

An Overview of Nanoemulsion: Definition, Preparation Methods and its Applications

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Abstract

Emulsions are a wide range of naturally occurring or processed products that sometimes appear as emulsions at certain stages of production. The importance of emulsion systems in the food industry is due to its rheological and physicochemical properties. The main limitation of their use is thermodynamic instability, and one way to solve this problem is to use nanoemulsions (NEs). NEs are very popular these days because of the small size of the droplets with a high surface-to-volume ratio. In this paper, emulsions are defined and then the compounds, properties, formulations, formation methods and applications of NEs as well as their advantages and disadvantages are examined. The formation of NE consists of two parts: high energy emulsification methods and low energy emulsification methods. High energy emulsification methods are divided into five sections: High-Pressure Homogenization, Microfluidization, Ultrasonic Emulsification, Nanoparticles and High Shear Mixers. Low energy emulsification methods include Phase Inversion Temperature (PIT), Phase Inversion Composition (PIC), Spontaneous Emulsification and Solvent Displacement. NEs are used to transmit beneficial compounds, followed by diseases control and prevention, and to produce food coatings and films and antimicrobial compounds, thereby increasing the shelf life of foods.

Keywords: Emulsions; Nanoemulsions; Formation Methods; Applications; Food Industry

Introduction

In recent decades, nanotechnology has become popular in many industries, especially the pharmaceutical and food industries, for the preparation of medicines and lipophilic substances, including flavorings, dyes, and fatty acids. Emulsions are present in a wide range of naturally occurring or processed products or appear as emulsions at some stages of production. The special physical, chemical and rheological properties of emulsions have made them very vital in the food industry. However, the main limitation of the use of emulsions is their thermodynamic instability. The use of NanoEmulsion (NE) systems is one way to deal with this limitation [1]. Over the years, NEs have been extensively studied. NE are unbalanced and incompatible systems that are water-in-oil (W/O) or oil-in-water (O/W) emulsions. The size of scattered phase particles in them is between 10 - 1000 nm, although some consider this range to be between 10 - 1500 nm. In another definition, in particular, NEs are considered to be only scattering systems with particle sizes less than 100 nm [2]. When NEs are considered thermodynamically a stable isotropic system, the two immiscible liquids combine to create a single phase assisting emulsifying agents such as cosurfactants and surfactants, and also the input energy is formed mechanically or physiochemically. The shape and size of particles dispersed in the stationary phase cause a distinction between emulsion (1 - 20 μm) and NE (10 - 200 nm). Also, long-term sustainability can be an important distinguishing feature between emulsions and NEs that can be made in 3 modes: 1- water in oil (W/O)

where water is dispersed in a continuous oil phase; 2- oil in water (O/W), in which the oil is distributed in a continuous water phase; and 3- bicontinuous phase. NEs come in various forms, from spherical swollen micelles to bicontinuous phase structures [3]. Since the production of NEs play a key role, the focus of this article is on formed hoe NEs and the uses of NEs in food industries. The present article also deals with the features, benefits and drawbacks of NEs.

Emulsion

One of the dispersions are emulsions, which are made of two immiscible liquid phases. These two phases are combined by surfactant and mechanical shear to form an emulsion. Because of an unstable thermodynamically character of all emulsions particle size of this usual emulsion continuously increases with time and finally separation of two phases will occur. Various kinds of emulsions are water-in-oil (w/o) and oil-in-water (o/w). continuously with time and finally separation of two phases will occur. Various kinds of emulsions are water-in-oil (w/o) and oil-in-water (o/w). These systems have low level of stability which can be increased using surfactants and other substances, these active surface components are called emulsifiers. Emulsifiers enhance emulsions stability via reducing interfacial tension between liquid-liquid and air-liquid. The surface-tension theory assumes that the interfacial tension between the two immiscible liquids are reduced using the emulsifiers or stabilizers. This process is achieved by lowering the repellent force within the two liquids and reducing the attraction within the two liquids. According to the oriented-wedge theory monomolecular layers of the emulsification agent are formed and curved around the droplet of an emulsion's internal phase. This phenomenon can cause their solubility in that particular liquid [4].

The emulsifying agent based on the plastic-or interfacial-film theory is placed at the boundary between the oil and water creating a thin film by absorbance into internal phase droplets' surface. The contact and later coalescence of the dispersed phase is avoided by this film. The physical stability of the emulsion is directly increase with tougher and more pliable film.

Repulsion theory describes that the emulsifying agent makes a film comprising globules on one of the immiscible phases. these repulsive forces suspend the dispersion medium by the immiscible globules. Based on the Viscosity modification theory, viscosity of the medium is raised by emulsifying agents and therefore they form miscible viscous suspension of globules [5].

Nanoemulsion

Emulsions with 50 - 1000 nm mean droplet diameters are termed NEs. Most common forms of NEs are mini-emulsion and submicron emulsion (SME), which are used as synonyms can be defined as emulsions with the average droplet size of 100 - 500 nm. NEs are two phase colloidal dispersions, which include an oil phase and an eques phase with the assistance of cosurfactant and surfactant at appropriate ratios. The features of phases and surfactants have a significant role in the NEs' functional features [1]. Non-polar molecules like essential and mineral oils, free-fatty acids as well as other lipophilic nutrients is used as an oil phase for the formulation of NEs [6]. The stability, formation, and properties of NEs depend on the chemical and physical features of the oil phase, including water solubility, viscosity, polarity, density, interfacial tension, refractive index, and chemical stability [2]. The aqueous phase can be formulated by mixing water with various proteins, polar molecules, and carbohydrates. The stability, physicochemical quality, and formulation of NEs depend on the polarity, ionic strength, pH, rheology, density, interfacial tension, refractive index, and phase performance of the eques phase depending on the concentration of the utilized constituent components and their types [1,6]. Figure 1 shows a NE and a macro-emulsion droplet size.



Figure 1: Picture of a nanoemulsion (left) and a macro-emulsion (right) with droplet diameters of 35 nm and 1 μ m, respectively [3].

Types

There are four types of NEs, including: Water-in-oil (w/o), Water-in-oil-in-water (w/o/w), Oil-in-water (o/w), Oil-in-water-in-oil (o/w/o). Varying the components of the emulsions can cause transformations between these types [2].

Theories

The reduction in the droplet size over the homogenization procedure of NEs can be explained by combining two theories of cavitation and turbulence.

Properties

By numerous physical features, NE becomes different from large emulsions, one of which is the NE's transparent appearance categorized according to the size of droplets. NE is in the range of 50 - 200 nm. However, droplets larger than 500 nm appear milky and cloudy. The rheological features of NE can be controlled by setting the dispersed phase, the size and volume of droplets and the composition of the salt. Compared to macroemulsions, the stronger elastic characteristics are other different qualities of NEs, which distinguishes NE from a rheological aspect. The size of the droplets and their distribution have a key role in the emulsions' stability. The stability of nanoparticles may be caused by the distribution of smaller droplets and the narrower distribution of size. Emulsions may represent exceptional stability based on the kinetics, however, phase separation ultimately occurs in emulsions because they are not thermodynamically stable. Viscosity is a measurement for measuring the stability. The sustainability of NEs formulas can be assessed by observing and controlling the changes in viscosity. Due to the size of their small droplets, NE is resistant to precipitation or cream formation. However, due to electrostatic and static stabilization and occurring flocculation, ionized and ethoxylated non-ionized surfactant are used to stabilize this phenomenon [1].

Emulsifiers or surfactants

Surfactant, which stands for surface active agent, are substances that greatly change the surface energy between surfaces. It is characterized by the dual behavior of its molecular structure, meaning that it has both hydrophobic and hydrophilic groups. Unlike external energy micronized emulsions, stable thermodynamic NEs are formed by the addition of surfactants as this reduces interfacial tension. A temporary emulsion will form when the oil and water are mixed. However, due to the blockage of scattered globules, the mixtures are divided into different phases [1]. Considerable concentrations of surfactants and emulsifiers, which are on the GRAS¹ list, are added to NEs. Small molecule surfactants, proteins, polysaccharides, and phospholipids are examples of emulsifiers. If surfactants are combined with oil and other constituent compounds in the right destabilizing such as Oswald Ripening in NEs can be prevented. Normally, the maximum repulsion is increased by the steric interactions owing to the emulsifier's adsorption layer over the particle in turn stabilizing the emulsions against coalescence and flocculation. Esteric stability in NEs is stronger and therefore makes a stable system possible. Over time, coagulation in particles can lead to different behaviors and may indicate uniform growth in which droplet size increases over time, or further leads to the separation of the initial phase (uneven growth). Coagulation in microemulsions is more common than on NEs. Since NEs droplet size is very small, there is no reversible aggregation of droplets. When deciding which surfactant to use in formation of NEs, the lipophilic-hydrophilic equilibrium system (HLB) can be applied. Over the years, it was proven that the HLB system determines the optimal surfactant required for the production of emulsions with the preferred properties (O/W or W/O). Based on this system, values of HLB above ten indicate hydrophobic surfactants, however, lipophilic surfactants possess the HLB values of less than one to ten. In some cases, surfactants alone cannot effectively reduce the interfacial tension of the water and oil phases, in which case another compound called cosurfactant is used. In fact, cosurfactant improves the performance of surfactant and reduces interfacial tension to a greater extent. Cosurfactants can be alcohols with long hydrocarbon chains [1,3].

¹Generally recognized as safe.

Method of formation of NE

There are two main ways to formulate a NE: Persuasion and Brute force.

Persuasion

First method is phase transition from near-optimal state through changes in single variable. This technique is working by changing in a formulation variable for example temperature or salinity for a near-optimal system (HLD near 0). For example, for a microemulsion, a larger temperature can be applied.

Transition the phase from near-optimal mode is the second method by changing in multiple variables where changes are made in more than a formulation variable, for instance using both greater temperature and further salt in a microemulsion.

Catastrophic inversion is the next available method leading to a low internal phase emulsion for inverting to the external phase.

Stabilizing nanodroplets via liquid crystal formation from a state near HLD = 0 is called phase transition stabilized by liquid crystal formation, which is the last known method [7].

Brute force

The procedure may include using a mixer with higher speed, a high-pressure homogenizer, a high frequency ultrasonic tool, a membrane with small pores, and so on. Apparently, the creation of W/O and O/W NEs via dispersion and high-energy emulsification techniques is relatively usual, however, the formation of emulsions via low-energy emulsification approaches or condensation is one of the physicochemical features of these systems in terms of the phase transition over the emulsifying procedure.

This can be done by using certain areas of the phase diagram through a very low interfacial tension, as the areas of microemulsions and liquid crystals, ending the emulsification procedure, the NEs formed. The characteristics of NEs like relative high kinetic stability, optical transparency and small particle size appear to rely on composition variables as well as the preparation variables including degree of mixing energy input, emulsification pathway and time [8].

Preparation methods

In the preparation of emulsions, the following items are considered: the process of emulsification, the condition of the constituent components (surfactant and oil and water phases) and the quantity of these in the system. NE is produced in 2 ways: High Energy Emulsification Methods using a mechanical device and low Energy Emulsification Methods using the chemical potential of constituents [9]. NEs possess a very small particle size ranges and is effectively produced utilizing high-pressure equipment. Microfluidization and high pressure homogenization are the most common approaches for production of NEs on an industrial and laboratory scales [8].

High energy emulsification methods

In these methods, the energy required to break the particles is supplied by mechanical devices such as high pressure homogenizers, ultrasonic generators, etc. to allow one phase to disperse into another phase in small particles shapes. These devices provide the required energy in the shortest possible time. The energy level to obtain nanoscale particles is very high, which is why it is inefficient for laboratory applications. However, in spite of the effectiveness of these high-energy approaches for reducing particle size, there are not suitable for heat-sensitive macromolecules and drugs like proteins, peptides, nucleic acids and enzymes caused by the high energy approaches with high pressure and temperature that can potentially damage heat-sensitive drugs and proteins [1].

High-pressure homogenization

The conventional method works at a pressure of 50 - 100 MPa. Although 350 MPa pressure can be achieved with new equipment, O/W NE with methylcellulose as a surfactant can be stable at pressures below 150 MPa [3]. In a standard method, the material is passed through a narrow gap of homogenizer in a high pressure within 50 - 100 MPa causing a destructive force like shearing, cavitation and so on. Hydraulic shear force and intense turbulence change the coarse emulsion to NE. The droplet size relies on the quantity of cycles, and the system's temperature and pressure. The higher pressure and cycles cause the smaller size of produced droplets. Furthermore, the droplet size relies on the composition of emulsion (e.g. aqueous phase, surfactant, and organic phase), emulsifier properties (adsorption kinetic, stabilizing, and interfacial tension depression features), and physicochemical condition under various phases [2]. High pressure homogenization can be processed at low temperature (cold high pressure homogenization technique) or at high temperature (hot high pressure homogenization technique), which is later used for the process of temperature sensitive drugs and materials. compared to other methods, high pressure homogenization possesses numerous benefits like easy scale up, small process time, and prevention of organic solvents. This method is widely used in industries, especially in the pharmaceutical and cosmetic industries [1,2].

Microfluidization

A device called a "microfluidizer" is used in this technology with high pressure. A positive displacement pump with a higher pressure makes the product to pass through the interaction chamber with small channels known as microchannels. The next step is passing through the microchannels to an impingement area forming tiny particles of the submicron range. In an inline homogenizer the aqueous and oily phases are combined and then processed to obtain coarse emulsion. Eventually, microfluidizer processes further the coarse emulsion, to achieve the stable and small-sized NEs. This technique is known as 'direct' emulsification technique not requiring pre-emulsifying as the dispersed phase. The big advantage of this method compared to the high-pressure homogenization method is the direct injection into the continuous phase over micro channels. Mechanically, the microfluidizer is a static mixer with a high velocity and without any moving parts. This method can be utilized at industrial and laboratory scales, therefore, it's a great advantage [1]. Basic principle of a microfluidizer is shown in figure 2.

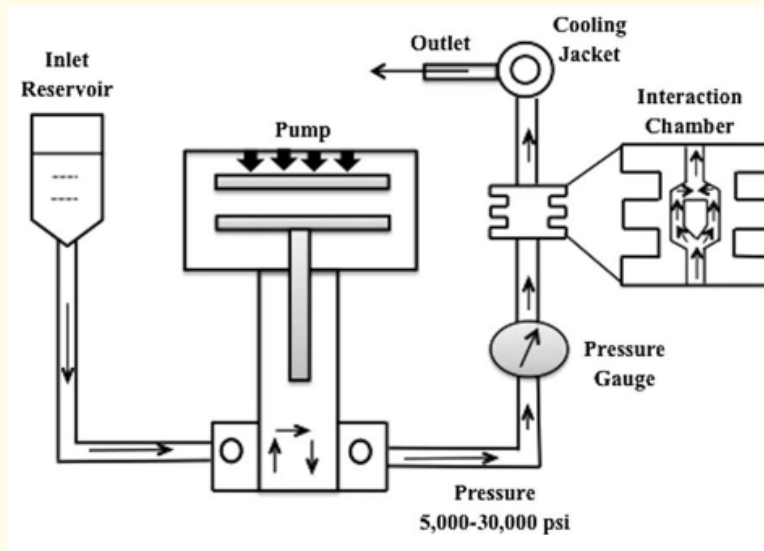


Figure 2: Microfluidizer: basic principle [55].

Ultrasonic emulsification

Another very effective way of reduction in droplet size is ultrasonic, which is suitable for small batches. Ultrasonic time in different range determines process efficiency. Large droplets are disrupted into smaller ones by ultrasonic energy of this equipment. The temperature is a linear function of the time, in ultrasonication. Ultrasonic and microfluidization at high temperatures both have the similar behavior. Ultrasonication time has a significant effect on particle size. Emulsion droplet size is not affected by incrementing the residence time over the optimal limit, and it is only the waste of energy. Therefore, droplet sizes decrease and droplet disruption increases is not expected by the enhancing the amount of energy. The emulsion droplet size is kept in the lowest by maintaining the input energy at a certain level. Usually, in ultrasound emulsification there is no over-processing, which is caused by the residence time of emulsion in emulsification region corresponding to the high sonication time in equipment, however, in interaction chamber, the residence time in the microfluidizer is almost millisecond [10].

Although the ultrasonication is simple, it leads to a less optimum heterogeneous distribution of nanodroplet size. Besides, ingredients damage is possible due to high-energy output. Coarse emulsion input to ultrasound determines distribution of droplet size. There is the produced NE with larger droplets diameter, when entering the coarse emulsion to sonication chamber with bigger emulsion droplet size and extended distribution [2,10].

Nanoparticles

A significant number of nanoparticle formulation approaches have NE patterns, which in turn create different ways. Therefore, it should be borne in mind that these NE formulation procedures can potentially affect the active principle and nanoparticles-encapsulated drugs [11]. Such potential differences may involve high-shear tools, contact with organic solvents, and drug sensitivity to temperature. Similarly, NE formulation procedures should be selected according to the performance of the treatment targets selected from nanocarrier suspension and their administration method. The selected drug administration route and the nature of the encapsulated medication determine the nanoparticle formulation procedures as well as the NE formation approaches. Water drops self-disperse within the oil when the oil possesses the right features and a sufficient concentration of nanoparticles, therefore, NEs will be formed if the nanoparticles self-assemble around them [1].

High shear mixers

Energy intensive procedures like homogenization, emulsification, grinding, dispersion, cell disruption, and dissolving are broadly performed by high shear mixers in the area of chemical reaction processes and agricultural and food manufacturing. High-shear mixers exist in both inline and batch configurations. Inline high-shear mixers will have either a rotor stator teathed configuration or a blade screen, whereas batch units possess axial or radial discharged kinds. Both inline high shear mixers and batch high shear mixers can be used together for the inline unit functions in a circulation loop downstream of a tank armed with the batch unit. The processing time is reduced and product quality improved by this method. There is a high speed rotor within a stationary stator. The emulsion or substance will be constantly attracted into the mixing head while the rotor rotates, and then the product will be ejected via the stationary stator in a high velocity.

When the hydraulic shear mixes the emulsion faster, the size of the droplets reduces [1,12].

Low energy emulsification methods

The low energy methods are Phase Inversion Composition (PIC), Phase Inversion Temperature (PIT), Solvent Diffusion and Solvent Displacement. Solvent diffusion method is also known as "self-emulsification" and "spontaneous emulsification". This technique is utilized

to prepare O/W NE. These systems' physicochemical features are oriented by the phase transition over the emulsification procedure [8,13].

Phase inversion temperature method (PIT)

Formation of NE without using the high shear forces is performed by this method, which is an emulsification technique with low energy. In recent years, the PIT method achieves more attention due to the benefits such as the lower cost. The PIT idea is worked by a kind of phase inversion in emulsions (transitional inversion), which is induced by altering the temperature affecting the system's HLB. Transitional phase inversion happens when the surfactant's affinity for the oil phase equilibrates for the water phase. Changing temperature can variate in the HLB or affinity of the surfactant. It is oriented by the alteration in affinity of polyoxyethylene-kind nonionic surfactants with temperature. O/W emulsion is produced at low temperature when the surfactant monolayer is more convex and possesses a big positive spontaneous curvature and becomes hydrophilic. At higher temperatures, W/O emulsion created as a result of dehydrating hydrophilic tail in a nonionic surfactant, the spontaneous curvature tends to be negative and hence more concave as well as the surfactant becomes lipophilic. At the intermediate or the HLB temperatures, a microemulsion (bicontinuous) or lamellar liquid crystalline phase region are observed when the spontaneous curvature becomes close to zero (not concave or convex). Within the HLB temperature, a very small-sized emulsion is made when the interfacial tension is very low [3]. It is possible that a macroemulsion with drop size of the 1 - 10 mm and higher can be formed by coalescence of nanodrops. The NE droplet does not coalesce immediately when some liquid crystal structures are created near HLB of 0 and/or when numerous surfactants exist. The droplet size is within the size of 50-100nm, however, the HLB is moved outside the unstable region. Hence, the emulsion is very unstable although emulsifying is preferred at the HLB temperature indicating that a quenching procedure should be undertaken to create fine and stable NEs, therefore, the ultimate NEs should be kept at a temperature higher than the PIT point. For preparing the emulsion at a temperature near the PIT and cooling or heating rapidly, it becomes to possible to produce kinetically stable emulsions with narrow size distribution and small droplet size. When cooling fast the emulsion, the W/O emulsion is inverted to an O/W emulsion, and by quick heating the emulsion, the O/W emulsion is inverted to an W/O emulsion. Coarse emulsions are created when the heating or cooling procedure is not fast. The classification instruments for determining the PIT point are viscosity, light microscopy, cryo-TEM, conductivity, dynamic light scattering, optical microscopy and turbidity [1,2].

Phase inversion composition method (PIC)

Here, a transition is obtained in the spontaneous curvature by altering the water volume fraction, not the temperature. denoted as the catastrophic phase inversion. For the emulsification technique, PIC, continuous phase components are gradually added to the dispersed phase components. Hence, a phase inversion happens along the emulsification pathway when appearing bicontinuous phase. The driving forces are small and the equilibrium system requires long time although nanoemulsification is a spontaneous procedure [2]. To prepare emulsions, PIC approaches are used including 5 steps: 1) first co-surfactant and surfactant (Smix) are combined, then Smix and oil are mixed to create oil phase; 2) water is inserted drop wise to the oil mixture and surfactant (the addition rate is very vital and needs to be set to guarantee it is slow enough to create the oil-in water phase or bicontinuous D phase. A very slow rate results in the increase droplet size owing to emulsion destabilization. Within a continuous oil phase, water droplets are formed by addition of water into oil (W/O microemulsion); 3) By increasing the water volume fraction, the droplets size becomes larger; 4) Incrementing the water volume fraction causes merging the droplets and forming lamellar or bicontinuous structures. Here, emulsion inversion point reaches altering the surfactant curvature and achieving the minimal interfacial tensions, thus, the small-droplet emulsions are created. By measuring the conductivity, emulsion inversion point can be estimated. A sharp increment will be observed in conductivity when in the inversion zone, W/O emulsion is converted to the O/W emulsion, however, by converting the O/W emulsion to W/O emulsion, a sharp reduction is found in conductivity. 4) Further incrementing the water content results in passing the emulsion inversion point and decomposing the bicontinues structure into smaller oil droplets. In this step, the droplet size is not changed by incrementing the water. A high surfactant

concentration is needed for a comprehensive solubilizing the oil near the emulsion inversion point. The PIC emulsification technique for preparing NEs has numerous advantages like lack of organic solvents, low preparation cost, long stability, thermodynamic stability, and good production feasibility [1,2].

Spontaneous emulsification

Another technique is spontaneous emulsification to obtain nano-sized emulsion. The chemical composition of the aqueous and oil phases and the surfactants are vital in this method including 3 stages that are 1) a homogeneous lipid phase containing a lipophilic surfactant and oil as well as another water-miscible solvent phase to prepare a hydrophilic surfactant. 2) The O/W emulsion is created when injecting the lipid phase in the aqueous phase under nonstop magnetic stirring; and ultimately, 3) the evaporation under decreased pressure to eliminate the aqueous phase. Small droplets of dispersed phase are coated with surfactant in the continuous phase due to the surfactant's high affinity to the aqueous phase or the oil causing the turbulence at the dispersed phase-continuous phase interface and when the surfactant is displaced toward the continuous phase. For producing very small emulsions, it is essential to trigger the turbulence at the interface of the two phases, hence, co-surfactants like propylene glycol, ethanol, and acetone can help greatly in this regard. Here, the organic phase will include a surfactant, oil, and a co-surfactant, however, the aqueous phase includes only water. The droplet size is affected by numerous factors including type, level, structure of the cosurfactant and surfactant, quantity of surfactant to the dispersed phase, nutritive or additive ingredients in the dispersed phase, type and level of the encapsulant and two phases, and the viscosity of the continuous and dispersed phases. To create NEs through this technique, chemical energy released owing to the dilution procedure is used with a continuous phase normally at a constant temperature with no phase transitions (no alteration in the spontaneous surfactant curvature) within the system over emulsifying [13]. Diluting the microemulsion with water results in NE. From the oil/water interface, the cosurfactant (alcohol) is diffused to the water phase disturbing the creation of the microemulsion and making it thermodynamically unstable, thus creating NEs. In the pharmaceutical and food industries, higher levels of cosurfactants and surfactant are not permitted owing to sensory, regulatory, and expenses. Some investigations were performed to reduce the amount of cosurfactants and decreasing the surfactant to dispersed phase ratio utilizing the spontaneous emulsification technique, which is extensively utilized in the pharmaceutical industry to create drug delivery systems and encapsulate as well as deliver lipophilic drugs. Nevertheless, some uses are definitely present for which this method may be beneficial. Mixing small quantities of bioactive lipophilic mechanisms into beverages is an example in this regard. Spontaneous emulsification is very beneficial for encapsulation bioactive compounds in the pharmaceutical and food industries and over high energy and other low energy approaches like shielding sensitive compounds against the severe circumstances of the high energy technique, particularly pressure and temperature, and its better thermal stability, capability for reducing surfactants, and removing cosurfactants, compared to the other low-energy methods [1,13].

Solvent displacement method

The solvent displacing method recognized as the nanoprecipitation technique is oriented by the interfacial deposition of polymeric nanoparticles after displacing a semipolar solvent miscible with water obtained by a lipophilic solution. NEs can obtain polymeric nanoparticles from in situ monomer polymerizing in the dispersed phase or utilizing a preformed polymer, which is dissolved in a volatile organic solvent as the NE's dispersed phase after the solvent evaporation. The fast diffusion of the solvent into the aqueous phase leads to producing small-sized NEs even in the nonexistence of mechanical stirring, in which the interfacial tension within the two phases is decreased and the surface area is incremented. The Marangoni effect directs this action, which is explained as mass transfer along two fluids' interface as a result of a gradient of the surface tension. Nevertheless, it includes poor hydrophilic drugs entrapment due to the hydrophilic surface and hydrophobic core of oil promoting the drug entrapment. Hence, it allows to solubilize water-insoluble drugs [14]. An enhanced solvent displacement method was recognized utilizing poly (d, l-lactide-co-glycolide) (PLGA) nanoparticles including different methods for improving the incorporation efficiency of highly water-miscible drugs by changing the aqueous phase pH and changes in the drug salt form. Changing the aqueous phase pH leads to altering the drug components' ionization form, in turn altering the molecule

charges and thus a better solubilizing. Using proper approaches, the organic solvent is removed from the NEs like vacuum evaporation, which can create NEs utilizing only simple stirring at room temperature and prepare parenteral. Nevertheless, this method has the drawbacks including production of small-sized emulsions of the dispersal phase when acquiring a large ratio of oil and solvent. However, this method is a totally appropriate, fast, reproducible, and economic one-step production process for preparing the monodisperse, small-sized polymeric nanoparticles [1].

Advantages

Azmi., *et al.* (2019) and Gurpreet and Singh (2018) pointed out that free energy and higher surface area make NEs an effective transport system [1,7]. In 2012, Yu., *et al.* showed that ultimate bioavailability and water solubility of lipophilic drugs are improved by it and to mask the bad taste of drugs [15]. Jaiswal., *et al.* in 2015 introduced NEs as It can be easily used for skin and mucous membrane because of non-irritant and non-toxic properties. Stability issues such as flocculation, coalescence, creaming and sedimentation are barely cooperated with NE. Therefore, different formulation such as creams, foams, sprays and liquids can be formulated by it [16]. Bouchemal., *et al.* (2004) claimed that vesicles and liposomes can be substituted by its application and lamellar liquid crystalline phases can be built around the NE droplets [17]. Bhatt and Madhav (2011) said in their study that Biocompatible surfactants formulation can be administered orally. In addition, the cultured cells growth and investigating the toxicity of oil-soluble drugs can be improved using of NEs due to the cultured cells growth making possible the toxicity studies of oil-soluble drugs. As well, the “rough” skin surface can be penetrated by NE because of their small size. NEs are appropriate for veterinary and human therapeutic purposes due to non-toxic effect on healthy animal and human cells [8].

Disadvantages

Kale and Deore (2017) saw the main drawback of NEs is the cost of manufacturing, which is expensive, and also claimed that Oswald Ripening was the most important issue in NE [18]. Lovelyn and Attama in 2011 stated in their study that high concentrations of surfactant and cosurfactant were required to stabilize nanoparticles, and also the ability to dissolve materials with high melting point was limited [19]. Azmi., *et al.* (2019) pointed out other disadvantages of NEs that environmental parameters like pH and temperature can affect the NEs stability and also, for use in pharmaceutical and food applications, the surfactant used must be nontoxic [1].

Applications in food industries

Today, NEs have received a great deal of attention in the food industry due to their high transparency of NEs and their smaller dimensions compared to their wavelengths [20]. The advantages of using NEs over conventional emulsions for this purpose are: increased bioavailability of lipophilic materials; ability to scatter weak light and therefore use in clear light product; use to modify product texture; high stability in particle accumulation and gravitational separation [21].

Transfer of useful compounds

Omega-3 fatty acids are usually low in diets, and numerous users turn to functional foods or supplements to increment these healthy fats intake. Fish oil is a most extensively utilized source of omega-3 fatty acids for supplementing with further health benefits than plant sources due to its high concentration of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). NEs can overcome the challenges of low solubility in water, poor oxidative stability and bioavailability of omega-3 fatty acid compounds in beverages and foods [22]. In 2017, Rasti., *et al.* assessed the application, suitability, and stability of fish oil nanoliposomes in water in dairy and bread products. Nanoliposomes were considerably lower in primary and secondary oxidation levels than bulk and microscopic fish oils and were a good enrichment tool for milk and bread [23]. Another study on fish oil by Ghorbanzadeh., *et al.* in 2017 with nanoliposomes in yogurt. Experimentation with peroxide and sensory analysis showed that liposomal structures were prosperous in enclosing DHA and EPA stable for 21 days,

and that the nanocapsulation of omega-3 fatty acids protected against oxidative degradation [24]. In 2015, Esquerdo, *et al.* used a NE of carp oil to make 15% of chitosan nanocapsules. Peroxide levels for nanocapsules was stable over storage, however, bulk oil peroxide levels incremented over 45 days of storage [25]. Salvia-Trujillo, *et al.* (2016), Walker, *et al.* (2015) and Belhaj, *et al.* (2010) examined the oxidative stability of 10% oil NEs in water utilizing fish oil as a source of omega-3 fatty acids. In addition, the existence of natural antioxidants like lemon oil, seaweed, sodium alginate, and astaxanthin increased the oxidative stability of resulting systems [26-28]. In 2015, Uluata, *et al.* examined the oxidative stability of 1% NEs in fish oil in water and produced systems with a droplet range of less than 100 nm. Quillaja saponin has been shown to be effective as a natural emulsifier owing to its oxidative and physical stability [29]. Krill is a small crustacean like shrimp that has a high content of DHA and EPA and is one of the microalgae. Krill oil has recently become one of the oily sources of omega-3 fatty acids and is similar to fish oil based on DHA and EPA although 30-65% of fatty acids are phospholipids that may increase bioavailability [30]. Wu, *et al.* (2016) evaluated the oxidative and physical stability of 1% Krill oil NEs in water and evaluated the effect of antioxidant polarity by adding Trolox and alpha-tocopherol antioxidants. Further polar Trolox have been shown more effective for antioxidants than alpha-tocopherols [31]. In another study of Zhu, *et al.* in 2015, nanostructure lipid carriers were prepared comprising high content of Krill oil for expanding its use in foods. It showed that lipid Nanocarriers offered bioactive of Krill oil potent protection against photooxidation [32]. Using carotenoids may decrease the incidence of some chronic diseases, however, their use in food is restricted due to their solubility in low water, chemical instability, and low bioavailability. Qian, *et al.* in 2015, effectively encapsulated beta-carotene in food NEs containing various types of carrier fats coated with non-ionic surfactants. Orange oil created stable NEs for encapsulating beta-carotene, while the bioavailability of beta-carotene in these distribution systems was so close to zero. Beta-carotene bioavailability was significantly higher in LCT² NEs than in MCT³ NEs. It has been also shown that NEs enriched in beta-carotene have resistance to chemical decomposition under similar gastrointestinal circumstances [21]. Meng, *et al.* (2019) prepared a tea polyphenols-beta-carotene oil-in-water (O/W) NE with the core oil phase comprising beta-carotene and the water phase including tea polyphenols. Tea polyphenols have been shown to be effective compounds for the oral bioavailability of beta-carotene and it improved the nanoproperties of beta-carotene NE during storage. Tea polyphenols increased the retention rate of beta-carotene [33]. In some supermarkets, trout is freshly kept at 4°C. Usually due to the spoilage bacteria activity, selling the fresh trout fillet will be prohibited after 48 hrs. Khoshbouy Lahidjani, *et al.* (2020) focused on the determination of the effects of curcumin through emulsion phase inversion on extension the shelf life of *Oncorhynchus mykiss*. This study investigates Curcumin essential oil-loaded NE, as a natural antimicrobial compound for trout fillet conservation; results showed that, specifically at 5% concentration, not only CEON was made with appropriate droplet size (around 15 nm) and greater polydispersity index (8.497 ± 0.127 and 15.06 ± 6.4 , respectively, in 5 and 10 days) but also enhancement of the organoleptic quality of rainbow trout fillets is resulted as an effect of its presence. It is shown that CEON at the different concentrations specifically at 5% can retard the growth of spoilage bacteria as well as improving the storability of fresh fish fillets of *Oncorhynchus mykiss* leading to the shelf life beside enhancement of the scores of organoleptic properties [34].

Therefore, it can be concluded that in food industry, beverages and pharmaceutical industries, there is a great interest in using oral NEs for encapsulating, protecting and distributing lipophilic functional substances like oil-soluble flavorings, preservatives, vitamins, nutrients and drugs. Due to their ability to improve the solubility of biological compounds and their ability to improve intestinal absorption by surfactants, nanomaterials are good agents for the distribution of insoluble food additives such as fish oil and lipophilic vitamins. NEs improve and widely distribute the nutrient biologically encapsulated nutrients in the gut [35]. As a result, by formulating NEs from vitamins, antioxidants, and omega-3 fatty acids in food and beverages, the desired beneficial compounds can be transferred to foods and beverages without changing the appearance and color of the product [36].

Food coatings and films production

In 2017, Tavakoli, *et al.* assessed the impacts of different nano-silver concentrations on chemical and biological features of specimens of nuts such as hazelnuts, walnuts, pistachios and almonds within different months. In most samples, overall microbial count, mold

²Long Chain Triglycerides.

³Medium Chain Triglycerides.

and coliform counts were significantly reduced by various concentrations of nano-silver (1, 2 and 3%) in comparison to control group, moreover the 3% nano-silver concentration was more effective ($P < 0.05$). Furthermore, this packaging resulted in an antioxidant impact particularly when using 2% and 3% nano-silver concentrations. Nanoparticles also prevented the molds growth and thus aflatoxin production in all treatments. Based on the results of biological and chemical tests, a significant impact of silver nanoparticles was indicated on incrementing the nuts' shelf life. Moreover, the longest shelf life was for pistachio, almond, hazelnut and walnut, respectively. Although shelf life was 13 months for control sample, it was 20, 19 and 18 months, respectively, for above nuts, indicating a considerable increment in the shelf life of treatment groups in comparison to the control groups. The findings of this study prove the effectiveness of nano-silver packing in incrementing the nuts shelf life [37]. Ehsani, *et al.* (2018) employed two different packing methods (Modified Atmosphere Packaging (MAP) using gas mixture) and nano silver particles. The strawberry packaging using silver nanoparticles has been analyzed during 16 days in the poly-ethylene covers with the thickness of 40 microns at the temperature of 50°C. The results of the two methods on the qualitative properties of strawberry at 5°C and at different time intervals indicated that both methods increased the shelf life of the fruit regards to improved sensory characteristics. The experimental data also indicated that the qualitative characteristics of strawberry, namely fruit color and tissue hardness have increased by using the presented approaches [38].

Nowadays, NEs are used in food coatings, which are a combination of proteins, polysaccharides, and lipids that can be sprayed on the surface of food or in the form of an oral film. Nanopackaging coatings are used for two purposes and in some cases for three objectives. In the first case, these coatings are utilized to increase the food products shelf life by incrementing the duration of the lag phase. The more this step is taken and the longer the delay in the lag phase, the more effective the performance and role of packaging coating will be, because this is important from the microbiological aspect in food products. It is worth noting that there is a difference in nanopackaging coatings in incrementing the shelf life or lag phase. In the second case, it is used for changing some of organoleptic properties such as smell, taste and even in some cases to change the taste of nanopackaging. In many materials, such as airlines, the distribution of food products causes the release of a specific vapor that stays in the cabin for a long time and is unpleasant for numerous passengers. Therefore, by adding flavor with a package while storing food products, this product will be desirable for customers. In the third case, this is vital for marketing and even attracting clients to the pallets of shops as a subject in the field of marketing food products [39].

Antimicrobial NEs

In 2018, Hassanzadeh, *et al.* developed a NE containing garlic essential oil to cover and protect the volatile compounds of garlic essential oil. This study showed that free radical holding capacity of NEs increased during storage. Enhancing the NEs' free radical scavenging activity over storage time indicated the controlled release of entrapped volatile compounds from the inner to the outer phases of the NE. Microbial experiments have shown that NE control with particle size less than 100 nm (NE free of garlic essential oil) also have antimicrobial activity. Pure garlic essential oil, as well as the formulated NEs strongly acted against gram-positive bacteria (*Staphylococcus aureus*) than gram-negative bacteria (*Escherichia coli*). It confirms the researchers' former claims regarding antimicrobial activity of NEs [40]. Swathy, *et al.* in 2018 examined the antimicrobial potency of black pepper (BPO) NE against pathogenic aquaculture (*Pseudomonas aeruginosa*). This study provides the characterization, formulation, biosafety and application of the BPO NE prepared utilizing high-pressure homogenization technique. This reveals that the BPO NE prepared utilizing high pressure homogenizing technique represented high antibacterial activity versus the destructive pathogen *Pseudomonas aeruginosa*, isolated from the shrimp farm. BPO NE is able to efficiently prevent the biofilm formation by *P. aeruginosa*. Over the *in-vivo* and *in-vitro* antibacterial effectiveness investigations, represented a decent therapeutic potential of formulated Black pepper oil NE against the bacterial infections similar to the antibiotics commercially available such as oxytetracycline. The expected minimum inhibitory concentrations of BPO NE were non-toxic to the non-target kinds such as *Artemia salina*. NE system is utilized as an auspicious bio-based therapeutic agent to control the bacterial infections in aquaculture farm resulting in the decreased mortality and concurrent increased aquaculture yield [41]. The antimicrobial and anti-biofilm features of *Zataria multiflora* essential oil (ZEO) and its NE were evaluated against *Salmonella typhimurium* and *Listeria monocytogenes* by Shahabi, *et al* (2017). The findings of this work revealed that ZEO NE can be prepared in droplet size less than 100 nm with a decent stability over a

21-day storage at ambient condition. Moreover, it was found that the ZEO NE's antimicrobial impact is powerfully reliant on the kind of antimicrobial assay, the concentration of NE and the kind of bacteria. ZEO NE's bactericidal activity was associated with the kind of bacteria, time of exposure, and ZEO concentration. Nanoemulsion inhibited both examined bacteria in milk and BHI, however, it presented a more inhibitory impact against *S. typhimurium* compared to *L. monocytogenes*. In comparison with ZEO, NE of ZEO possessed further antibiofilm features on one-day old biofilm of *S. typhimurium* and *L. monocytogenes* on polystyrene surface, furthermore, contrary to ZEO, NE's antibiofilm features were improved by the increased concentration. Generally, the results of this work indicated that converting ZEO into NE improves the antibiofilm activity obviously indicating that the preparation technique plays a key role in emerging ZEO NE with better antimicrobial activity [42]. In a study by Paudel, *et al.* (2019) various formulations of cinnamon oil NE were established by ultrasonication utilizing Tween 80 as an emulsifier. Dynamic light scattering was utilized to define the particle size of emulsion. The antimicrobial effectiveness of cinnamon oil was found through NE Microbroth dilution assay on *Salmonella spp* and *Listeria monocytogenes*. In our work, the average diameter of NE was 9.63 ± 0.3 nm and cinnamon oil NE's minimum inhibitory concentration (MIC) for *Listeria Salmonella spp.* was *monocytogenes* was 0.039% v/v and 0.078% v/v, respectively. In comparison to the water control, 0.5% NE represented the reductions of 5.5 and 7.7 log in *Salmonella spp.* and *Listeria monocytogenes*, respectively. The data indicated that cinnamon oil NE is utilized as an active natural microbial control agent for melons [43]. The antimicrobial properties of natural polyunsaturated essential oils of *Polylophium involucreatum* and its performance in incrementing the shelf life of a type of shrimp were evaluated by Bahrami, *et al.* in 2019. The average size of the prepared 10% NE particles was 68.3 nm and the average diameter of *Escherichia coli* and *Staphylococcus aureus* growth inhibition zone for NE in agar diffusion was 9 and 10.4 mm, respectively. The average diameter of growth inhibition zone in vapor phase diffusion for 10% NE was zero against the mentioned bacteria. The minimum inhibitory and bactericidal concentrations for 10% NE were 50000 µg/L against *S. aureus* and 25000 µg/L for *E. coli*. Furthermore, pH, weight reduction percentage, and overall viable count, and psychrotrophic overall count microbial indices in NE treatments underwent fewer were changed in comparison to the control treatment. Furthermore, color assessment results revealed that there were no meaningful alterations within NE treatments ($P > 0.05$). The results showed that the use of 10% NE in terms of the *Polylophium involucreatum* reduce the number of microbes and increase storage time [44].

Scientists have found that oil in water NE have antimicrobial properties in the range of 200 - 600 nm. These particles selectively blend with the cell wall of bacteria or virus coatings without affecting the Eukaryotes in the tissue and begin to destroy pathogens. On the other hand, resistance in the strains is not caused by this non-specialized mechanism [45].

Packaging materials	Scattered phase of NE	Food	Reference
Chitosan coating	Mandarin essential oil	Green bean	[46]
Methylcellulose film	Clove bud and Oregano essential oils	Sliced bread	[47]
Sodium alginate	Lemongrass essential oil	Fresh-cut Fuji apples	[48]
Chitosan coating	Carvacrol, mandarin, bergamot and lemon oils	Green bean	[49]
Jujube gum edible coating	Nettle essential oil	Beluga sturgeon fillets	[50]
Thymol-quinoa protein/chitosan coating	Thymol	Cherry tomatoes	[51]
Quinoa protein/chitosan coatings	Thymol	Strawberry	[52]
Chitosan coating	Lemongrass oil	Grape berry	[53]
Carnauba wax coating	Lemongrass oil	Plum	[54]

Table 1: Apply NEs included in polymer matrix to protect food.

Conclusion

Due to their unique properties and better stability than conventional emulsions, NEs have a great potential in a wide range of industries, including food, pharmaceutical and cosmetic. Selecting the precise method and optimizing the conditions to improve the stability of

NEs will aid those industries to develop their production with greater capacity leading to their widespread use in them. Recent research has shown the benefits of many NEs in the production of natural and antimicrobial substances. The performance of these materials stems from their small size and high surface-to-volume ratio. This performance makes antimicrobial NEs interact more with microbial cells, or NEs containing bioactive materials -increase biological access and digestibility of these emulsions. Those above abovementioned advantages highlight the importance of conducting extensive researches addressing production of functional and industrial nanoparticles, especially NEs.

NEs have shown significant potential for food conservation. In this regard, several studies have shown their applications alone or in polymeric matrixes, in which they have played as an antimicrobial food shelf life. Oil extracts and oily compounds extracted from plants are most widely used in their hydrophobic phase to prepare NEs that show biological activity. NEs, when combined with film-forming polymers, can play an active role in food industry in form of food films or coatings. In case of antimicrobial activity of food packaging composite containing NEs, researchers are actively looking for a standardization protocol for NEs preparation as the data currently available in research papers have been obtained through a variety of methods, making them impossible to compare with each other.

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