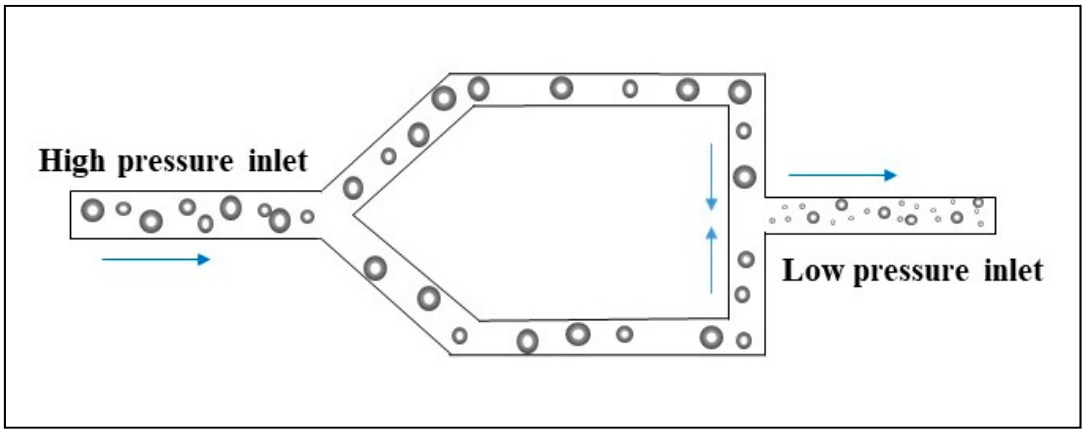

Figure 3. Schematic image of a high pressure microfluidizer.

4.1.3. Ultrasonic Emulsification

The ultrasonic emulsification method is proficient in minimizing the size of NEs. In ultrasonic emulsification, sonotrodes called a sonicator probe provide the energy to break down the particle size as it contains piezoelectric quartz crystal, which can expand and contract according to an alternating electric voltage. The tip of the sonicator probe forms mechanical vibration when it comes into contact with the liquid and this cause cavitation to occur. Cavitation is the formation and collapse of vapor cavities in liquid. Thus, emulsions can be produced directly using this method. It is mainly used in laboratories where an emulsion droplet size as low as 0.2 µm can be produced [37]. A two-step mechanism has been suggested for ultrasound emulsification: First, interfacial waves are produced in an acoustic field to break the dispersed phase into a continuous phase. Then, the formation of acoustic cavitation collapses micro-bubbles into smaller droplets through the pressure fluctuations. The formation of NEs droplets is controlled by the interaction between droplet break-up and droplet coalescence. Although ultrasound employs great shear force for droplet rupture, the rate of droplet coalescence is also dependent on the surface activity and concentration of the surfactant [38–42]. However, the disadvantage of this method is that only small batches of NEs can be prepared. Some studies have suggested the formation of surfactant-free stable and transparent NEs with ultrasonication such as that reported by Nakabayashi et al. [43] by using tandem acoustic emulsification.

4.1.4. Nanoparticles

There is a new interest in making nanoparticle stabilized nanoemulsions. A considerable number of nanoparticle formulation methods are based on NE templates, which in turn are generated in various ways. It must, therefore, be taken into account that the active principles and drugs encapsulated in nanoparticles can potentially be affected by these NE formulation processes [44]. Such potential differences may include drug sensitivity to temperature, high-shear devices, or even contact with organic solvents. Likewise, NE formulation processes must be chosen in light of the function of the selected therapeutic goals of the nano-carrier suspension and its administration route. This requires the nanoparticle formulation processes (and thus the NE formation methods) to be more adapted to the nature of the encapsulated drugs as well as to the chosen route of administration [45,46]. If the oil has the right properties and a sufficient concentration of nanoparticles, then water drops self-disperse within the oil. The nanoparticles then will self-assemble around them to form nanoemulsions [43]. Primo et al. prepared O/W nanoemulsions where the continuous phase consisted of suspended magnetic nanoparticles [47]. This work associated colloidal nanoparticles with biocompatible magnetic fluids, which resulted in a new drug delivery system (DDS) for application in photodynamic therapy (PDT) and magnetic hyperthermia treatment.

In addition, the different kinds or morphologies of the generated nanoparticles can be broken down into polymeric nanospheres, solid lipid nanoparticles (SLNs), or polymeric or lipid nanocapsules [21].

The links between NE formulation processes and nanoparticle morphology are neither obvious nor systematic, and should be tackled with particular detachment [48].

4.1.5. High Shear Mixers

High shear mixers have been widely used in energy intensive processes such as homogenization, dispersion, emulsification, grinding, dissolving, and cell disruption in the fields of agricultural and food manufacturing and chemical reaction processes. The mixers, which are also known as rotor stator mixers, high shear reactors, and high shear homogenizers, are characterized by their high rotor tip speeds (ranging from 10 to 50 m/s), highly localized energy dissipation rates near the mixing head, very high shear rates (ranging from 20,000 to 100,000 s^{-1}), and relatively higher power consumption than conventional mechanically stirred vessels, which are caused by the centrifugal forces generated from the relative motion between the rotor and the stator equipped with narrow spacing (ranging from 100 to 3000 nm) [49]. High shear mixers are available in both batch and inline configurations. Batch units will have radial or axial discharged types, while for inline high shear mixers, they have either a blade screen or a rotor stator teethed configuration. Batch high shear mixers can be used together with inline high shear mixers where the inline unit functions in a circulation loop downstream of a tank equipped with the batch unit. This can further improve the product quality and decrease the processing time. They consist of a rotor that turns at high speed within a stationary stator. When the rotor rotates, the substance or emulsion will continuously attract into the mixing head and will be ejected through the stationary stator in high velocity. The size of the droplets will decrease as the hydraulic shear mixes the emulsion faster [50].

4.2. Low Energy Emulsification Methods

Similar droplet sizes can be achieved while using both the low and high energy methods, which relies on the system and composition variables. However, it has also been claimed that high energy methods allow for the preparation of NEs with higher oil-to-surfactant ratios compared with low energy methods [51]. However, NEs with high oil-to-surfactant ratios prepared by low energy methods have also been reported. Low energy methods, unlike the high energy methods, are ruled by the behavior of the systems and intrinsic physicochemical properties. It follows therefore that high energy methods present natural predispositions to preserve the formation processes of NEs droplets, against even the smallest possible alterations of the formulation such as the incorporation of the initiator, surfactant, monomer, and others [51,52]. For certain commercial applications, the low energy technique is better because it has simple implementation and the use of expensive or sophisticated manufacturing equipment is not required, like those needed for high-energy homogenization. Low energy emulsification, known as the physicochemical approach, comprises of phase inversion temperature (PIT), phase inversion composition (PIC), spontaneous emulsification, and the less known D-phase emulsification (DPE) methods.

4.2.1. Phase Inversion Temperature Method

In the phase inversion temperature method (PIT), NEs are spontaneously formed by changing the temperature–time profile of the components, and prompt temperature changes hinder the occurrence of coalescence and thus, the formation of stable NEs. At room temperature, the combination of oil, water, and nonionic surfactant demonstrates a positive curvature. The impact of surfactant concentration on the formation and stability has been reported in previous work [53–56]. Furthermore, the PIT method is based on the alterations in the dispersity of polyoxyethylene-type nonionic surfactants with temperature. With increasing temperature, these kinds of surfactants will turn lipophilic due to the dehydration of the polyoxyethylene chains. At low temperatures, the surfactant monolayer has a large positive spontaneous curvature forming oil-swollen micellar solution phases (or O/W microemulsions), which may coexist with an excess oil phase. At high temperatures, the spontaneous curvature becomes negative and water-swollen reverse micelles (or W/O microemulsions) coexist with

an excessive amount of the water phase. At intermediate temperatures, the hydrophile–lipophile balance (HLB) temperature and the spontaneous curvature tend to be zero and a bi-continuous, D phase microemulsion containing comparable amounts of water and oil phases that coexist with both excess water and oil phases is formed [57,58]. In a research conducted by Astaraki [58], the production of NEs of *n*-dodecane in water using PIT, and the impact of the adjustments in NaCl and surfactant concentration on PIT and droplet size of *n*-dodecane was studied. Raising the NaCl concentration and using Brij30 as the surfactant caused a decrease in PIT. Additionally, the author found that the effect of the changes in concentration variation of the surfactant (Brij30) on the reduction in PIT and droplet size was more than that in the concentration of NaCl in the aqueous phase. In one study involving PIT, either the temperature or composition induced the inversion point and the surfactant phase structure (bi-continuous microemulsion or lamellar) affecting the size of the droplets [47]. Studies on NE formation by the PIT method have revealed a relationship between the minimum droplet size and complete solubilization of the oil in a microemulsion bi-continuous phase, independently of whether the initial phase equilibria were single or multiphase. The PIT method using nonionic surfactants and hexadecane or isohexadecane as oil component to produce NEs has also been investigated [57]. At 20 wt% of the oil and surfactant concentrations between 4 and 8 wt%, successful NEs with a droplet size in the range 30–130 nm were produced. With the increase in surfactant concentration, the NE droplet size and polydispersity index were reduced, which could be attributed to the rise in the interfacial area and the reduction in interfacial tension.

However, the PIT method cannot be applied when ionic surfactants are used as the temperature will not modify the spontaneous curvature of these systems. The PIT emulsification method utilizes extremely low interfacial tensions (102–105 mNm^{-1}) to promote the emulsification process [59].

4.2.2. Phase Inversion Composition Method

The relatively easy formation and low energy costs have given the phase inversion composition (PIC) method the great potential for scale-up applications. Furthermore, this process is more suitable for the emulsification of short-chain alkanes prepared at 25 °C. When the PIC method is employed, a phase inversion occurs when the continuous phase is slowly mixed over the component that will create the dispersed phase [60]. In order to obtain small and uniform droplets, both phases need to cross the emulsification path, a zone where a liquid crystal (lamellar or cubic) or bi-continuous phase exists. Therefore, the dispersed phase is intimately mixed with the continuous one and, when an additional continuous phase is added to reach the final composition of the NE, a reorganization of the dispersed phase into small droplets is likely [61]. In the phase inversion method (PIC), chemical energy from the reaction of the components forms a fine dispersion, resulting from the phase transitions produced by the emulsification pathway. The phase transition is produced by varying the composition of the emulsion and keeping the temperature constant or vice versa. The phase inversion temperature was first reported by Shinoda et al. [62]. It was concluded that the increase in temperature results in the chemical changes of polyoxyethylene surfactants through the degradation of the polymer chain with temperature [63]. When the components of the continuous phase are gradually added to the dispersed phase, the water volume fraction will be raised in nanoemulsification by the PIC. Phase inversion will occur and the bi-continuous phase will take place [35]. Probably, the intermediate bicontinuous structure favors the trapping of one phase into the other, leading to the formation of droplets in droplets inclusion. [64].

Maestro et al. [65] investigated the effect of the PIC in the formation of O/W NEs in the W/oleylammonium chloride-oleylamine-$C_{12}E_{10}$/hexadecane ionic system. They showed that it was necessary to cross the direct cubic liquid crystal phase along the emulsification path. The study also showed that to obtain small sized NEs, it was important to apply an appropriate stirring rate and to stay in this phase with sufficient time to mix all of the oil into the liquid crystal. A comparison of a cationic surfactant (oleylammonium chloride) with an anionic surfactant was also investigated in their work. When emulsions form, nanoemulsification is easier because the oil has been thoroughly

combined with all of the components. Structural studies made with both cationic and anionic systems confirmed that the size of the "micelles" that form the cubic phase was the same or slightly smaller than the size of the NEs droplets obtained, depending on the emulsification path, which seems to suggest that the NEs are formed in both cases by a dilution process of this cubic phase. In the PIC, the process would have extended the preparation time rather than the one implied in spontaneous emulsification techniques because even though spontaneous, the driving forces are less [66]. Other than that, to produce NEs, the PIC is more difficult as it needs to cool a larger volume of sample in a big tank compared to the PIT, which has a quicker cooling process as the volume is small and only uses test tubes soaked in ice [61]. Additionally, with the PIC, conditions such as mixing and the additional rate should be taken into account to ensure sufficient transition of phases, irrespective of the scale. For instance, the geometric ratio and form factor should be held constant when using larger sizes. In this method, it is also presumed that the fluid characteristics, for example, diffusivities, density, and viscosity will be kept constant. If the two systems (small and big hatches) are geometrically the same under these conditions, regardless of the scale, they can be described by a dimensional relationship [67]. Still, PIC nanoemulsification has a few potential advantages including low costs and the simplicity of apparatus [68]. The smallest size of the droplets (30 nm) has been produced using this technique [69]. The PIC method is presented in Figure 4.

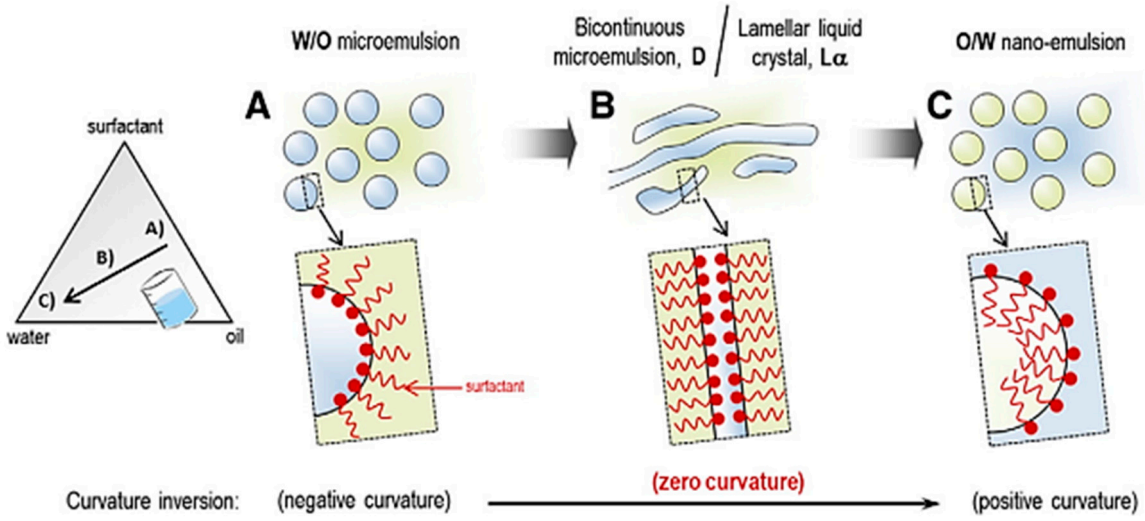

Figure 4. Schematic representation of the production of NEs by the Phase Inversion Composition (PIC) method. Reproduced with permission from Solans & Solé, Current Opinion in Colloid & Interface Science; published by Elsevier, 2012 [70].

4.2.3. Spontaneous Emulsification

Spontaneous emulsification is another method in which nano-sized emulsion can be obtained. The chemical composition of both the oil and aqueous phases and the help of surfactants is really important in this technique [19]. Three stages are involved in this method, namely, (1) a homogeneous lipid phase consisting of oil and a lipophilic surfactant and another phase of a water-miscible solvent and hydrophilic surfactant were prepared; (2) the O/W emulsion is formed when the lipid phase is injected in the aqueous phase under nonstop magnetic stirring; and finally, (3) evaporation under reduced pressure is employed to remove the aqueous phase [24]. Small droplets of dispersed phase covered with surfactant in the continuous phase will occur because of the high affinity of the surfactant to the oil or the aqueous phase causes turbulence at the interface of both the dispersed phase and continuous phase as well as whether the surfactant is displaced toward the continuous phase. To produce very small emulsions, the turbulence at the interface of the two phases should be triggered and cosurfactants such as ethanol, acetone, and propylene glycol can be a great help. In these cases, the organic phase will

contain oil, a surfactant, and a cosurfactant while the aqueous phase consists of water. The influence of many factors such as level, type, structure of the surfactant and cosurfactant, amount of surfactant to the dispersed phase, additive or nutritive constituents in the dispersed phase, level and type of the two phases and encapsulant, and the viscosity of the dispersed and continuous phases will affect the droplet size. To form NEs using this method, chemical energy released due to the dilution process with a continuous phase is used, usually at a constant temperature without any phase transitions (no change in the spontaneous surfactant curvature) in the system during emulsification [70]. A nanoemulsion will be obtained by the dilution of the microemulsion with water. From the oil/water interface, the cosurfactant (alcohol) diffuses to the water phase, which will disturb the formation of the microemulsion and make it thermodynamically unstable, thus forming NEs [71]. The schematic diagram is presented in Figure 5.

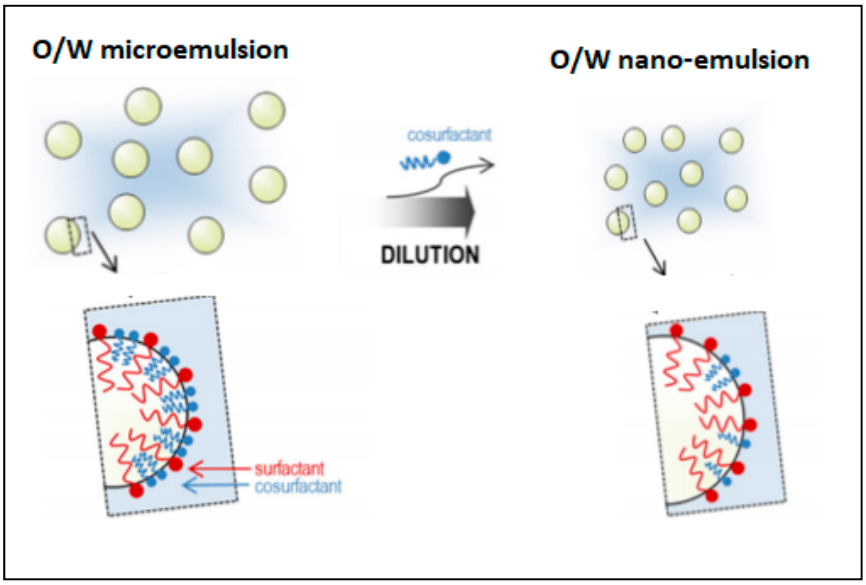

Figure 5. Schematic representation of the self-emulsification method by the dilution of an O/W microemulsion. Reproduced with permission from Solans & Solé, Current Opinion in Colloid & Interface Science; published by Elsevier, 2012 [70].

In the food and pharmaceutical industries, high levels of surfactant sand cosurfactants are not allowed due to regulatory, cost, and sensory reasons. Some studies have been undertaken to decrease the quantity of cosurfactants as well as in reducing the surfactant to dispersed phase ratio [12,59] by using the spontaneous emulsification method. This technique has been widely applied within the pharmaceutical industry, where it is used to form drug delivery systems to encapsulate and deliver lipophilic drugs [60]. However, there are definitely some utilizations in which this approach may be useful, for example, mixing small amounts of bioactive lipophilic components into beverages [72]. Spontaneous emulsification is very advantageous in encapsulating bioactive compounds in the food and pharmaceutical industries [73] and has several benefits over high energy and other low energy methods such as shielding sensitive compounds against the severe conditions of the high energy method, especially temperature and pressure, and its capability to reduce surfactants [74], better thermal stability, and the withdrawal of cosurfactants if compared with other low energy techniques [11,75].

4.2.4. Solvent Displacement Method

The solvent displacement technique is also known as the nanoprecipitation method. This method is based on the interfacial deposition of polymeric nanoparticles after the displacement of a semi-polar solvent that is miscible with water from a lipophilic solution [76]. Polymeric nanoparticles can be obtained from nanoemulsions either by in situ monomer polymerization in the dispersed phase or using a preformed polymer (dissolved in a volatile organic solvent) as the dispersed phase of the nanoemulsion, followed by solvent evaporation [77]. The production of small-sized NEs even in the absence of mechanical stirring is mainly caused by the rapid diffusion of the solvent into the aqueous phase where interfacial tension between the two phases is reduced and the surface area is increased. This is governed by the Marangoni effect, which is defined as mass transfer along an interface between two fluids due to a gradient of the surface tension. [23]. However, it has poor entrapment of hydrophilic drugs. This can be explained as oil has a hydrophobic core and a hydrophilic surface, where the hydrophobic core promotes the entrapment of the drug. Therefore, it enables the solubilization of water-insoluble drugs [78]. An improved solvent displacement approach has been established by using poly (D, L-lactide-co-glycolide) (PLGA) nanoparticles, which includes various approaches to improve the incorporation efficiency of highly water-miscible drugs such as by varying the pH of the aqueous phase and alterations in the drug salt form. Altering the pH of the aqueous phase results in changing the ionization form of the drug components, which in turn changes the charges of the molecule, thus leading to better solubilization. The organic solvent is eliminated from the NEs through appropriate methods such as vacuum evaporation. This method can produce NEs using only simple stirring at room temperature and is used for parenteral preparation. However, the drawback of this method is that it produces small-sized emulsions of the dispersal phase, where this method acquired a large ratio of solvent and oil. Nevertheless, for the preparation of monodisperse, small-sized polymeric nanoparticles, this technique is a totally convenient, reproducible, fast, and economic one-step manufacturing process [79]. Table 2 summarizes the different methods of formulating NEs in both high and low energy methods, while Table 3 shows the formation of NEs and their applications in industry.

Table 2. The different methods of NEs formulation based on low and high energy methods.

No.	Method of Formulation	Emulsifiers	Condition	Results and Main Findings	Ref.
1	High pressure homogenizer	Tween 80, Tween 60, Tween 40, Tween 20	Diameters dispersed particles: 132–184 nm, Size distribution: 40–400 nm, - Constant: 50 °C, 100 MPa (first stage), 10 MPa (second stage), 3 cycles. concentration: 4%–12%, - Constant: Tween 20, concentration: 10%, temperature: 30–70 °C, first stage pressure: 60–140 MPa, second stage pressure: 6–14 MPa.	Smallest particle sizes and narrowest size distribution: Tween 20 - Particle sizes ↓: ↑ Pressure, cycle, temperature. - Physical stability ↓: ↓ temperature. - Physical stability ↑: ↑ pressure, cycle. - Degradation during storage.	[80]
2	High-pressure homogenizer	SDS, Tween 20, *β*-lactoglobulin, Sodium caseinate	- Oil phase: 5 wt% (corn oil/octadecane) with 95 wt% - Aqueous phase: emulsifier (1–10 wt%), glycerol (0–50 wt%), sodium phosphate (10 mM), sample-to-buffer: 1:100, pH: 7, 2 min pressures: 4–14 kbar	Smaller droplet sizes: Tween 20, SDS (d~60 nm). - Mean particle diameter ↓: ↑ Pressure, passes number.	[81]
3	High pressure homogenizer, Microfluidizer	SDS, Tween 20, Sodium caseinate	Oil-in-water produced 10 wt% silicone oil with 90 wt% aqueous phase: (3 wt% Tween 20 and 0–50 wt% glycerol).	Droplet sizes, after 1st pass: microfluidizer < homogenizer, droplet sizes, after repeated pass: homogenizer < microfluidizer. - ↑ Viscosity: ↑ droplet size due to greater resistance to deformation	[82]
4	High pressure homogenizer	Tween 80 (1% *v*/*v*)	Temperature: 20 °C Pressure: 50, 100, 150 MPa	Smaller droplet sizes: 6 nm, at 150 MPa, 10 cycles. - ↑ Pressure & cycles: ↓ droplet size, viscosity, whiteness index.	[83]
5	Ultrasonication	Tween 80	Oil concentration: 6% *v*/*v*, Oil: surfactant ratio: 1:1, 1:2, 1:3, 1:4 *v*/*v* 20 kHz, 750 W, T < 10 °C probe diameter: 13 mm	Smaller droplet sizes: 29.3 ± 0.2 nm at emulsion concentration: 1:4 *v*/*v*. ↓ droplet size: ↓ time, ↑ emulsion concentration.	[56]
6	Ultrasonication	Tween 80	Oil concentration: 16.66%, Water: 66.68% *v*/*v*, 250 rpm, 20 kHz, 750 W, time: 0, 5, 10, 15, 20, 25, 30 min	Smaller droplet sizes: 3.8 nm at 30 min. ↓ droplet size: ↑ time.	[84]
7	Ultrasonication	Sorbitane trioleate + polyoxyethylene	Oil concentration: 10 wt%, co-surfactant: 1%, Oil: surfactant ratio: 0.26–0.94, 20 kHz, diameter: 20 mm, 20 °C, 100–140 s	Smaller droplet sizes: <100 nm, 0.6–0.7 at 18 W, 120 s.	[85]

Table 2. *Cont.*

No.	Method of Formulation	Emulsifiers	Condition	Results and Main Findings	Ref.
8	Phase inversion composition (PIC)	POP(D230-2OA)	20 °C, 30 min, 300 rpm	Smaller droplet sizes: ≈37 nm at D230-2OA concentration: 7.89 wt%. - ↓ droplet radius, ↓ droplet size distribution: ↑ D230-2OA concentration. - ↓ PIT: with ↑ NaCl Concentration. - ↑ NaCl concentration: initial droplet radius↓ . - ↑ NaCl concentration: ↓ electrostatic repulsion	[86]
9	Phase inversion composition (PIC)	Oleylamine chloride, Potassium oleate, Oleic acid.	25 ∘C, 750 rpm, water: 80% w/w, O/S ratios: 30/70-60/40. Oleylamine/C12E10 ratios: 20/80, 30/70, 40/60, 50/50.	- Smaller droplet size: smaller O/S ratio, due to high concentrations of surfactant permit stabilization of more surface, smaller droplets can be formed.	[65]
10	Phase inversion composition (PIC)	Span20, Tween 20, $C_{12}E_4$, $C_{18}E_{10}$.	$C_{12}E_4$–$C_{18}E_{10}$ (50/50 wt. ratio)/isopropyl myristate (oil/surfactant ratio, OS = 1.10)/water (80 wt%). - Tween20–Span20 (42.8/51.8 wt. ratio)/paraffin (OS = 2)/water (70 wt%). - Potassium oleate–oleic acid–$C_{12}E_{10}$ (oleic acid/$C_{12}E_{10}$ ratio = 0.6)/hexadecane (OS = 1.3)/water (80 wt%).	Smaller droplets size: at 600 mL vessel. Smaller droplets: low addition rates imply long addition times. the stated requirement for a proper NEs formation through a low energy method is achieved when oil is incorporated more into this phase with the help of long times to reach equilibrium in the viscous zone.	[61]
11	Phase inversion temperature (PIT)	$\overline{C}12\overline{E}4$, $\overline{C}12\overline{E}6$	Oil concentration: 20 wt%, isohexadecane concentration: 20 wt%, surfactant concentration: 4 wt%, 8 wt%, 25 °C.	Smaller droplets size: 25–32 nm at XC12E6 (8 wt%). - Droplet size increased with time. - ↓ HLB temperature: ↑ surfactant concentration.	[24]
12	Phase inversion temperature (PIT)	POP (D230, D400)	- Aqueous phase: tetradecane/POP (0.78 wt%) + NaCl (50 mM). Surfactant concentration: 4.76, 6.04, 7.89 wt%, POP unit: 2.5, 6.1, 300 rpm, 20 min	Droplet radii: 20–300 nm Small droplet size: changing surfactant concentration, NaCl concentration, the number of POP units surfactant, and the degree of unsaturation of hydrocarbon chain in POP surfactant. - Hydration of the short POP chains affected the temperature	[86]
13	Phase inversion temperature (PIT)	Brij30	- Organic phase: *n*-dodecane (20 wt%) + Brij30 (4 wt%, 8 wt%) - Aqueous phases: NaCl (0.01, 0.05, 0.10, 0.25, 0.50, 1.00 M), 15 °C	Smaller droplet sizes: 8.6–14 nm. ↓ PIT: ↑ NaCl concentration and surfactant. - ↑ T: ↓ emulsion conductivity.	[58]

Table 2. *Cont.*

No.	Method of Formulation	Emulsifiers	Condition	Results and Main Findings	Ref.
14	Spontaneous emulsification	Span 80, PGPR	Water content: 10 wt%, crocin solution: 0.1%, surfactant content: 10 wt% (SWR = 100%), oil content: 80 wt%, stirring: 700 rpm	- Smaller droplet sizes: PGPR. - PGPR stable for a long time Droplet size, ↑ encapsulant concentration: ↓ PGPR and ↑ Span 80. ↓ droplet size: due to ↑ surfactant adsorption density and ↑ crocin hydrophobicity causes shrinkage in water droplets.	[19]
15	Spontaneous emulsification	Span 80, Span 85, Lipoid S75 Tween 20, Tween 80, Pluronic F68	-Organic phase: oil (400 mg, Miglyol 812, Myritol 318, hexyl laurate or α - tocopherol), lipophilic surfactant (86 mg). - Aqueous phase: water (80 mL), hydrophilic surfactant (136 mg). 25 °C, stirring: 30 min, evaporation: 45 min, water-miscible solvent: acetone	- Smallest droplets size: 171 ± 2 nm, at: Lipoid S75, Pluronic F68, α-tocopherol/acetone, EtAc-acetone, MEK-acetone mixtures at 15/85 and 30/70% (v/v): acetone replacement. ↓ droplet size: ↑ viscosity, ↑ concentration aqueous and organic phase	[74]
16	Spontaneous emulsification	Tween 20, Tween 40, Tween 60, Tween 80, Tween 85.	- Organic phase: oil (10 wt%, (MCT + VE)), surfactant (10 wt%). - Aqueous phase: 80 wt%, pH 3.0, 0.8% citric acid, 0.08% sodium benzoate. stirrer: 500 rpm 25 °C.	- Smallest droplets size: 55 nm, Tween 80, at: PDI≈0.12, VE: 8%, MCT: 2%, SER: 10 wt%. - ↓ Smaller droplet: ↑ temperature, ↑ stirring speed. - ↓ Smaller droplet: ↑ temperature, ↓ viscosity, ↑ solubility.	[11]

↓ means decrease while ↑ means increase.

Table 3. The formation of NEs and their applications in industry.

No.	Formulation	Limitations	Technique of Preparation	Characterization	Application	Ref.
1	Lemon myrtle and anise myrtle essential oil in water NEs	Hydrophobic nature	Ultrasonication	Particle size and PDI Turbidity Density Stability Antibacterial activity	NEs showed enhanced antibacterial activity and stability	[87]
2	Formation of NEs containing Ibuprofen	Slightly soluble in water Poor flow and compaction	Phase inversion composition method	Size and PDI Zeta potential Stability Permeation of ibuprofen	Good stability and possible to use in topical application	[88]
3	NEs incorporating citral essential oil	unstable and hydrophobic under normal storage conditions, thus can easily lose its bactericide activity	Ultrasonication	Droplet size Encapsulation ratio Transmission electron microscopy Stability Antimicrobial activity	Can be used in the antimicrobials activity in the agrochemicals, cosmetics, and pharmaceutical industries.	[7]
4	NEs of coenzyme Q10	Poor bioavailability within skin membrane	Sonication	Particle size Zeta potential Stability Encapsulation efficiency Human skin cell behavior	Can be used in topical application	[89]
5	NE-based formulation for topical delivery of heparinoid	Hydrophilic nature. Difficult to penetrate skin stratum corneum	High-pressure homogenization	Droplet size Morphology Viscosity In vitro permeation Skin resistance evaluation	Formulations represent a potential strategy for providing a localized therapy for the treatment of superficial thrombophlebitis	[90]
6	Phenytoin-loaded alkyd NEs	Water-insoluble	Phase inversion method	Size and PDI Loading efficiency Effect on cell viability Effect on cell proliferation	Possible for topical wound healing application	[91]
7	NEs encapsulating curcumin	Curcumin is the least stable bioactive component of turmeric (*Curcuma longa*) plant	Ultrasonication	Particle size Encapsulation efficiency Zeta potential	An effective delivery system for curcumin in functional foods	[92]

Table 3. *Cont.*

No.	Formulation	Limitations	Technique of Preparation	Characterization	Application	Ref.
8	Formulation of oil-in-water (O/W) NEs of wheat bran oil	Poor solubility in water systems	Ultrasonication	Droplet size Stability Antioxidant Anti tyrosinase activity	Suitable for use in the food industry	[93]
9	O/W NEs containing sweet fennel essential oil	Hydrophobic nature	High-pressure homogenization	Size and PDI Viscosity Antioxidant activity Stability	Application of sweet fennel oil NEs as a potential candidate for antioxidant topical formulations.	[94]
10	Neem oil (*Azadirachta indica*) NEs	Hydrophobic	Ultrasonication	Size and PDI Transmission electron microscopy Viscosity pH stability Zeta potential	Effective larvicidal agent.	[13]

5. Advantages and Disadvantages

There are considerable advantages of NEs. The size of NEs makes it suitable for drug delivery as it has a larger surface area, which could improve the absorption of drugs through many routes [85]. A large surface area also affects the transport properties of the drug, which is an important factor in sustained and targeted drug delivery [95]. In addition, given their small size, NEs are generally more stable than conventional emulsions because reduction under gravitational pull can be avoided to a large extent. Thus, no creaming and sedimentation have been associated with NEs, which means longer shelf storage can be achieved [96]. There are many ways to produce NEs and some methods require little or no energy (heat or mixing) at all, with the help of a surfactant in their formulations. However, there are also methods that need mechanical devices to break the droplets into a smaller size. This shows that NEs are versatile and can be tailor-made accordingly. Other than that, NEs have been used to help in solubilizing lipophilic drugs and in covering the unpleasant taste of the drugs. NEs are a promising way to deliver fish oil into liquid food systems with the abilities to protect the oil from oxidation, increase oral bioavailability, and mask undesirable off-tastes [97]. A study by [97] showed that NEs could improve vitamin D bioavailability in mice. Another study by [98] proved that the oral bioavailability of poorly soluble drugs could be improved with NEs. NEs are not considered to be toxic as the components in NEs are basically water, oil, and surfactant. The surfactant used in the NEs has been approved as safe for human consumption. Therefore, it is less likely to cause irritants to human. Furthermore, NEs require a lower concentration of the surfactant when compared to microemulsions. NEs have been said to be the best substitutes for less stable liposomes. Due to their lipophilic interior, NEs are more suitable for the transport of lipophilic compounds than liposomes. Similar to liposomes, they support the skin penetration of active ingredients and thus increase their concentration in the skin. NEs can be used as a delivery system for many types of drugs with wide physical properties and chemical structures. Additionally, NEs have a variety of applications in diverse areas such as food, drug delivery, cosmetics, pharmaceuticals, and material synthesis [86,87]. Table 4 summarizes the advantages of NEs when compared to other delivery systems.

Table 4. Advantages of NEs.

No.	Advantages	Ref.
1	Small sized droplets of NEs having larger surface area thus, enhancing absorption.	[99]
2	Less energy required to produce NEs.	[99]
3	Aids in solubilizing lipophilic drugs and covers the terrible flavor of the drugs.	[60,100]
4	Considered not toxic and not causing irritant in nature.	[37]
5	The stability of chemically unstable compounds can be improved by NEs as it can defend them from oxidative and light degradation.	[101]
6	Various formulations of NEs can be formed (e.g., creams, liquids, and sprays)	[100]
7	May substitute liposomes and vesicles	[74]
8	Improves the bioavailability of a drug	[60,102]

Even though NEs offer a great number of advantages to the technology, the system still has some major limitations. Table 5 summarizes the disadvantages of NEs.

Table 5. Disadvantages of NEs.

No.	Disadvantages	Ref.
1.	To stabilize the nanodroplets, NEs need support of high concentration of surfactant and cosurfactant	[102]
2.	Capability to solubilize high-melting substances is limited.	[100]
3.	Environmental parameters such as temperature and pH could influence the stability of NEs.	[63]
4.	For utilization in pharmaceutical applications, surfactant used must be non-toxic	[63]

6. Application of NEs in Industry

6.1. Food Industry

The utilization of NEs in the food industry is leading to promising changes, especially in covering the disgusting and unpleasant tastes or smells of some bioactive elements, the prolonged stability of food ingredients, and enhancing the digestibility of food. The bioavailability of certain components could also be increased and the evaporation of food smells as well as air-induced food degradation could be decreased with the help of NEs [103].

The digestibility quality of food and natural extracts could also be enhanced by using NEs. Food digestibility is a determination of the amount of food absorbed by the gastrointestinal tract into the bloodstream. β-carotene flavored NEs with improved digestibility have been utilized [90]. Other than that, formulations of NEs have heightened the solubilization of lycopene, a type of carotenoid pigment, and phytochemicals that can be found in red-colored fruits and vegetables.

NE formulation is considered as a functional behavior for foodstuffs because of their increased surface area and small droplet size. As above-mentioned, in order to remain stable during processing and storage, an emulsifier is needed in the formation of NEs [104]. NEs can be produced using different emulsifiers that act in antimicrobial preservation, thus improving food safety. Recently, the exploration of biosurfactants for emulsification has gained interest among researchers as there is high demand for chemical-free and organic produce in food. Saponin has been extracted from the fruit pericarp of *Sapindus mukorossi*. Successful NEs of basil oil have been formulated using a biosurfactant from an aqueous extract of *S. mukorossi* (0.4%) through ultrasonication to produce small droplet sizes of 37.7 and 57.6 nm. The NEs at 1000 ppm possessed antimicrobial activity against *Penicillium chrysogenum* and *Aspergillus flavus*, which are considered as common food spoilage fungi [105]. Quillaja saponins (QS) have also been used to stabilize avocado oil-based NEs [91]. Increased thermal stability has been displayed with the incorporation of QS in NEs, which is an advantage to be used in the development of pasteurized and sterilized emulsion-based food products [104]. In addition, essential oils have been receiving great interest from the food industry [106] due to their natural antioxidant and antimicrobial properties. However, the disadvantages of essential oil are their high volatility, hydrophobic nature, and high reactivity with other components in the food, which cause a loss of functionality and this, in turn, limits their use in the food industry [107]. Therefore, nanoencapsulation is one way to achieve the stability of these essential oils in food application, namely NEs because they have the capability to improve the antimicrobial activity of the essential oils, have high compatibility with food, and great physical stability [108]. The limitation of essential oils in food is attributed to their low water solubility, hence NE formation is an important approach to overcome this challenge. The delivery systems of essential oils loaded in NEs in food offers many advantages with regard to the effects of essential oils on natural action, physicochemical equilibrium, and product behavior [95]. For instance, to effectively utilize the antimicrobial activity of linalool, the active component of essential oils of several plant species like coriander, rosewood, and cinnamon, it was encapsulated into NEs. The size of the stable NEs droplet was 10.9 ± 0.1 nm in diameter. The linalool NEs showed two-fold improved antibacterial activity against *Salmonella typhimurium* through their enhanced ability to break the cell membrane. Moreover, compared to pure linalool (without NEs), the linalool NEs effectively displayed an 11.5% higher antibiofilm activity. NEs have also efficiently decreased the *S. typhimurium* biofilm on the surface of cut pineapple. Moreover, the sensory analysis presented the acceptance of fresh-cut pineapple with linalool NEs treatment [109]. A NE-based edible sodium caseinate coating containing 3 wt% and 6 wt% ginger essential oil (GEO) was used to prolong the shelf life of chicken breast fillet. The active coatings possessed antibacterial potential. NEs based edible coatings with 6% of GEO NEs reduced the total aerobic psychrophilic bacteria of refrigerated chicken fillets for 12 days [110]. Bhargava et al. [111] studied the application of oregano oil-NEs and their result suggested the application of oregano oil-NEs to fresh produce as a beneficial antimicrobial control strategy, the data of which is shown in Figure 6.

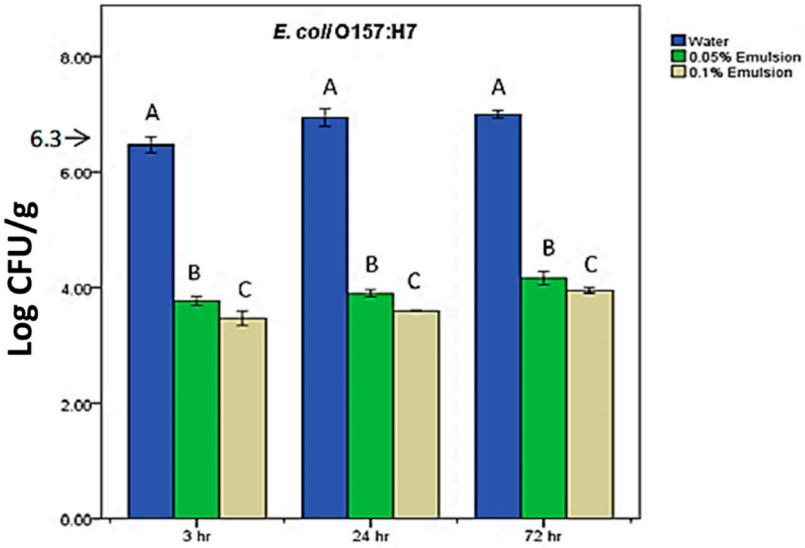

Figure 6. Inhibition of *Escherichia coli* on fresh lettuce by oregano oil NEs. Reproduced with permission from Noori et al. Food Control, Published by Elsevier, 2018 [110].

The potential implementation of NEs in improving food digestibility has been reported [100] for easier digestion with NEs when was curcumin incorporated in the oil phase was compared to when the curcumin was consumed directly, due to the easy lipid digestion step in NEs. Golfomitsou et al. [112] developed oil-in-water (O/W) edible NEs as carriers of vitamin D (D3: cholecalciferol) using polysorbate 20, soybean lecithin and their mixtures as emulsifiers, then used the developed NEs for the fortification of dairy emulsions, with droplets size of <200 nm. Vitamin D3 with different concentrations (0.1 to 0.5 μg/mL) was encapsulated in the oil cores of the NEs. Whole-fat milk was intensified with the vitamin-enriched NEs and maintained stable for at least ten days. The NEs also displayed antiradical properties [112]. Vitamin D3 has also been encapsulated in NEs using Kolliphor, CCTG (caprylic-/capric triglyceride), and the aqueous phase (sodium chloride solution), respectively [113]. The sensory evaluation indicated the suitability of the developed NEs for the fortification of beverages [113]. Borba et al. [114] formulated β-carotene NEs with corn oil by applying high-pressure homogenization, with an average size of around 300 nm. The β-carotene-NEs were treated and stored at three different temperature in two conditions: with and without the presence of light for up to 90 days. The results displayed no physical destabilization occurred, retaining around 70% to 80% of the carotenoid even after pasteurization and sterilization processes [114]. NEs have been suggested as a carrier of Brazilian propolis extracts for use as a natural food preservative as the extracts showed good antibacterial and antioxidant activities. From the results obtained, the NEs successfully developed by the phase inversion method can be used as a food preservative, thus avoiding degradation and covering the unpleasant flavor of propolis [115]. Furthermore, the applications of NEs in the food industry are presented in Table 6.

Table 6. Recent applications of NEs in food industry.

No.	NEs*; Type	Method of Fabrication	Size (nm)	Key Features	Application	Ref.
1	beeswax–starch (BW-S)-NEs; O/W*	Microfluidization with Tween-80	77.6 ± 6.2	Antifungal activity against *R. stolonifer*, *C. gloeosporioides*, and *B. cinerea*, and the pathogenic bacterium *S. Saintpaul*	Edible coatings to preserve fresh food products.	[116]
2	Jujube gum (JG)-based-NEs containing nettle essential oil (NEO): O/W	Homogenization with Tween-40	63.1 ± 6.2	3.5% NEO and 12% JG showed the best antimicrobial activity.	Jujube gum edible coating for Beluga sturgeon fillets.	[117]
3	Ginger essential oil (GEO)-NEs; O/W	Ultrasonication with Tween-80	57.4 ± 2.7	Antimicrobial activity against two food pathogens: *Listeria monocytogenes, Salmonella typhimurium*	Edible coating for chicken breast fillet	[110]
4	linalool NEs; O/W	Ultrasonication with Tween-80	10.9 ± 0.1	*S. typhimurium*	Antibiofilm agent	[109]
5	(1) DHA* and (2) EPA* NEs; O/W	Emulsion Phase Inversion (EPI) method with Tween-80 and Tween-85	(1) 145 ± 2.5 (2) 155 ± 2.5	Tea polyphenols were added as antioxidants	Enhances food fortification and large-scale production	[118]
6	Turmeric extract NEs powder (TE-NEP); O/W	High-speed homogenization & Ultrasonication and spray drying with Tween-80	~280	Antioxidants. The TE-NEP was stable in simulated gastric conditions.	Fortification of milk, increasing shelf-life, 21 days.	[119]
7	Cumin seed oil (CSO) with corn-oil NEs Whey protein isolate-guar gum (WPI-GG); O/W	Ultrasonication and high-speed homogenization with Tween-80	~75	Antifungal activity against *Aspergillus flavus*	Food preservative	[106]
8	Cinnamon essential oil (CEO) NEs; O/W	Ultrasonication with Tween-80	65.98	Antifungal activity against *Aspergillus niger*, *Rhizopus arrhizus*, *Penicillium* sp., and *Colletotrichum gloeosporioides*	High potential for food and agricultural applications	[120]
9	Clove oil (CO) with canola oil anionic NEs; W/O*	High-speed homogenization with purity gum ultra (PGU)	150–200	Antimicrobial activity against Gram-positive (*Listeria monocytogenes* and *Staphylococcus aureus*) and Gram-negative (*Escherichia coli*)	Potential for preservatives	[121]
10	Basil oil NEs; O/W	Ultrasonication with saponin	37.7–57.6	Antimicrobial activity against *Penicillium chrysogenum* and *Aspergillus flavus*	Preservatives against food spoilage pathogens	[105]

* Nanoemulsions = NEs * O/W = Oil-in-water, W/O: Water-in-oil *DHA = docosahexaenoic acid, *EPA = eicosapentaenoic acid.

6.2. Cosmetics

The low viscosity and transparency of NEs are among the aesthetic properties that have made them fascinating for use in the cosmetics industry. Other than that, with small-sized droplets below 200 nm, NEs definitely have a high surface area that enables better delivery of the active ingredients to the skin which is very quality of high demand in cosmetics. NEs are very practical when compared to macroemulsions in the cosmeceutical industry as there is no inherent creaming, sedimentation, flocculation, or coalescence. By using high energy equipment during the process and manufacturing, the use of potentially irritating surfactants could be reduced or even fully avoided. Nano-gel technology to create mini-emulsions from oil-in-water concentrate have been proposed, and is suited to minimizing trans-epidermal water loss, enhanced skin protection, and the penetration of active ingredients [122]. This would be advantageous for sun care products, moistening, and anti-ageing creams as it would be helpful in giving skin care formulations a good skin feel.

Emulsions have been widely used in cosmetics. In contrast to pharmaceutical ointments that can penetrate deep into the skin, cosmetic products are meant only for the immediate surface of the skin (i.e., the epidermis). The most common types of emulsion that are used in cosmetics are water-in-oil (W/O) or oil-in-water (O/W). NEs are broadly applicable in the cosmetic industry in the form of creams, moisturizers, and lotions because of the easy absorption of active constituents to provide effective action due to the small size of the droplet and the ability to trim down the water loss from the skin. The merit of using NEs in cosmetics is the small droplet size and absence of creaming and flocculation, which facilitate the uptake by antigen-presenting cells and lead to a refined product formulation [123]. Ribeiro et al. [124] formulated O/W NEs containing *Opuntia ficusindica* (L.) Mill hydroglycolic extract and xanthan gum with droplet sizes varying from 92.2 to 233.6 nm. The O/W NEs containing 1% of *O. ficusindica* (L.) Mill extract was stable for 60 days. In addition, this formulation increased the water content of stratum corneum, showing its moisturizing efficacy to be a good product for cosmetics [124]. NEs were formulated by Pengon et al. [125] using coconut oil NEs and varied amounts of surfactants such as polyethylene glycol octyl phenyl ether (PGO) and polyethylene glycol hydrogenated castor oil (PHC). The droplet size of NEs consisting of 5% (w/w) PHC was 0.162 µm. A smaller size of coconut oil NEs could be obtained by increasing the amount of PHC [125]. NE formulations were prepared from the hydroalcoholic extracts of *Vellozia squamata* leaves and stems with high antioxidant activity by using the phase inversion method. Stable formulations were obtained from both extracts from leaves and stems. Antioxidants are well-recognized as anti-ageing agents, hence are suitable for cosmetics formulation [126].

NEs have also been used as a vehicle for controlled delivery and as an effective transport vehicle in cosmetics. NEs will reduce trans-epidermal water loss. The Kemira nano gel-NE based carrier system is a patented system for cosmetic purposes; it will improve skin cell production and the penetration of active pharmaceutical ingredients (API) as well as provide a good skin feel [127]. Topical administration itself offers ample advantages and by combining it with NEs, this formulation may provide an improved way of drug delivery system. It can bypass the hepatic first-pass metabolism of the drug and related toxicity effects. A comparative study showed that after 1 h, the hydration power of the NEs was higher than the body milk and body water; after 24 h, the results portrayed the long-lasting impact of the NEs when compared to the other two [123]. These results are shown in Figure 7.

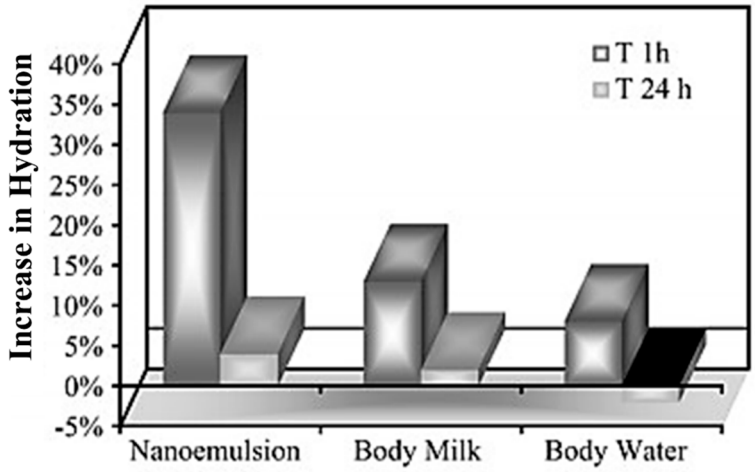

Figure 7. Increase in hydration of the fore-arm stratum corneum 1 h and 24 h after treatment with different products. Reproduced with permission from Sonneville et al. Advances in Colloid & Interface Science, Published by Elsevier, 2004 [128].

There are few examples of patented NEs used in the cosmeceutical industry. L'Oreal (Paris, France) has utilized NEs based on phosphoric acid fatty acid esters in cosmetics, dermatological, pharmaceutical, and/or ophthalmological fields as well as NEs based on ethylene oxide and propylene oxide block copolymers and their uses in the cosmetics, dermatological and/or ophthalmological fields [129].

6.3. Drug Delivery

NEs have been shown to be resourceful and functional novel drug delivery systems. Throughout the years, NEs have been proposed for various usages as drug delivery systems because of their capability to solubilize non-polar active compounds. NEs in drug delivery have varied purposes and one is as effective carriers for bioactivation, helping its administration through various routes such as transdermal, topical, and oral delivery. Their parenteral delivery has been used for supplying nutritional requirements, controlled drug release, vaccine delivery, and for drug targeting to specific sites [20]. A high level of topical antimicrobial activity has been achieved by NEs that has only been previously accomplished by systemic antibiotics [122]. The NEs have wide spectrum activity against bacteria (e.g., *E. coli*, *S. aureus*) and fungi (e.g., *Candida*, *Dermatophytes*). Due to the strict requirements of the intravenous administration route, particularly the need for the formulation droplet size to be lower than 1 μm, NEs totally have the advantage over other systems. Parenteral administration of NEs is used for many purposes, namely nutrition such as fats, carbohydrates, vitamins, and others [126]. Fine particles of NEs formulations have caused them to have prominent advantages over macroemulsion systems when delivered parenterally. NEs have extended residence time in the body as it is cleared more slowly than coarse particle emulsions. NEs have many advantages over conventional oral formulations for oral administration including greater absorption, enhanced clinical potency, and reduced drug toxicity. Therefore, NEs have been shown to be perfect in delivering drugs such as steroids, hormones, diuretics, and antibiotics [128]. Vyas et al. [130] validated that primaquine, when incorporated into oral lipid NEs, displayed powerful antimalarial activity against *Plasmodium bergheii* infection in mice at a lower dose level of 25% when compared to the conventional oral dose; and a drug concentration higher by at least 45% lipid NEs of primaquine enhanced oral bioavailability by the liver when compared with the pure drug.

For bioactive compound delivery, NEs is one of the most assuring ways as they provide protection and permit their dispersion in aqueous matrices. The feasibility of stirred media mills to produce W/O NEs loaded with active pharmaceutical ingredients (API) using plant oils and various types of the non-ionic emulsifier polysorbate are shown. The impact of the oil and surfactant type

surfactant-to-oil-weight-ratio (SOR) on the size of NEs at similar stressing conditions were studied thoroughly. From the results, at constant conditions and SOR, the type of the used plant oil and surfactant did not affect the droplet size and the smallest achievable median droplet size was 20 nm. Compared to a formulation containing the similar quantity of the non-dissolved micronized drug, the release test with fenofibrate-loaded peanut oil-polysorbate 80-water NEs displayed significantly faster drug distribution [131]. Phosphatidylcholine (PC) is a natural emulsifier that can be modified enzymatically to improve its functionality, for example, as lysophosphatidylcholine (LPC). A NE was prepared using a 10:1 ratio of emulsifier:phytosterols. The NE prepared with LPC was less stable, despite its higher water affinity, than the NE prepared with PC [132].

6.3.1. NEs in Anti-Cancer Treatment

Uncontrol and abnormal growth of cell proliferation can be either due to the genetic modification, activation of oncogenes, or inactivation of tumor suppression genes at the molecular level leading to the proliferation of cancer cells, tissue infiltration, and organ dysfunction [133]. The growth of tumor tissues is designated with active angiogenesis and vascular density to preserve the blood supply for their growth. Furthermore, the progression of tumor is supported by a microenvironment, which consists of the extracellular matrix, adipocytes, pericytes, immune cells, activate fibroblast, glial cells, epithelial cell, vascular cell, endothelial cell, and protein [134]. The significant changes in physiology, structure, and function of the components of the microenvironment in term of its angiogenesis, oxygenation, pH, perfusion, and metabolic state lead to the development of tumor into a malignant phenotype [135].

The physiological barriers such as hepatic and renal clearance, enzymolysis, hydrolysis, and endosomal/lysosomal degradation hinder the therapeutic agent in reaching the target tumor or cancerous cells [136]. Furthermore, the existence of the P-glycoprotein (Pgp) adjunct with the complexity of tumor microenvironment inhibits traditional chemotherapy from reaching the tumor mass. The efficacy of the anticancer drug is limited by the lack of selectivity of the cancer cell, poor solubility, toxic to normal tissues, and low therapeutic coverage causing severe side effects and low cure rate [137]. Chemotherapy drugs function by defeating all proliferation and dividing cells such as red blood cells, hair follicles, gut epithelial, lymphatic cells, and bone marrow, which makes chemotherapy not likely for long-term treatment [138]. Moreover, the properties of anticancer drugs somehow exhibit poor aqueous solubility and are highly hydrophobic, thereby fail to target the cancerous site [139].

The development of a successful delivery system such as NEs that has a high solubilization capacity of hydrophobic drugs, ease of production, long term stability, and imaging methods make it a promising drug delivery system [140]. The presence of such technology is meant to selectively target the cancer cells, so the therapeutic and imaging agent can be delivered to the tumorous site, thus increasing the success of treatment at an early stage [139]. Significant modification of nanoparticles properties has been explored throughout the years to improve and achieve the specific target in the treatment. For example, NEs were modified with a specific ligand to target cells, tissues, or organs together with a fluorescent dye for imaging [138]. Additionally, the lipid-rich NEs that contain fatty acids such as omega-3 and omega-6 fatty acids, linoleic acid, non-glucose-based calories, and vitamins E and K have been used as colloidal carriers for several chemotherapy drugs, diagnostic, and imaging agents that are normally conjugated with multifunctional moieties for diagnosis and image-guided drug delivery for cancer therapy [141]. Table 7 lists a few multifunctional NEs advancements for cancer therapy.

With proper knowledge, the versatile nature of drug delivery systems where a hydrophobic and hydrophilic drug are able to be encapsulated with the effect of a different ligand, targeting site, and imaging system allows the real-time monitoring of treatment progression.

Table 7. Multifunctional NEs for cancer diagnostic and therapy.

Drugs	Targeting Ligand	Imaging Agent	Ref.
PIK75 (PI3K inhibitor)	EGFR specific peptide folate	NBD-C6-ceramide	[142]
Doxorubicin	Folate	DHPE (fluorescence)	[143]
Paclitaxel	Anti-PSMA mAb, J591	Superparamagnetic iron platinum NPs (SIPP) for MRI Rhodamine (fluorescence)	[144]
Doxorubicin Mdr1-siRNA	αvβ3-specific RGD4Cp TATp	Cy5.5 (fluorescence)	[145]
Docetaxel Plk1-siRNA	Herceptin mAb	Nile red (fluorescence)	[146]

6.3.2. NEs in Vaccine Delivery

NEs as a vaccine carrier is actively being researched. The current effective and efficient method is to deliver an inactivated organism to a mucosal surface, so that an immune response will be generated. Research has shown genital mucosa immunity may be obtained with vaccines that are administered into the nasal mucosa [147]. Proteins were delivered to the mucosal surface by using NEs to be adjuvant and facilitate the absorption of antigen-presenting cells.

The antigen can be loaded in the nanocarrier by several mechanisms such as physical adsorption, encapsulation, encapsulation with coating, encapsulation with targeting, chemical conjugation, and conjugation with a targeting mechanism. The physical adsorption of the antigen onto a nanocarrier can be achieved either by a charge or hydrophobic interaction, which exerts weak interaction that leads to the dissociation of the antigen and nanocarrier in the body. Regarding the encapsulation, antigens are mixed with nanocarrier precursors during synthesis, resulting in the encapsulation of antigen into a nanocarrier and when the nanoparticle degrades in the in vivo environment [148].

The first application that is now receiving clinical trials is the nanocarrier for influenza and HIV protein. Moreover, a recombinant HIV gp 120 antigen mix in NEs has been introduced to mice and guinea pigs through intranasal immunization demonstrate robust serum anti-gp 120 IgG [149]. Another pronounced example is the pandemic flu vaccine AS03, which has been approved as a constituent of Prepandrix® [150]. AS03 is also a fundamental of other vaccines including Arepanrix® for the prevention of influenza caused by H1N1 and H5N1. Examples of other oil-in-water emulsions as vaccine adjuvants are listed in Table 8.

Table 8. List of NEs as adjuvants.

Adjuvant Name	Composition	Application	Ref.
MF59®	O/W Squalene emulsion	Influenza	[151,152]
AS03	SB62 adjuvant and twofold diluted form of O/W squalene	H5N1 and H1N1	[153]
AS02	Immune-stimulatory agents such as MPL and triterpenoid saponin molecules	Malaria, HIV, and tuberculosis	[154]
MPL®SE	Combination of monophosphoryl lipid and a stable squalene emulsion	Leishmaniasis	[155]
AF03	Thermoreversible O/W emulsions	H1N1 influenza	[156]
DETOX®	Composed of bacterial cell wall and monophosphoryllipid A (MPL) dissolved in squalane and Tween 8	Melanoma	[157]

Choosing the right adjuvant, antigen, and emulsion composition will have to consider the balance between the immunogenic benefits and the safety profile of any formulation. This is the major concern in vaccine development as it directly affects the benefit–risk scale. Therefore, thoughtful selection of the oil composition, adjuvant, surfactant, and antigen for the particular disease could provide more efficiency and increase the efficacy of vaccines against a pandemic disease.

6.3.3. NEs in Anti-Inflammatory Treatment

The combination of oils and emulsifiers enhance the absorption of two phytochemicals that are being used in treating two major chronic inflammatory diseases: periodontitis [158] and bowel disease (Crohn's disease and ulcerative colitis) [159]. Periodontitis is a chronic inflammatory disease that affects the supporting structures of the teeth with multifactorial etiology action of microbial, genetic, environmental, and host factor involved. A state of chronic inflammation will occur with the escape of oxygen-free radicals by inflammatory cells (polymorphonuclear lymphocytes). Enzymes and toxic by-products released by the periodontal pathogenic microflora further help this destructive process by breaking down host cell membranes and extracellular matrices to obtain nutrients crucial for their growth [160].

In Crohn's disease, the whole intestinal wall may be affected by inflammation and is usually transmural and discontinuous, while in ulcerative colitis, it is often continuous, primarily impacting only on the mucosal lining of the colon and rectum [161]. Many reasons might lie behind the cause of the diseases including complex interactions between oxidative stress, immunoregulation, changed inflammatory mediator levels, microbial pathogens, and genetic factors [162]. Phytochemicals have been reported by recent studies to be useful in recovering both diseases. Quercetin, a type of bioflavonoids that have cured periodontitis [163], and diterpenoid isolated from *Andrographis paniculata* to treat bowel diseases [164], have demonstrated possible antimicrobial activity, reducing inflammatory markers, and anti-inflammatory, antioxidative [165], and anticancer activities [166]. However, both components have low aqueous solubility (0.07 mg/mL in water), which has led to low bioavailability, and due to fast and extensive metabolism, they have low oral absorption. Absorption of both phytochemicals can be improved with the mixture of oils and emulsifiers as carriers [167]. Hence, for lipophilic drug loading, NEs could be an appropriate drug delivery vehicle. The rate of absorption is better and variability in absorption is avoided and NEs also facilitate in solubilizing lipophilic drug, increasing bioavailability, and enable rapid and efficient penetration of the drug moiety. In situ nanoemulgels could be produced when NEs are incorporated into the polymer solution, which allows sustained and controlled drug delivery and facilitate administration, thus patient compliance with drug will be further improved [158].

7. Conclusions and Future Perspectives

Nanoemulsions (NEs) have great potential in a wide array of industries including the food, pharmaceutical, and cosmetics sectors due to their unique features and better stability over conventional emulsions. Selecting the accurate method and optimizing the conditions for the improved stability of NEs will help in the development of high-throughput production and their widespread application in food, beverage, and pharmaceutical industries based on their specific needs. NEs are considered to be one of the most promising systems to improve solubility, bioavailability, and functionality of nonpolar active compounds, which promotes their applicability in drug delivery systems. Aside from their large potential, NEs are not completely stable as they are metastable, thus more studies are required to generate stable NEs for manufacturing. The application of NEs still holds challenges that need to be addressed in terms of both the production process, especially their cost, and of the characterization of both the resulting NEs and the food systems to which they will be applied in terms of product safety and acceptance. The elucidation of interactions between the drug and NE components require further research for a better understanding of the influence of NE formulation on drug release and drug uptake by different routes. Therefore, formulating NEs with biocompatible materials and approval from FDA is a prerequisite for future application not only in pharmaceutical, but in the medical, food, and cosmetics sectors.

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