Chapter

An Update on Nanoemulsions Using Nanosized Liquid in Liquid Colloidal Systems

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Abstract

Nanoemulsions, kinetically stable and thermodynamically unstable colloidal liquid-in-liquid dispersions with droplet sizes in the order of 20–500 nm mainly consist of oil, surfactants, co surfactants and an aqueous phase. There are various methods for the fabrication of Nano-emulsions which can be divided based on the energy required—High energy emulsification methods and Low energy emulsification methods. High energy emulsification includes methods like Ultra sonication, high pressure homogenization using either microfluidizers or high-pressure homogenizers. Low energy emulsification has drawn attention since they are soft, nondestructive and cause no damage to encapsulated molecules and includes methods like phase inversion temperature, solvent displacement, phase inversion composition method. Nanoemulsions are best suited for drug delivery systems because of their lipophilic nature, optical clarity and surface area. Owing to their nature to prevent flocculation and inherent creaming, nanoemulsions find an important place in the cosmetic industry also. This chapter provides an insight into the use of nanogels, emulsion based wet wipes and PEG free nanoemulsions in cosmetics. In the food industry, nanoemulsions are utilized for the production of functional foods. Some of the patented nanoemulsions and their commercial applications have also been mentioned.

Keywords: nanoemulsions, high pressure homogenization, ultrasonication, phase inversion temperature, solvent displacement, phase inversion composition, drug delivery, penetration pathways, cosmetics, nanogels, PEG free emulsions, wet wipes, functional foods, patented nanoemulsions

1. Introduction

In this chapter we will be briefing about the emulsion and its types. We will also be discussing in detail about nanoemulsions, its types, fabrication, application and its properties.

1.1 Emulsion systems and its types

An emulsion system generally consists of two or more liquids that are immiscible. They are a type of colloids, which are two-phase systems of matter. In emulsion

systems, the two phases are dispersed and continuous. One liquid is dispersed (the disperse phase) in the other (the continuous). The different types of emulsion systems can include: oil-in-water (o/w), water-in-oil (w/o), and oil-in-oil (o/o) [1]. The oil-in-oil phase can be polar oil dispersed in non-polar oil, or vice versa. An emulsifier is usually used to disperse immiscible liquids. The emulsifier also plays an important role in the formation and long-term stability of the emulsions. Emulsions can also be classified on the type of emulsifier or the structure of the system. Emulsions being liquids do not have any static internal structure. The droplets are assumed to be statistically distributed in the liquid matrix. According to IUPAC, in emulsions the droplets can be amorphous, liquid-crystalline, or any mixture. The droplet diameters in the dispersed phase range between 10 nm and 100 μm (which may exceed the size limits for colloidal particles) [2]. Some common example of emulsion systems are homogenized milk, some cutting fluids for metal working, egg yolk is an emulsion with the emulsifying agent lecithin, butter is an emulsion of water in fat, and an emulsion of silver halide in gelatin is used as a coating in the photosensitive side of a photographic film [3].

Emulsion system can be classified based on their droplet size as macroemulsion, nanoemulsion, and miniemulsion (**Table 1**).

Emulsion systems find a wide range of applications in the field of food, cosmetics, agriculture, pharmaceuticals (preparation of drugs and drug delivery).

1.2 Nanoemulsions

As the name suggests, the size of the droplets in this type of emulsion is in nanometer ranges. They not only differ in size but also in the many properties and method of preparation. The main difference between nanoemulsion and conventional emulsion (macroemulsion) is the size and shape of the droplets in the continuous phase. In macroemulsion, the shape is usually spherical but in nanoemulsions a variety of shapes can be seen like swollen micelles and bicontinuous structures. Though micro and nanoemulsions are similar in their sizes the method of preparation differs between them. Both of them require energy inputs, but nanoemulsions mostly use mechanical shear while micro emulsions make use of spontaneous emulsification methods. Microemulsions also need a high surfactant concentration compared to nanoemulsions. The application of nanoemulsion in pharmaceutical, food, cosmetic, and chemical industry is comparatively more than microemulsion since moderate surfactant concentration is sufficient for their making [5].

Nanoemulsions are said to be kinetically stable and thermodynamically unstable. Their stability can be altered by their preparation methods like adding specific co-surfactants. They usually use high energy methods for their preparation but low energy based methods can also be used with the help of some special conditions using certain chemical potential of the component [6]. Nanoemulsions are said to be transparent, biodegradable, and biocompatible. Normal emulsions usually undergo sedimentation by gravity, which is overcome by nanoemulsions. Nanoemulsions exhibit Ostwald ripening phenomenon. Due to this, small

Emulsion type	Droplet size (μm)
Macroemulsion	1–100
Microemulsion	10–100
Nanoemulsion	20–500

Table 1.
Emulsion type and its droplet size [4].

molecules collide and form large globules. To overcome this, co-surfactants are added or second oil is added to the dispersion phase. Proper manufacturing procedure also helps overcome Ostwald ripening [7]. Nanoemulsions provide a wide surface area and so allow active components to penetrate easily and faster. Another important characteristic of nanoemulsion is their transparent optical property. This is mainly due to their size, which is one fourth of the wavelength of visible light [8]. Nanoemulsions have the ability to solubilize both hydrophobic and hydrophilic substances, and hence enhance their permeability and bioavailability [9]. This makes them very useful as drug delivery systems for both the type of drugs.

Nanoemulsions are also said to have tunable rheological properties. They are tuned by controlling the dispersed phase volume, droplet size or the addition of salt and depletion agents [4]. Hence nanoemulsions can be tuned from being a free flowing fluid to a gel like substance [10]. Addition of polymers also tunes the rheological properties. The polymers associate either with themselves or with the nanoemulsions. A thermo reversible gel was made, where a polymer gelator (with two hydrophobic end groups) was added. At temperatures greater than the gelling temperature, the polymer's two hydrophobic ends bridges with the nanoemulsion droplets making them a gel. At lower temperature, they detach and hence return to a transparent fluid like structure.

There are three types of nanoemulsion based on the composition:

- Oil in water: oil droplets are dispersed in continuous aqueous phase.
- Water in oil: water droplets are dispersed in continuous oil phase.
- Bi-continuous (double): micro domains of oil and water are interdispersed within the system [11].

1.3 Current trends in nanoemulsions

As already mentioned, nanoemulsions are being used in a wide range of fields. There is a lot of research and development work done in the field of nanoemulsions. Many bioactive substances are present in natural available substances, emulsification of these bioactive components is a trending research topic. In September 2018, water compatible form of coconut oil through nano-emulsification was developed [12]. The nanoemulsion was made successfully using PHC as a surfactant at a concentration of 5% {w/w}. Nanoemulsions have also found an important space in field of pharmaceuticals. Many of the oral drugs synthesized do not have aqueous stability almost insoluble) and have low bioavailability. A low energy method to make composite hydrogel beads encapsulated with single and multiple hydrophobic drugs was developed [13]. This makes nanoemulsions a promising carrier of hydrophobic drugs. It was shown that nanoemulsions were used to enhance the antileishmanial activity of *Copaifera* spp. oleoresins against both *Leishmania amazonensis* and *Leishmania infantum* strains [14].

Recently a new technique for making Pickering nanoemulsions using Silica nanoparticles was developed which is highly scalable and energy efficient. Nanoemulsions are usually stabilized using surfactants. The use of surfactants has some disadvantages which include surfactant desorption and Ostwald ripening. Hence a new interest of making nanoparticle stabilized nanoemulsion (Pickering nanoemulsions) has evolved. Nanoparticles have higher desorption energy barrier. However, the limitation of nanoparticles as stabilizing agent was obtaining the size in nano-range. In the traditional method to make Pickering emulsions (high energy

and low energy methods, described in the next section) many steps were involved, a single step method was developed using vapor condensation. Moreover the traditional methods used in the preparation of Pickering nanoemulsions had some disadvantages. High energy methods reduced the adsorption of the particles on the droplets while, low energy methods were unable to produce Pickering nanoemulsions and clogging of nanoparticles was seen. The concentration of nanoparticles required in the new methods was also less compared to that required in traditional methods. In this process, oil was taken and cooled below the dew point, during which the water condenses on the oil. If the oil has the right properties and sufficient concentration of nanoparticles, then water drops self-disperse within the oil. The nanoparticles then will self-assemble around them to form nanoemulsions [15]. Nanoemulsions are studied in great detail due to their potential applications. Improvements in their preparation methods and the fields in which they can be used are the ongoing trends in nanoemulsions.

2. Fabrication

The fabrication of nanoemulsion involves the preparation of macroemulsions and then it's conversion to nanoemulsion by various methods, all of which can be categorized into either Low energy or High energy methods [5, 16]. Techniques which involve modification of factors responsible for the hydrophilic–lipophilic balance come under Low energy methods and those that use mechanical devices to break down the particles to small sizes are referred to as high energy methods. As much as composition is responsible for the properties of the nanoemulsion so is the technique used for its preparation. In this section a brief insight is given on a few widely used methodologies.

2.1 High energy methods for emulsion formation

In contrast to the low energy methods for nanoemulsion formation, high energy methods require the use of many devices which uses mechanical or chemical energy as input to form small droplets because they are non-equilibrium systems which cannot be formed spontaneously [17]. These devices often entail a huge initial cost as well as expenses to maintain throughout use. The purpose of these devices in high energy methods is to provide intense mechanical energy that helps to break up macroscopic phases or turn larger droplets into smaller droplets [18]. These devices provide forces so strong that it disrupt water and oil phases to form nanoemulsions. In high energy methods, input energy density is about 108–1000 W/kg. The required energy supplied is in very shortest duration of time to the system in order to obtain homogeneous small sized particles. In addition to this, the high energy methods for 55 nanoemulsion formation are not limited by the types of oil and emulsifiers that can be used like the low energy methods are. At present high energy methods are more frequently utilized in the food industry than low energy methods with high pressure valve homogenization, microfluidization, and sonication being the most common [19]. All this high energy methods are impacted by emulsion component characteristics (i.e. oil, type, surfactant type, surfactant concentration, viscosity, etc.) and equipment characteristics (i.e. size of the equipment, pressure used, number of passes/time in equipment, design, etc.). The input energy density is about 108–1010 W/kg [20]. These parameters should be optimized for each and every system and high energy method.

2.1.1 High pressure valve homogenizer (HPVH)

HPVH is the most popular method used for the production of nanoemulsions. The most common use is in applications from ketchup processing to milk homogenization and to manufacture nanoemulsions that particle sizes are up to 1 nm [18]. When using a HPVH, a coarse emulsion is initially made using a high-speed mixer, fed into the input valve of the HPVH, and then flowed between the valve seat and valve at a high velocity. The macroemulsion is forced to pass through a small orifice at an operating pressure between 500 and 5000 Psi [18]. Since several forces like hydraulic shear, intense turbulence and cavitation act together extremely small droplet sized nanoemulsions are achieved. The process is repeated till the final product reaches our desired droplet size and polydispersity index (PDI). Lower the PDI means higher uniformity of droplet size in nanoemulsions. Mono-disperse samples have PDI lesser than 0.08, narrow size distribution range is 0.08–0.3 and PDI greater than 0.3 indicates broad size distribution [18].

With an increase in velocity, the pressure decreases causing an instantaneous pressure drop and encouraging the coarse emulsion to impinge on the impact ring [21]. Sometimes HPVH passes through two valves and thus emulsion production will break up into two stages: in the first stage the droplets are broken up and in the second stage a lower pressure is utilized to disrupt any 'flocs' formed by the initial valve [22]. Obtaining submicron levels requires large amount of energy and high temperature which can deteriorate the components. Thermolabile compounds like proteins, enzymes and nucleic acids may be damaged easily [18] (**Figure 1**).

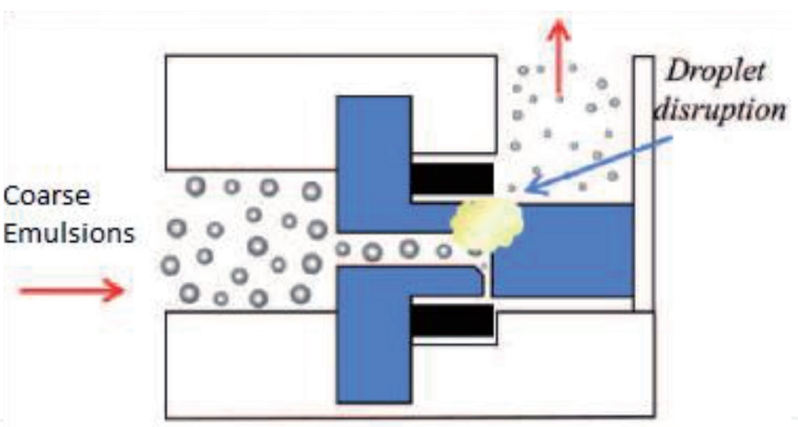

Figure 1.
Schematic representation of high pressure valve homogenizer [18].

2.1.2 Sonication

Emulsions produced by sonication use ultrasonic homogenizers (UH) to provide high intensity of ultrasonic waves to the sample. The frequency of the waves (29 kHz or larger) is higher than the maximum audible frequency of human ear (16–18 kHz) [17]. These waves provide around 56 disruptive forces to breakup oil and water phases thus forming small droplets on the principle of cavitation. Input energy comes from a sonicator probe which can be directly placed in the sample. There are two mechanisms which take part in sonication [17]. Firstly, acoustic field creates interfacial waves which makes oil phase to disperse in the continuous phase as droplets. Secondly, ultrasound provokes acoustic cavitation which provides formation and collapse of microbubbles respectively since there is a pressure fluctuation

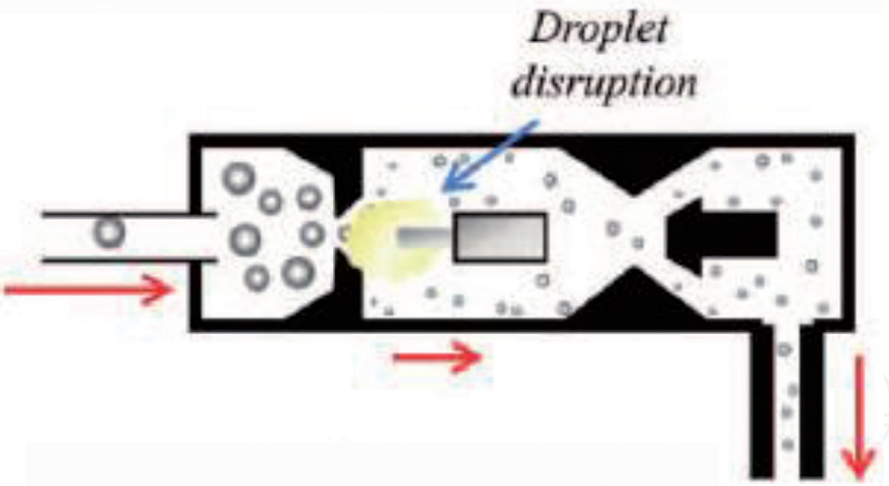

Figure 2.
Schematic representation of ultrasonic jet homogenizer [23].

of a single sound wave [23]. By this enormous levels of highly localized turbulence is generated and it causes micro implosions which disrupt large droplets into sub-micron size. Since most of the ultrasonic systems emits sound field which are inhomogeneous, so in order to have droplets to experience highest shear rate, recirculation of the emulsion through the region of high power must be provided and on repeating recirculation we obtain uniform droplet size at dilute concentration [18].

Presently sonication has been well established for the laboratory scale but it may be difficult to implement on a production scale because of issues like low throughput. Optimization of parameters (like emulsifier type, amount emulsifier and viscosity of phases) is necessary to prepare nanoemulsions having fine droplets [18]. Even, the high local intensity provided by sonication could lead to detrimental quality effects by way of protein denaturation, polysaccharide polymerization or lipid oxidation of the emulsion components [23] (**Figure 2**).

2.1.3 Microfluidization

Microfluidization is the most widely employed and novel technique in the pharmaceutical and cosmetic industry in order to acquire fine emulsions [18]. High pressure is provided by device called Microfluidizers (MF). Initially a coarse emulsion is made using a high speed mixer which is then fed into the hood and accelerated at high velocities within the channels using a pumping device and the macroemulsion to go through the interaction chamber by the high pressure forces and thus nanoemulsions with submicron ranged particles are produced [17]. The channels are made to collide into each other within the interaction chamber [21]. Uniform nanoemulsion can be produced by repeating the process many times and vary the operating pressure to get desired particle size [18].

The main parts of a MF include a fluid inlet (where the coarse emulsion is fed), a pumping device (to help move the emulsion through), and the interaction chamber or nozzle (where the particle collision occurs) [22]. A collision between crude emulsion jets from two opposite channels in the nozzle of microfluidizers is observed. The mobility of crude emulsion is supplied by a pneumatically powered pump that has capability of compressing air up to pressures between 150 and 650 MPa [18]. This high pressure forces the crude emulsion stream to go through microchannels and after the collision of two opposite channels enormous level of shearing force is produced. Hence, by the help of this force fine emulsions are produced [23] (**Figure 3**).

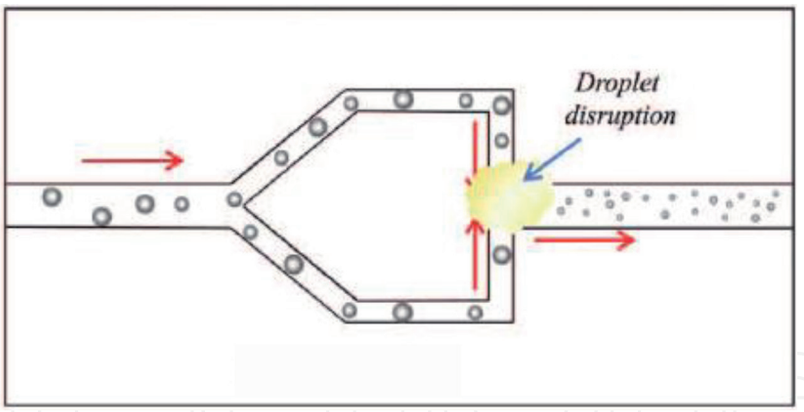

Figure 3.
Schematic representation of microfluidizer [23].

2.2 Low energy methods

Requiring no expensive equipment, easier implementation and better efficiency in terms of energy are the reasons for the growing interest in low energy methods [16, 17, 24, 25]. Moreover, encapsulation of drugs and macromolecules can be carried out due to mild operating temperatures. The necessity for higher amounts of surfactants may be a downside [17]. The whole concept of low energy synthesis has its roots in modification of factors responsible for the hydrophilic–lipophilic balance of the surfactant-oil–water mixture [26]. These include environmental factors like temperature, composition and the chemical potential of the components. Spontaneous Emulsification (SE) and Phase Inversion are two commonly implemented synthesis [17, 24].

2.2.1 Spontaneous emulsification

An emulsion can be fabricated by diluting a biphasic system leading to diffusion of one phase to another. This is usually done by adding the organic phase into the aqueous phase and then a surfactant which is water miscible. The migration of the surfactant causes disorder at the interface of the two phases leading to an increase in the surface area along with the formation of oil droplets in the aqueous phase [16].

To obtain nanoemulsions, the same dilution process is performed on microemulsions. The properties of the nanoemulsion depend on the oil viscosity, surfactant hydrophilic–lipophilic balance and solvent miscibility with water. With the help of an appropriate dilution procedure and composition, both W/O and O/W microemulsions can be used to obtain nanoemulsion. While obtaining it from O/W microemulsion the composition of microemulsion and the procedure of dilution does not matter, whereas while starting with W/O microemulsion the dilution procedure and /or the composition of microemulsion matters. O/W and W/O nanoemulsions can be formed even without a surfactant, this is called the Ouzo effect also known as Solvent displacement method [24, 27, 28]. This phenomenon has mainly been used for fabricating polymeric nanoparticles or nanocapsules using nanoemulsion as a template in drug delivery [25].

2.2.2 Phase inversion

As addressed earlier, there are different types of Nanoemulsions, either oil in water (O/W) or water in oil (W/O). Phase inversion, as the name suggests, is a fabrication method that involves conversion of O/W to W/O emulsion or vice versa. It utilizes the energy released during this conversion for the formation of droplets. This physical process can be brought about by varying the temperature or phase

volume ratio, giving rise to phase inversion temperature (PIT) method and phase inversion composition (PIC) method [29].

In these emulsification methods it is very important to know the behavior of the surfactant as it plays a significant role in minimizing both droplet size and polydispersity of the nanoemulsion formed. Its properties also depend on the kinetics of the emulsification process, especially if they have high viscosity [27].

2.2.2.1 Phase inversion temperature

The Phase inversion temperature (PIT) method is used when the surfactants are sensitive to changes in temperature. The principle of this method is based on the changes in surfactant spontaneous curvature (molecular geometry) with temperature. For example, in poly(oxyethylene)-type non-ionic surfactant, increase in temperature causes dehydration of the poly(oxyethylene) chains whereas at low temperature these chains are hydrated and hence are hydrophilic in nature. At one temperature the surfactant exhibits both hydrophilic and lipophilic properties, this temperature is known as HLB temperature (Hydrophilic–Lipophilic Balance) [17, 27]. So, at this temperature the surfactant is equally soluble in the oil and aqueous phase [16, 17].

Using PIT very small sizes of droplets can be obtained. At the HLB temperature due to the low interfacial tension the surfactant forms a layer but as soon as the temperature is changed by quick cooling or heating, the surfactant molecules move from one phase into another resulting in the formation of small oil droplets. The movement of the surfactant molecules depends on its hydrophilicity or lipophilicity of its chain which in turn depends on temperature [16, 17] (**Figure 4**).

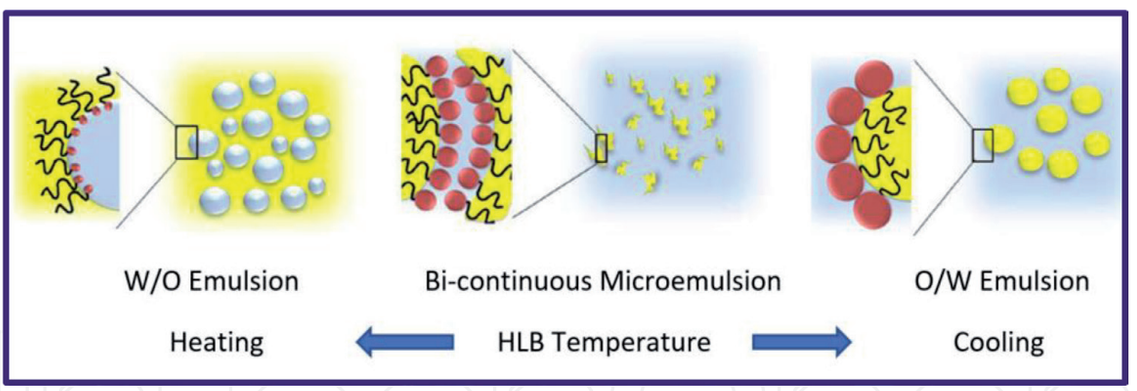

Figure 4.
Shows the curvature of surfactant and the favorable emulsion formed by heating and cooling [16].

2.2.2.2 Phase inversion composition

Phase inversion composition is performed when the surfactant properties changes due to dilution of one of the phases. It involves dilution of oil phase with water or vice versa which causes an increase or decrease in hydration degree of surfactant. In phase inversion composition, phase transition takes place at constant temperature. At one point in the dilution process the affinity of the surfactant becomes equal for both the phases that is it exhibits both hydrophilic and lipophilic properties. This point is known as the emulsion inversion point [4]. At this stage a layer of microemulsions is formed. A slight change in the proportion of oil and water causes instability of the microemulsion layer which disintegrates to form nanoemulsion that are kinetically stable. It was found out that with further

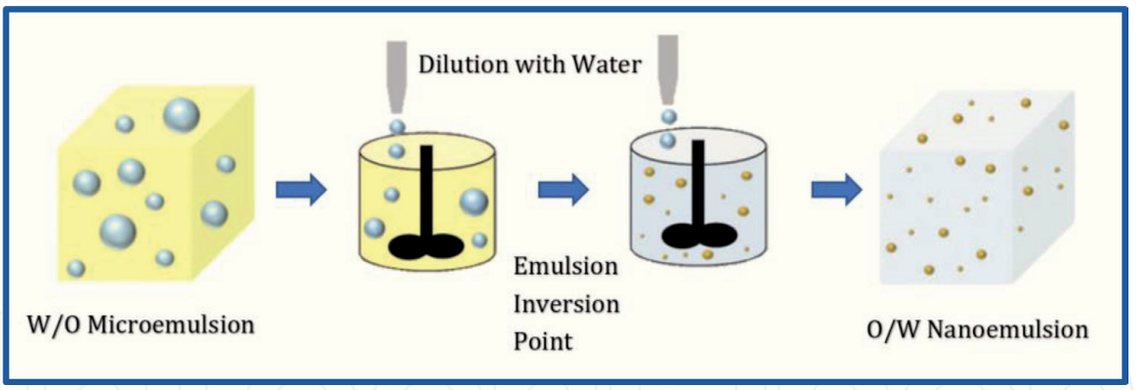

Figure 5.
Shows the process of phase inversion by dilution with aqueous phase [4].

dilution the droplet size does not change [28]. The properties of the nanoemulsion obtained depends on conditions such as shear rate and the addition rate [30]. Heat sensitive compounds can be encapsulated by using this fabrication method for nanoemulsions.

To obtain an O/W nanoemulsion, initially a W/O microemulsion (consisting of surfactant) is required to which aqueous phase is added in a controlled manner. The resulting system is stirred for breakdown of the residues and for homogeneity [24]. This process is depicted in **Figure 5**.

3. Applications of nanoemulsions

3.1 Drug delivery

A great attention is given towards the use of nanoemulsions in research, dosage form design and pharmacotherapy owing to their optical clarity, ease of preparation, thermodynamic stability and increased surface area. Some of the problems associated with conventional drug delivery systems such as low bioavailability and noncompliance which can be overcome by nanoemulsions are discussed here (**Figure 6**).

3.1.1 Parenteral delivery

It is the most effective form of drug delivery system usually adopted for active ingredients with low bioavailability and narrow therapeutic index. Here the therapeutic peptides or drugs prepared in the form of solutions or suspensions, are given as injections. Intravenous, intramuscular and subcutaneous drug delivery systems are the most commonly used parenteral routes.

Dissolution of enormous amounts of hydrophobic compounds coupled with mutual compatibility and ability to safeguard drugs from hydrolysis and enzymatic degradation make nanoemulsions ideal vehicles for parenteral transport [32]. Nanoemulsions help in sustained and controlled drug delivery through parenteral routes. Since nano emulsions are cleared more slowly (more residence time) than the coarse particles, they are advantageous over macroemulsion systems when delivered parenterally [33].

Nanoemulsions loaded with thalidomide have been synthesized. A dose as low as 25 mg leads to plasma concentrations which can be therapeutic when delivered through this system [34].

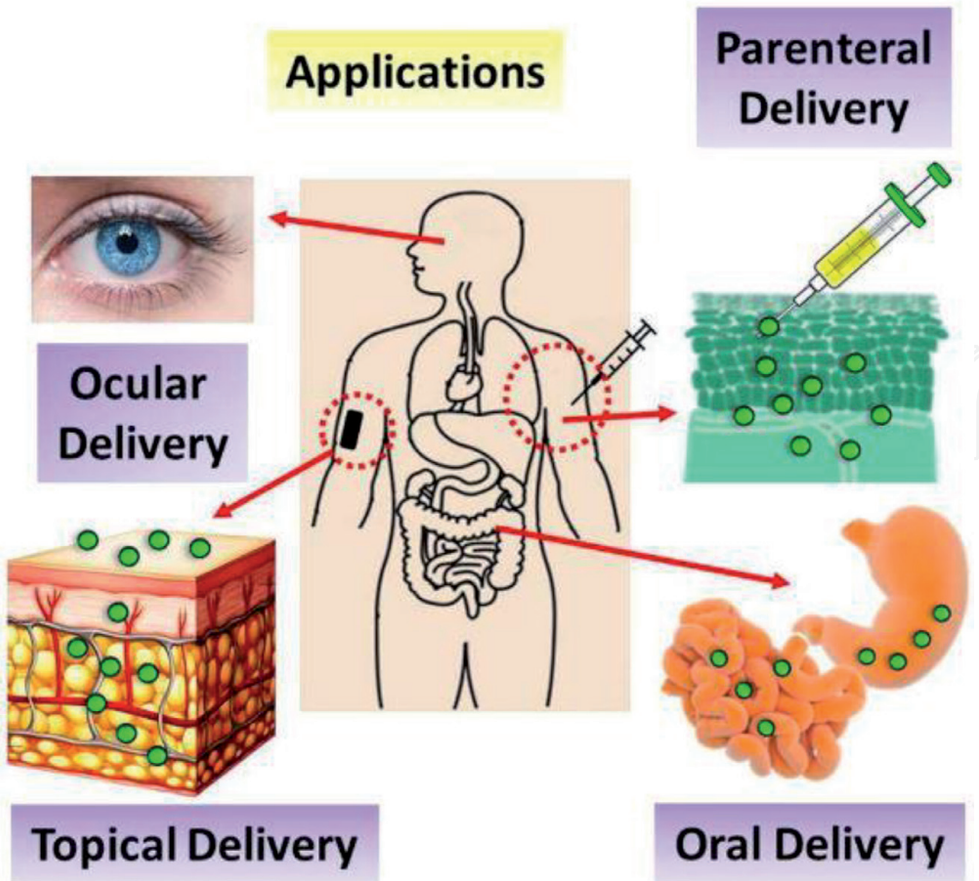

Figure 6.
Applications of nanoemulsions in drug delivery [31].

3.1.2 Oral and topical drug delivery systems

Owing to patient compliance, convenience, ease of formulation and higher absorption in the intestine, oral drug delivery is the most widely distributed and preferred form of drug administration.

When compared to conventional oral formulations, nano emulsion formulations provide several benefits in oral drug administration. Some of these benefits include increased absorption, improved clinical potency and decreased drug toxicity [33]. Hence, drugs such as steroids, hormones, diuretics and antibiotics can be ideally delivered using nano emulsions.

Topical drug delivery also has several advantages over other modes of drug administration such as the avoidance of hepatic first pass metabolism, reduction of toxicity and targeted drug delivery to the affected portion of the skin. Here self-administration is also possible. The transparent nature and fluidity of nanoemulsions not only gives a pleasant skin feel but also helps in eliminating the drug input by just removing the transdermal patch without any irritation [32].

Owing to the large surface area of the droplets, nanoemulsions enable rapid penetration of active ingredients through the skin. This is one of the most valuable properties of nanoemulsions due to which the use of special penetration enhancers which cause incompatibility of the formulation can be minimized [33].

3.1.3 Ocular and pulmonary drug delivery

For the treatment of eye diseases, drugs are delivered topically in ocular dosage forms such as solutions, suspensions and ointments. Due to physiologically

protective mechanisms such as tear dilution, lacrimal drainage, protein binding and enzymatic degradation which are activated as soon as the ophthalmic solutions of the drug are applied, typically less than 3% of these topically applied drugs permeate the corneal epithelium, reach the aqueous humor and finally enter the systemic circulation. O/W Nanoemulsions (Oil in Water nano emulsions) have been researched for ocular administration to dissolve poorly soluble drugs, to increase absorption and also to attain prolong release profile [33].

Cationic submicron emulsions are promising carriers for DNA vaccines to the lung since they are able to transfect pulmonary epithelial cells thereby inducing cross priming of antigen-presenting cells and directly activate dendritic cells, resulting in stimulation of antigen-specific T-cells [35].

There might be adverse side effects of oils and surfactants on the alveoli of lungs. Hence extensive studies are required for the development of successful inhalable submicron emulsions for pulmonary delivery [32].

3.2 Nanoemulsions in biotechnology

Nanoemulsions serve as a waterproof medium for bio-catalytic or enzymatic reactions to occur. The enzymes in low water content exhibit greater solubility in non-polar reactants and higher thermal stability. As a result, the thermodynamic equilibrium also shifts towards condensation [36].

Reactions such as synthesis of esters, peptides and sugar acetals transesterification, hydrolysis and steroid transformation are catalyzed by enzymes in nanoemulsions. Lipases are the most widely used class of enzymes in microemulsion-based reactions [33].

3.3 Nanoemulsions as non-toxic disinfectant cleaners

The non-toxic disinfectant cleaner developed by Enviro Systems Inc. has wide applications in commercial markets such as healthcare, hospitality, travel, food processing, and military. This product which kills a wide spectrum of bacteria, virus and fungi in 5–10 minutes without any hazards needs no warning labels. This can be absorbed through the skin, inhaled or swallowed without causing any irritation to the eyes and does not cause any harmful effects [33]. One such NE is Parachlorometaxylenol (PCMX) marketed as EcoTru [36].

3.4 Nanoemulsions in the food sector

Lipophilic compounds such as flavors, omega3fatty acids, vitamins, nutraceuticals and preservatives can be encapsulated, stabilized and delivered using nanoemulsions. This is one of the emerging fields in the food industry [37]. Research is mainly focused on nanoemulsion technology that is suited for functional foods.

3.4.1 Encapsulation of lipophilic components using nano-emulsions

Encapsulation is a useful technique to deliver bioactive molecules within living cells. Here, the bioactive ingredient is entrapped in a core or filled within a carrier (coating, matrix, membrane, capsule, or shell) [38].

This technology is used in food industry to:

- Mask the unpleasant taste or odor of some bioactive materials.
- Increase the bioavailability of some components.

- Improve stability of food ingredients.
- Decrease air-induced food degradation.
- Reduce Evaporation of food aroma.

Another important application of this technique that is worth mentioning is in probiotics [38]. (Probiotics are the microorganisms that provide health benefits when consumed in adequate amounts) (**Figure 7**).

Biologically active lipids such as omega-3 fatty acids can be encapsulated by nano-emulsions from food grade ingredients. Omega-3 fatty acid supplementation has a protective effect against cancer, cardiac death, sudden death, cognitive aging, asthma, inflammation and myocardial infarction [38]. α-Linolenic acid (ALA), an Omega-3 fatty acid, is one of two essential fatty acids together with linoleic acid. ALA is necessary for health and cannot be synthesized within the human body [38].

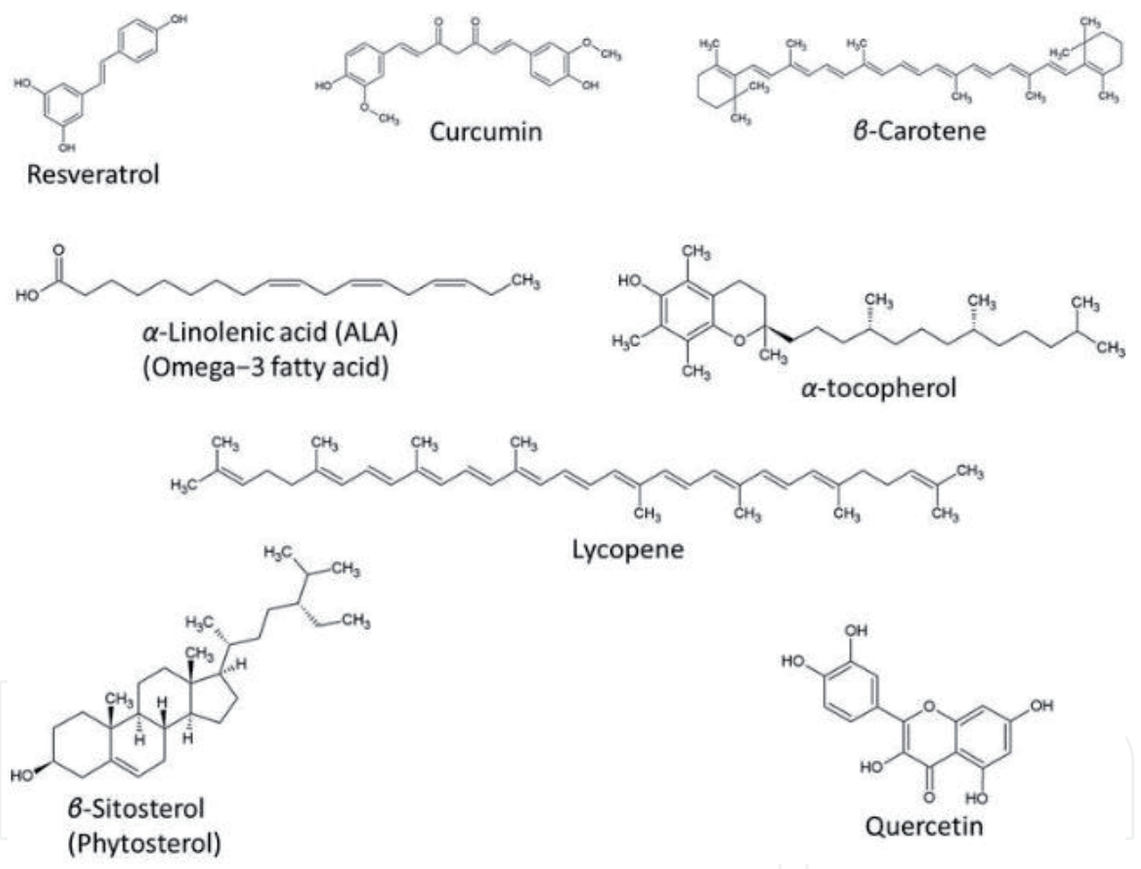

Figure 7.
Applications of nano-emulsion based delivery systems in food industry [38].

3.5 Nanoemulsions in cosmetics

What are cosmetics? *'Personal Care Products' or 'Beauty Products' such as skin creams, lotions, perfumes, lipsticks, fingernail polishes, eye and face make-up products, hair dyes and deodorants which are used by people to cleanse or change the look of the face or body are cosmetics. They do not alter the body's structure and function. Cosmetics are superficial and can also be therapeutic.*

Nanoemulsions are potential vehicles for optimum dispersion of active ingredients and their controlled delivery in particular skin layers. Their lipophilic interior makes them more suitable for the transport of lipophilic substances when

compared to liposomes. Small sized droplets and high surface area of nano-emulsions contribute greatly in inhibiting inherent creaming, flocculation, sedimentation and coalescence which are frequently observed in macroemulsions [33]. They have gained popularity in cosmetics due to ease of permeability and penetration into the skin owing to their small size and high surface area, solubility, transparency and color.

Advantages of using Nanoemulsions in cosmetics

- As mentioned earlier, nano-emulsions help to overcome problems such as inherent creaming, flocculation, coalescence, and sedimentation.
- Relatively less surfactants (5–10%) [39] are used for nano-emulsion formulation (approved for human use) making them non-toxic and non-irritant. Hence, they can be easily applied onto the skin and mucous membranes [40].
- Healthy human and animal cells are not damaged by nano-emulsions. As a result, they are best suited for human and veterinary therapeutic purposes [40].
- Nano-emulsions can also be easily formulated in the form of foams, cream, liquids, sprays.
- Significant improvement in dry hair aspect (after several shampoos) is obtained with a prolonged effect after a cationic nanoemulsion use [39].

Oil in water nanoemulsions, due to their lipophilic interior have numerous applications in cosmetics such as formulation of lotions, sunscreens and skin creams, hair care products and make up removal substances. Other extremely important and fast growing applications include Emulsion based wet wipes and PEG (Polyethylene glycol) free nanoemulsions [40].

3.5.1 PEG free nanoemulsions and emulsion based wet wipes

The recent trends are shifting towards highly effective safer and natural cosmetic products. Cosmetic manufacturers are developing new methods to prepare nano versions of formulations for better permeability, effectiveness and increased customer satisfaction. This new technology is based on manufacturing low viscosity oil in water nanoemulsions which are free of synthetic chemicals like PEG. The phase inversion method of fabricating nanoemulsions leads to an important application in the cosmetic industry -formulating lotions to be impregnated in wet wipes. These are primarily used for make-up removal and wet wipes [11].

Industries are working on developing low energy methods coupled with low input homogenizers and absence of PEG, energy input for heating/cooling steps to formulate natural products [11]. The main constituents of this formulation are PEG free emulsifiers, cosmetic oils in high amounts and co-surfactants. When water is added to such a liquid and clear oil phase, a temporary micro-emulsion is formed which is then converted to stable, low-viscosity nanoemulsion. This low viscous phase is beneficial as it helps in converting the emulsion from water in oil to oil in water nanoemulsion. This step being dependent on water concentration is termed as phase inversion concentration which occurs by elimination of the co-surfactant into water. Some of these products developed are TEGO Wipe DE and TEGO Wipe DE PF which are based on nanoemulsions impregnated in wet-wipes and also used for lotions and sprays [41, 42].

3.5.1.1 Skin as a barrier and penetration pathways through the skin

The human body is protected from external harm such as chemical and micro-organism intrusion, UV exposure, dryness and mechanical damage by a natural barrier, the skin.

Hence the multi-layered skin serves as the first line of body defense. The external and internal layers of the skin mainly include the stratum corneum (composed of dead keratinized cells) and below the stratum corneum are the epidermis, dermis and the subcutaneous tissue. The excellent barrier properties of the skin are due to the presence of lipid matrix (containing ceramides, fatty acids, cholesterol and cholesteryl esters) among the keratinized cells which has cement like property [28].

When a drug or an active ingredient is topically applied on the skin surface, there theoretically three different ways through which the drug/active ingredient can penetrate through the skin. These are known as 'The Penetration Pathways'. The penetration pathways are:

- The intercellular pathway
- The hair follicle pathway
- The transcellular pathway

The intercellular pathway: This is the most widely known pathway. In this pathway, diffusion of the active ingredient occurs through the stratum corneum via the lipid layers surrounding the corneocytes.

The hair follicle pathway: The hair follicles are surrounded by a dense network of blood capillaries which support efficient penetration. These serve as reservoir for the topically applied active compound.

The transcellular pathway: This is the less understood pathway. Here the drugs are directly transported through the lipid layers and corneocytes to the living cells (**Figure 8**).

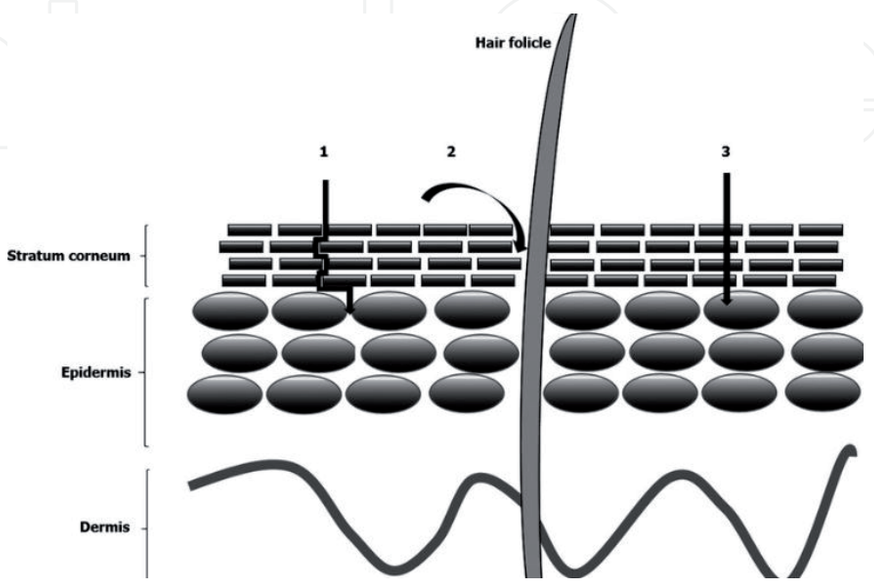

Figure 8.
Penetration pathways of the active ingredient through the skin. (1) Represents the intercellular pathway, (2) represents the hair follicle pathway and (3) represents the transcellular pathway [28].

3.5.2 Nanogels

While nanoemulsions are an efficient vehicle for transferring and administering topical drugs into the body, they have some limitations. These are low viscosity, spreadability constraints due to skin as a barrier and rheological properties.

To overcome these problems associated with nanoemulsions, a hydrophilic gelling system was integrated with nanoemulsions to increase the efficiency of transdermal drug delivery. These integrated systems are termed as nano emulgels [43].

Nanoemulgel are usually three-dimensional, spherical gels composed of a cross-linked network of polymeric (natural or synthetic substances) [44]. They are highly preferred over other nanomaterials for drug delivery due to their unique and advantageous features. The most important ones being biocompatibility, stimuli–response behavior softness, their ability to swell up to achieve a controlled, triggered response at the target site. They also protect the guest molecules i.e., the molecules they are carrying from degradation and elimination.

The versatility of their architecture allows for incorporation of a plethora of guest molecules ranging from inorganic nanoparticles to biomacromolecules like proteins and DNA with suitable modifications of the materials used for their construction without compromising their gel behavior. This multi-functionality and stability is hard to find in other types of nanoparticulate systems [43, 45, 46].

Nanogel properties can be used in various fields to achieve biomedical applications.

Stimuli response behavior: This involves the response of the nanogels to the external environment in the body such as pH, temperature, redox reactions, enzyme concentration etc. It employs the unique ability of the gel network to swell and unwell for this purpose. The nanogels can be composed of different materials depending on the type of response to be initiated. The deswelling and swelling occurs in the presence of changes in pH and concentration of the surrounding environment. For example, a gel network made of polysaccharide functionalized with PBA (aminophenyl boronic acid) is used to detect the fluctuations in glucose concentration, pH, concentration of the cationic and anionic groups bound to the gel and the PBA grafted to the gel which induces the release insulin by deswelling [44].

Another very important feature is protecting the cargo molecules from degradation and elimination and early clearance carrying small molecules for drug delivery by retaining them within the gel via hydrogen-bonding and hydrophobic interactions. Cationic gel polymers are also useful in carrying molecules of opposite charges such as oligonucleotides, proteins, RNA molecules or a combination of them to achieve multi-target drug delivery. This has been proven to be useful for cancer treatment in animals.

These hydrogels show immense amount of versatility, biocompatibility and fluid like transport properties which make them ideal carriers for imaging probes and scanning techniques such as optical imaging and multi-modal scanning [46]. It is also useful for anti-aging, skin care and moisturizing creams [31].

4. Conclusions

Nanoemulsions are a relatively new class of dispersions which have gained popularity due to their high efficiency in delivery. There have been a lot of efforts and research to develop the preparation methods of nanoemulsions. This emerging component of nanotechnology has become an irreplaceable part and parcel of the cosmetic and pharmaceutical industries. Further research and development in this field can prove to be very crucial for these industries. Nanoemulsions have a huge potential to change the approaches to many fields as discussed in this chapter and

it can also play much more important roles in the future due to its uniqueness and increasing research in its field.

5. Future scope

The market for nanoemulsions is expected to grow at the rate of 8.8% between the years 2018 and 2023 [47].The growth is expected to be driven by the increasing demand for the treatment of chronic diseases and vaccine development. Nanoemulsions have huge potential to improve the efficacy of cancer immunotherapy by multiple folds. The major hindrance to the growth is the expensive manufacturing methods and scaling up with cost effectiveness. The technological innovation and scaling opportunities is expected to decrease the cost of production. Due to its unique properties, nanoemulsions can also become an active component in the chemical, agricultural and engineering fields. Nanoemulsions can also find an application as drug delivery platforms to noval phytopharmaceuticals given the new interest in herbal drug formulations in the world [32].

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