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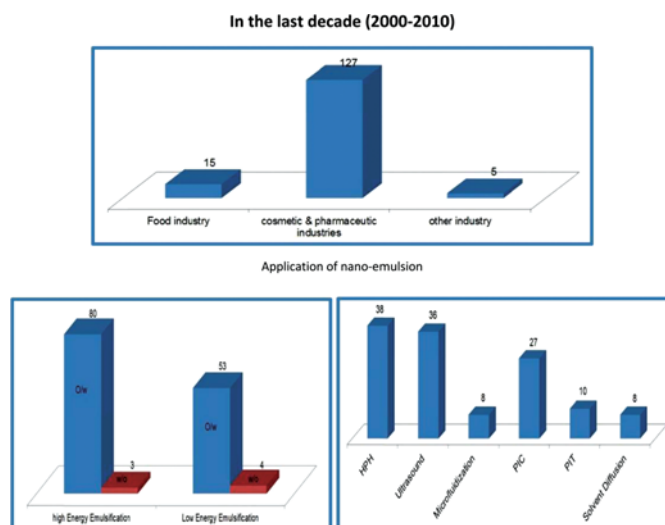
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Preparation and Application of Nanoemulsions in the Last Decade (2000–2010)

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GRAPHICAL ABSTRACT



An emulsion is a system containing two immiscible phases: a dispersed phase and a continuous phase. Components needed to prepare an emulsion are oil, water, surfactant, and energy. The nature of surfactant determines the type of emulsion (oil-in-water (O/W) or water-in-oil (W/O)). A nanoemulsion is an emulsion with 20–200 nm droplet size. The required energy to form a nanoemulsion can be obtained from a mechanical device (high-energy emulsification) or from the chemical potential of the components (low-energy emulsification). High-energy emulsification consists of high-pressure homogenization (HPH), ultrasonication, and microfluidization and low-energy emulsification consists of phase inversion temperature (PIT), phase inversion composition (PIC), and solvent diffusion. O/W nanoemulsions have been studied more than W/O nanoemulsions and the preparation of nanoemulsions with high-energy emulsification is more reported than low-energy emulsification. The small droplet size of a nanoemulsion enhances the emulsion stability; therefore, nanoemulsions have various applications in the industrial field, such as personal care and cosmetics as well as health care, food, and agrochemicals. Pharmacy and cosmetics are fields where more direct applications of nanoemulsions are proposed.

Keywords High-pressure homogenization, nanoemulsion, phase inversion composition, phase inversion temperature, ultrasound

1. INTRODUCTION

An emulsion is a system containing two immiscible phases, one of which is the dispersed phase as droplets (internal phase) and the other is the continuous phase (external phase).^[1] There are two types of emulsions: water-in-oil or inverse emulsion and oil-in-water or direct emulsion.^[2] Emulsions can be categorized into three groups depending on the emulsion droplet size (EDS): micro

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(10–100 nm), mini (nano) (100–1000 nm), and macroemulsions (0.5–100 mm).^[3,4]

The inherent stability of an emulsion increases as the droplet size decreases. This is evident from the Stokes-Einstein equation, which expresses that sedimentation rate depends on the square of the radius of the droplets.^[5] There are many degrees of freedom in the preparation of emulsions, such as emulsification process and conditions, the type and amount of surfactants, the location of surfactant, the presence of electrolytes and co surfactants, etc.^[1]

If only mechanical agitation is used, dispersion of the dispersed phase in a continuous phase is usually unstable. This is because, if stirring stops, the two phases are separated. To overcome this problem, that is, to make a kinetically stable emulsion, the surfactant or emulsifier is added to the emulsification system as a third component. The nature of the surfactant determines the type of the emulsion. If the surfactant is oil-soluble the resulting emulsion is a water-in-oil (W/O) emulsion. On the other hand, if the surfactant is water-soluble the continuous phase of emulsion is water and the emulsion formed is an oil-in-water (O/W) emulsion.^[6] Generally, the phase in which the emulsifier is most soluble is considered as a continuous phase. The choice of right emulsifier is very important. The desired stability of emulsion cannot be usually obtained by using a single surfactant. It is known that a surfactant with a broad chain length distribution usually makes a more stable emulsion. Moreover, the emulsion stability can be improved by utilizing a mixture of surfactant.^[1] In this way, the dispersed phase from coalescing into a macroscopic phase is prevented.^[7]

Griffin^[8,9] based on the stability of the emulsion, introduced the concept of hydrophilic-lipophilic balance (HLB). The HLB number is a measure of the size and strength of the two hydrophilic and lipophilic groups in an emulsifier molecule. Rather than the over-all efficiency of the emulsifier, this number indicates what kind of an emulsion is produced.

It is better to use a mixture of surfactants with the same HLB number. The mixed HLB values were calculated by the following equation:

$$HLB_{mix} = HLB_1 W_1\% + HLB_2 W_2\% + \dots,$$

where W% is weight percentage of each surfactant.^[10] HLB number affects spontaneous emulsification and EDS. For formation of O/W emulsions Surfactants with HLB >10 are suitable.^[11]

Since the 1980s, attention has been focused on emulsions with nanometric droplet size, which are referred to as nanoemulsions, mini-emulsions, fine-disperse emulsions, homogeneous emulsions, submicron emulsions, or unstable microemulsions.^[10] Nanoemulsions can be divided in to two groups based on droplet size namely transparent or

translucent (50–200 nm) and milky (up to 500 nm).^[12] As nanoemulsions have a small size, they often possess long-term physical stability and their properties are superior to the conventional emulsions.^[10] Nanoemulsions can be produced at moderate surfactant concentration (in the range of 4 to 8 wt%) while for formation of microemulsion with high concentration of surfactants is needed (usually in the range 10–30 wt%).^[12] One can produce nanoemulsions by two methods: high-energy and low-energy emulsification methods.^[10]

In this review, we will discuss four topics: Section 2 is dedicated to fundamental principles of emulsification process and the role of surfactants. In Section 3, we consider production of nanoemulsions using high-energy emulsification which consists of HPH, microfluidization, and ultrasonication. In Section 4, production of nanoemulsions using low-energy emulsification, which consists of PIT, PIC, and solvent diffusion is considered. Application of nanoemulsions and some examples of it are given in Section 5.

In this article, the methods of preparation of nanoemulsions, the pattern of usage of each method and various application of nanoemulsions in the past decade (2000–2010) is studied.

2. FUNDAMENTAL PRINCIPLES OF EMULSIFICATION PROCESS AND THE ROLE OF SURFACTANTS

Components needed to prepare an emulsion are oil, water, surfactant, and energy. The total free energy of formation of an emulsion (ΔG) can be obtained using the following equation:

$$\Delta G = \Delta A\gamma + T\Delta S,$$

Where ΔA is the increase in interfacial area, γ is the interfacial tension, T is the temperature of process, and ΔS is the amount of change in entropy. The value of ΔG is positive because the value of entropy of dispersion $T\Delta S$, which is positive, is greater than absolute value of consumed energy ($|\Delta A\gamma|$). The positive ΔG leads for nonspontaneous emulsion formation and hence energy is required to have produced the droplets. The formation of large droplet emulsions (macroemulsions) is easy. Therefore, to produce macroemulsions, high speed stirrers such as the Ultraturrax or Silverson Mixer is adequate. In contrast to the formation of small drops (nanoemulsions) is difficult and requires a large amount of energy.

During emulsification various processes occur, among which disruption of droplets, adsorption of surfactants and droplet collision are some examples. Each of the above processes occurs numerous times during emulsification and the time of each process is about a microsecond. This highlights the dynamic nature of the emulsification process and events that occur in a microsecond range are very important.

Surfactant reduces the interfacial tension (γ) and, consequently, the droplet size is reduced. Some mixtures of surfactants lead to lower interfacial tension than when either is used individually. In addition, surfactants have an important effect on the deformation and disruption of droplets and prevent coalescence during emulsification. Surfactants with $HLB > 7$ form O/W emulsions and $HLB < 7$ form W/O emulsions. The disperse phase volume fraction (Φ) is the most important factor in emulsification. Increasing the disperse phase volume fraction causes an increase in droplet collision and, hence, coalescence during emulsification. In addition, increasing Φ , leads to increase of the viscosity of the emulsion, which could change the flow from being turbulent to being laminar. The increase in Φ induces turbulence depression in turbulent flow resulting in larger droplets. In addition, if polymers are added to the system, turbulence depression tends to remove the small eddies and, hence, larger droplets will be formed.^[13]

The required energy to form nanoemulsions can be obtained from mechanical device or from the chemical potential of the components. Preparation of nanoemulsions can be categorized in two groups: i) dispersion or high-energy emulsification methods and ii) condensation or low-energy emulsification methods.^[14]

3. HIGH-ENERGY EMULSIFICATION

High-energy methods use intense mechanical forces to disrupt droplets into smaller droplets, and typically involve the use of mechanical devices.^[15,16] The methods in this category have a drawback, which is that they need high energy to prepare nanoemulsions and, therefore, they are unfavorable for many industrial applications.^[13] The formation of nanoemulsion droplets directly depends on controllable formulation parameters such as the amount of energy, the amount of surfactant and the nature of the components.^[17]

High-energy methods can be categorized in three groups: i) HPH,^[14,15] ii) microfluidization,^[18,19] iii) ultrasonication.^[14,15]

HPH and microfluidization can be used at both laboratory and industrial scale while ultrasonication is primarily used at laboratory scale. Although high-energy methods are effective in reducing droplet size, they are undesirable for labile drugs and macromolecules, such as proteins and nucleic acids, for which low-energy emulsification methods are used.^[20]

3.1. HPH

Conventional HPH works in 50–100 Mpa pressure. Although with new equipment pressure of 350 Mpa is reachable, O/W nanoemulsion with methylcellulose as a surfactant can stable with the pressure less than 150 Mpa.^[14] In,^[21] the authors prepared nanoemulsions by a simple homogenizer to avoid high-pressure condition. They prepared nanoemulsion containing Itraconazole by simple,

conventional homogenization using Ultra-Turrax homogenizer, at a speed of 24000 rpm.

In a standard procedure, materials are passed among the narrow gap of homogenizer in high pressure (50–200 Mpa). This high pressure causes a strong disruptive force such as shearing, collision, and cavitation. Intensive turbulency and hydraulic shear cause coarse emulsion change to nanoemulsion.^[22] The droplet size depends on the number of cycles, the pressure, and temperature of the system. The more the number of cycles and the pressure, the smaller the size of droplets produced^[22,23] (Figures 1 and 2).

In addition, this size also depends on emulsion composition (e.g., organic and aqueous phase and surfactant), emulsifier's characteristic (e.g., adsorption kinetic, interfacial tension depression, and stabilizing properties), and physicochemical condition of different phases (e.g., viscosity and interfacial tension).^[23] HPH can be processed in high temperature (hot HPH technique) or in low temperature (cold HPH technique), which then later is used for processing temperature labile drugs.^[24] Comparing to other procedures, HPH has many advantages such as easy scale up, avoidance of organic solvents, and small process time. HPH is widely used in many industrials specially in pharmacy and cosmetic.^[25] The pattern of usage of HPH is illustrated in Figure 3.^[19,23,26–81]

3.2. Microfluidizer

Oil and aqueous phase are mixed together and enter the homogenizer to produce coarse emulsion. This coarse emulsion enters the microfluidizer to produce stable nanoemulsions. In the microfluidizer, a high-pressure pump is used. This pump, which works in high pressure up to 2000 psi, forces the produced emulsion to pass through the interaction chamber, which has some microchannels. Therefore, the emulsion's droplet will be very small.^[20,22] The diameter of nanoemulsions' droplets depends on the pressure of the operation and the number of microchannels in interaction chamber. As illustrated in Figures 3 and 4, the more the pressure and the number of cycles, the smaller the size of

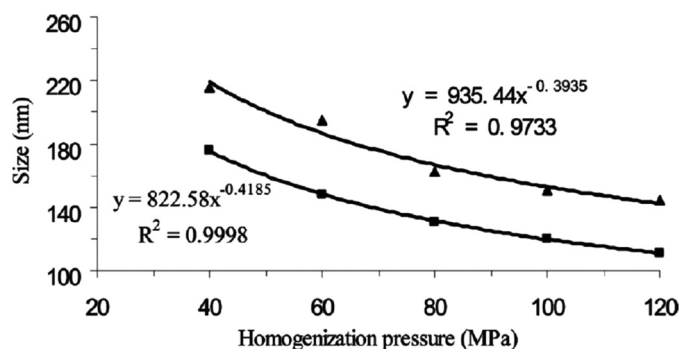


FIG. 1. Effect of homogenization pressure on droplet size of nanoemulsion: HPH (▲); microfluidization (■).^[19]

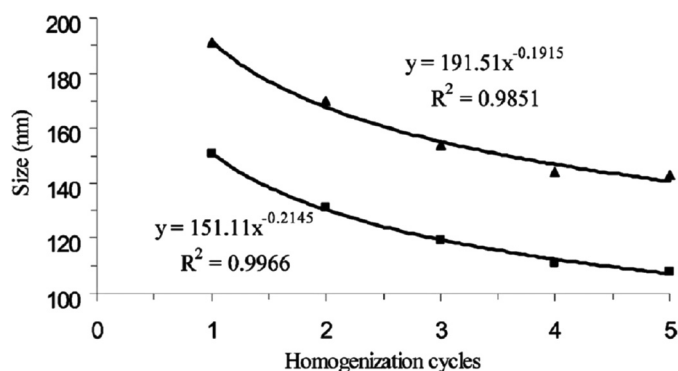


FIG. 2. Effect of homogenization cycles on droplet size of nanoemulsion: HPH (▲); microfluidization (■).^[19]

nanoemulsions' droplets. The produced nanoemulsion can be filtered through a 0.2 μm filter under nitrogen to remove large droplets and have a uniform nanoemulsion.^[20]

Generally, inertial forces in turbulent flow along with cavitation cause droplet disruptions in the microfluidizer. The advantage of microfluidizer is that the distribution of droplets in nanoemulsion is narrower than that of other emulsifying devices. However, microfluidization is unfavorable in specific cases, such as high pressure and longer emulsification time, since it leads to re-coalescence of emulsion droplets and an increase in EDS. The temperature of nanoemulsions at the exit of the interaction chamber is linearly dependent on pressure and emulsification time. Higher temperature leads to a decrease in viscosity and interfacial tension and facilitates droplet breakup. The most important problem in high-energy emulsification is the increase in temperature which leads to re-coalescence of emulsion droplets and increase in EDS. To alleviate this and to have small droplets, a cooling jacket is used. The effect of the cooling jacket on temperature of emulsification is shown in Figure 4.^[82]

The input energy during microfluidization can be improved by increasing the operation pressure or the time of emulsification. This is done by repeating the operation in two or more cycles. The final EDS is the result of competition between disruption of droplets and re-coalescence of them.

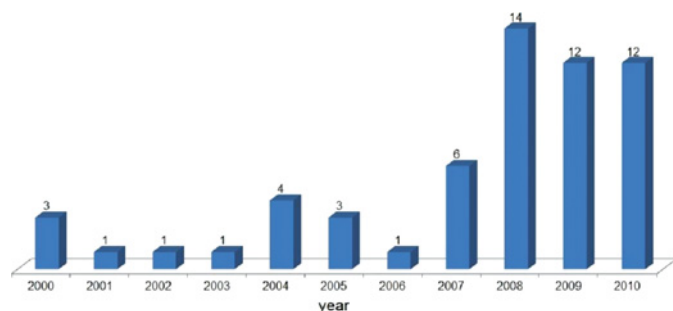


FIG. 3. The pattern of usage of HPH in the last decade. (Figure available in color online.)

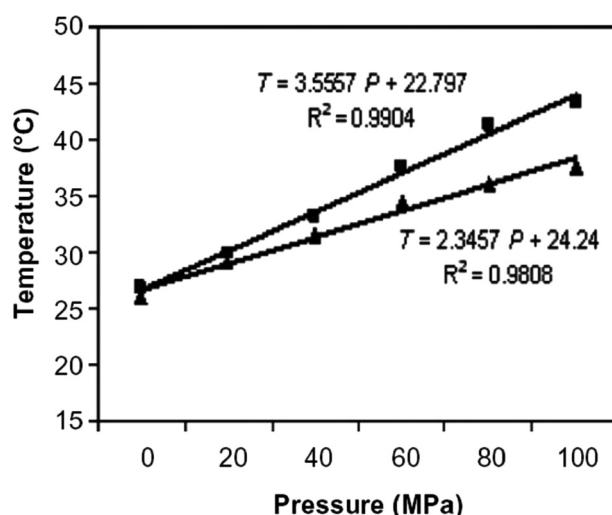


FIG. 4. Effect of emulsification on temperature of emulsions: microfluidization at one cycle – with cooling (▲), and without cooling (■).^[82]

Due to high input energy disruption of droplets is high. As long as the disruption is successful, new droplets are produced. However, new droplets are thermodynamically unstable and tend to re-coalescence. If the re-coalescence is higher than the disruption, the EDS increase. Increasing the energy over the optimum limit causes over-processing because, in high flow rates, the average time of residence of emulsion decreases. Therefore, the stability of the new interface is low due to slow adsorption of the emulsifier. This results in the re-coalescence being decreased with residence time and the EDS being increased. Fast stabilizing new interface through choosing proper and sufficient surfactant molecules can be used to prevent droplet re-coalescence after disruption of large droplets. This prevention can be done using hydro-dynamical effect, for example, increasing the viscosity of continuous phases.^[82] The pattern of usage of microfluidizer is illustrated in Figure 5.^[18,19,29,82–101]

3.3. Ultrasound

Ultrasound is very effective in decreasing the droplet size; however, it is appropriate for small batches. The process

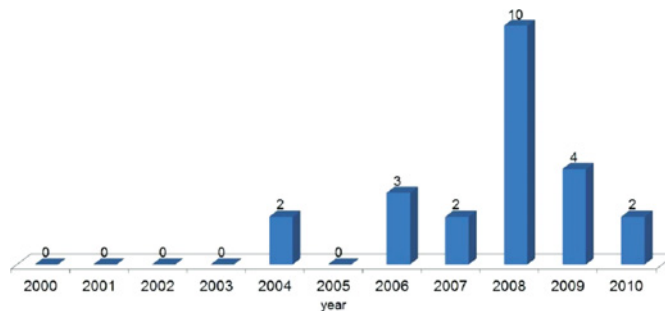


FIG. 5. The pattern of usage of microfluidizer in the last decade. (Figure available in color online.)

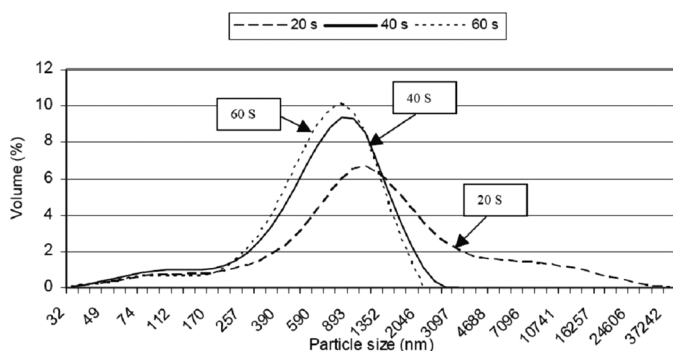


FIG. 6. Effect of 3 different ultrasonication residence time on particle size.^[89]

efficiency depends heavily on ultrasonication time in different amplitudes.^[14] In this equipment, ultrasound energy large droplets disrupt to smaller ones.^[22] In ultrasonication, the temperature is linear function of the time. Ultrasonication has a similar behavior to microfluidization at a high temperature. The ultrasonication time has an important effect in droplet size. As the time increases, the amount of energy increases as well, leading to more droplets to be disrupted and, therefore, to a decrease in EDS. Increasing the residence time over the optimum limit has no effect on EDS, but wastes energy (Figure 6). Therefore, one should not expect that droplet disruption increases and droplet sizes decreases when the amount of energy increases. The input energy should maintain at a level at which the EDS is the lowest. Usually there is no over-processing in ultrasound emulsification. This is because residence time of emulsion in emulsification region, which is equivalent to sonication time, is high in equipment, while the residence time in interaction chamber in the microfluidizer is about millisecond.^[82]

Despite the simplicity of the ultrasonication, it results in a less than optimal heterogeneous distribution of nano-droplet size. Moreover the ingredients would suffer from the damage due to high-energy output.^[22] The distribution of the size of droplets depends on coarse emulsion input to ultrasound. If the coarse emulsion entered to sonication chamber has larger EDS and vaster distribution, the produced nanoemulsion will have droplets with larger

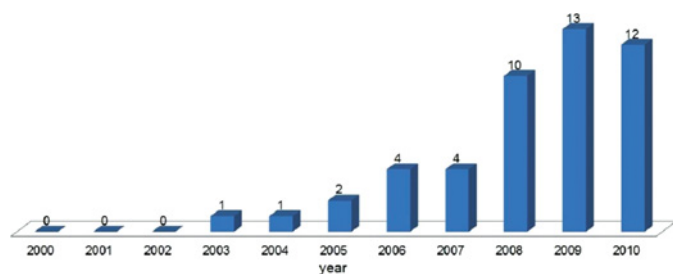


FIG. 7. The pattern of usage of ultrasound in the last decade. (Figure available in color online.)

diameter.^[82] The pattern of usage of ultrasound is illustrated in Figure 7.^[15,82,89,102–145]

4. LOW-ENERGY EMULSIFICATION

Nanoemulsion, in addition to high-energy methods, can be obtained by low-energy methods. Such methods only require gentle mixing and involve the physicochemical properties of the surfactants and co-surfactants.^[17,146–148] To form a nanoemulsion, this method involves only a low amount of energy. For the mixing process, the magnetic stirring must be fast enough. But stirring did not break the droplets and the yield of emulsification and droplet size did not depend on the rotation rate of the magnetic stir bar.^[149]

These methods have been extensively attractive in both theoretical studies and practical applications,^[150] because of their low equipment cost.^[10] Low-energy methods are based on the spontaneous formation of emulsions under specific system compositions or environmental conditions which are results of change in interfacial properties.^[151] These changes can be achieved through different ways, such as keeping the composition fixed while the temperature is changed (PIT) and the temperature is kept constant and the composition is changed (PIC).^[147,152]

Low-energy emulsification to form nanoemulsion can be categorized in three groups: i) PIT,^[12,153] ii) PIC,^[146,147] iii) solvent diffusion.^[14,154]

4.1. PIT

PIT method which was introduced by Shinoda,^[155,156] is an emulsification technique with low energy, which provide the formation of nanoemulsions without the use of high shear forces.^[157] Advantages like being low cost make the PIT method achieves more attention in recent years. The PIT concept is based on one type of phase inversion in emulsions (transitional inversion) induced by changing temperature which affect the HLB of the system (vertical arrow in Figure 8).^[13]

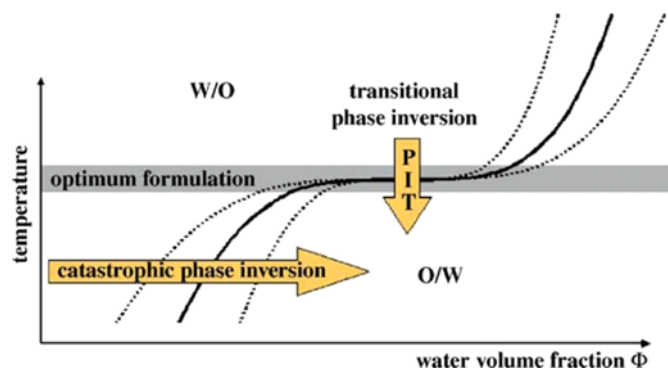


FIG. 8. Phase inversion of emulsification.^[146] (Figure available in color online.)

When the affinity of the surfactant for the water phase equilibrates its affinity for the oil phase Transitional phase inversion occurs. The variation in the affinity or HLB of the surfactant can be performed by changing temperature.^[6] It is based on the changes in affinity of polyoxyethylene-type nonionic surfactants with temperature. At low temperature, the surfactant monolayer has a large positive spontaneous curvature (more convex) and becomes hydrophilic and hence O/W emulsion is produced. At high temperatures, because of dehydration of hydrophilic tail a nonionic surfactant, the spontaneous curvature becomes negative (more concave) and the surfactant becomes lipophilic and, therefore, W/O emulsion is produced. At intermediate temperatures (the HLB temperature), the spontaneous curvature becomes close to zero (neither convex nor concave) and a microemulsion (bicontinuous, D) or lamellar liquid crystalline phase region appears. The interfacial tension is very low at the HLB temperature, and hence very small-sized emulsions are produced.^[14,148] It is possible that these nanodrops coalesce to form a macroemulsion with drops in the 1–10 mm range and beyond. If there exists a large amount of Surfactant and/or if some liquid crystal structure are formed near HLB of 0, then the nanoemulsion droplet does not coalesce immediately and while the HLB is moved away from the unstable region, the droplet size remains in the 50–100 nm range.^[158] Therefore, although emulsification is favored at the HLB temperature, the emulsions are very unstable.^[14] This means that a quenching process needs to be undertaken to produce stable and fine nanoemulsions, and the final nanoemulsions need to be stored at a temperature far from the PIT point.^[148] If the emulsion prepared at a temperature near the PIT is rapidly cooled or heated, kinetically stable emulsions with small droplet size and narrow size distribution can be produced. If the emulsion is rapidly cooled, the W/O emulsion invert to an O/W emulsion, and if the emulsion is rapidly heated, the O/W emulsion invert to an W/O emulsion occurs.^[146,159] If the cooling or heating process is not fast, coarse emulsions are formed.^[14]

The mechanism of formation of the W/O nanoemulsion from a D microemulsion is shown schematically in Figure 9. In Figure 9a, the temperature is below the PIT, therefore,

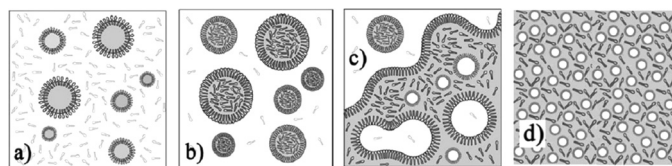


FIG. 9. The mechanism of phase inversion temperature for producing of W/O nanoemulsions (adapted with permission Anton and Vandamme.^[151]) (a) temperature is below the PIT, (b) temperature is increased, (c) temperature is at the PIT, (d) temperature is above the PIT.

the nonionic surfactant are hydrophilic, and hence O/W macroemulsion is produced. If temperature increases, the surfactant gradually becomes lipophilic and is solubilized by the oily phase (Figures 9b). In Figure 9c, the temperature increases and reaches PIT, therefore, a bicontinuous microemulsions is formed. If temperature is brought above the PIT, the O/W emulsion inverts to W/O emulsion, and because of minimum interfacial tension in PIT, the droplet of emulsion is small and W/O nanoemulsion is produced (Figure 9d).^[151] The difference in droplet size, before and after inversion can be clearly be seen (Figure 10). The crude emulsions (before inversion) are “milky” and opaque meaning that large droplets. However, the nanoemulsions (after inversion) are almost transparent.^[157]

The characterization tools for determination of the PIT point include: conductivity,^[153,160,161] viscosity,^[157] dynamic light scattering,^[12,162] cryo-TEM,^[157] light microscopy,^[157] turbidity,^[153] optical microscopy.^[153]

By monitoring the changes of the conductivity and turbidity with temperatures in emulsion system with nonionic surfactant for preparation W/O nanoemulsion (Figure 11), there will be a sudden drop in the conductivity curve and sudden increase in turbidity curve (inverse relation), this is because, with increasing temperature, O/W emulsion change to an intermediate phase and then change to W/O emulsion. For preparation of O/W nanoemulsions, the result of this experiment is reversed. An average temperature between the temperatures at the maximum and minimum

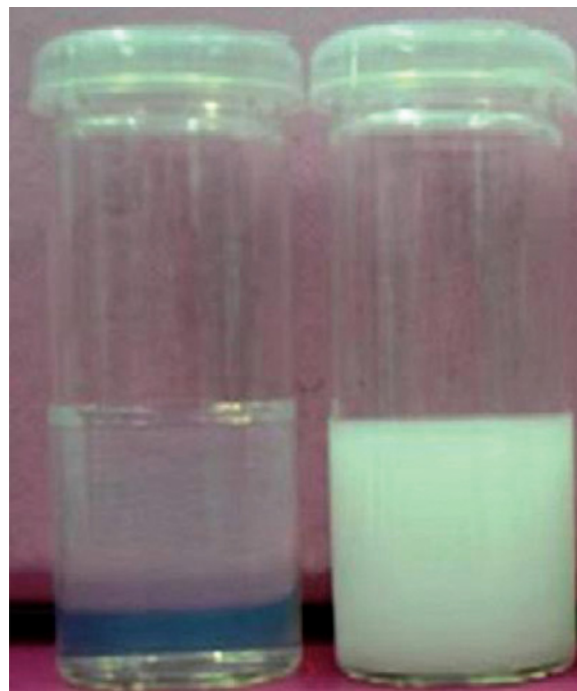


FIG. 10. Nanoemulsion before inversion (right) and after inversion (left).^[157] (Figure available in color online.)

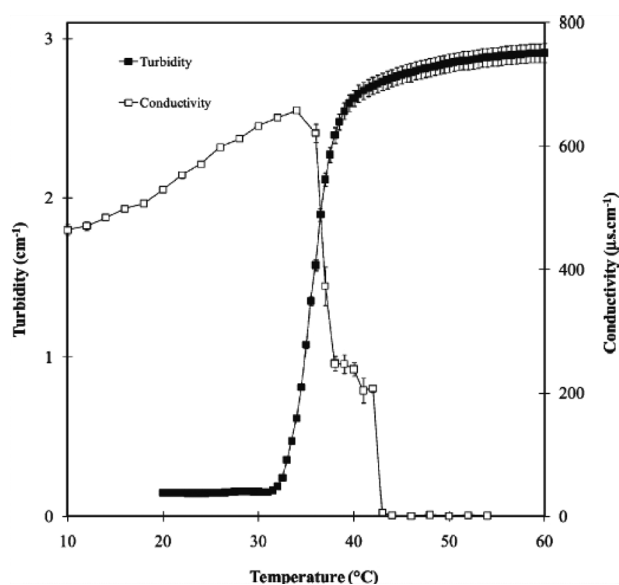


FIG. 11. The relation between turbidity and conductivity versus temperature.^[153]

conductivity and turbidity value consider as PIT point.^[12,153] The pattern of usage of PIT is illustrated in Figure 12.^[12,148,151,153,157,160,162–178]

4.2. PIC

a. In this technique a transition in the spontaneous curvature obtained by changing the water volume fraction, Instead of the temperature. This transition is referred to as catastrophic phase inversion (horizontal arrow in Figure 8).^[146,148] For PIC, the emulsification method continuous phase components are slowly added over the dispersed phase components. As a result, in some place along the emulsification path, a phase inversion occurs in which bicontinuous phase appears.^[179] Although nanoemulsification is a spontaneous process, the driving forces are small and reaching equilibrium system needs long time.^[180] Emulsions are prepared using

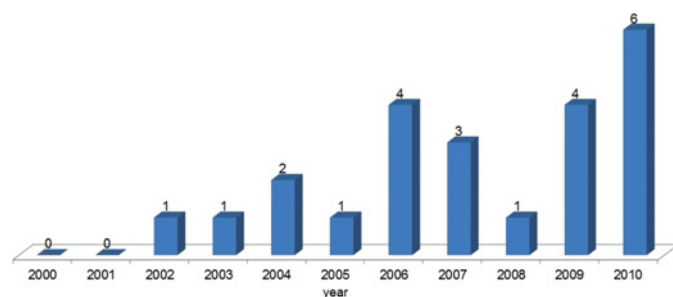


FIG. 12. The pattern of usage of PIT in the last decade. (Figure available in color online.)

PIC methods as illustrated in Figure 13 in five steps: i) first surfactant and co-surfactant (Smix) are mixed, then oil and Smix mixed together to form oil phase; ii) water is added drop wise to the surfactant and oil mixture (the addition rate is very important and should be adjusted to ensure it is slow enough such that the bicontinuous D phase or oil-in water phase is formed; if this rate is very slow, the droplet size increases due to emulsion destabilization. Water droplets are produced in a continuous oil phase by adding water into oil (W/O microemulsion); iii) as the water volume fraction increased, the droplets start to become bigger; iv) an increase in water volume fraction causes droplets to merge together and bicontinuous or lamellar structures to be formed; at this time emulsion inversion point is reached, which surfactant curvature changes and minimal interfacial tensions are achieved and, therefore, the emulsions with small droplet is formed; the emulsion inversion point can be determined by conductivity measurement. If in the inversion zone, W/O emulsion converts to O/W emulsion (Figure 14), a sharp increase in conductivity will be observed; in contrast if O/W emulsion converts to W/O emulsion, a sharp decrease in conductivity will be observed; v) further increasing the water content, the emulsion inversion point is passed and the bicontinuous structure decompose into smaller oil droplets; from this stage increasing the water does not change the droplet size. For a complete solubilization of the oil near the emulsion inversion point, a high surfactant concentration is required.^[146,148,181,182]

The PIC emulsification method for preparation of nanoemulsions enjoys many advantages, such as, low preparation cost, absence of organic solvents, good production feasibility, long stability, and thermodynamic stability.^[183] The pattern of usage of PIC is illustrated in Figure 15.^[10,15,16,146,147,150,152,179,181–214]

4.3. Solvent Diffusion

Solvent diffusion emulsification technique depends on the many parameters, such as, interfacial tension, interfacial

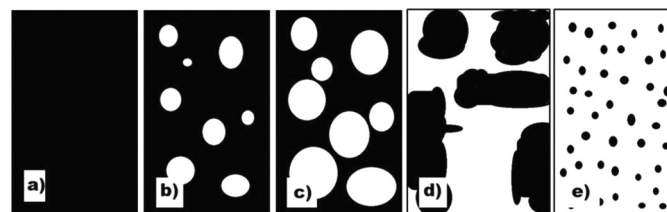


FIG. 13. The mechanism of phase inversion composition for producing of O/W nanoemulsion: water (□), and oil (■). (a) oil phase, as the water volume increases: (b) forming water droplets, (c) the droplets become larger, (d) forming bicontinuous structures, (e) forming O/W nanoemulsion.

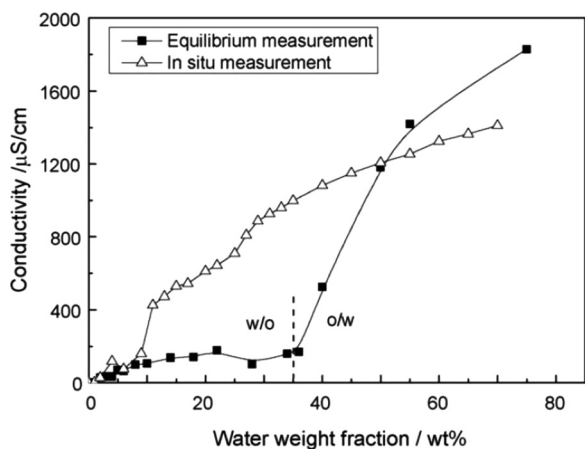


FIG. 14. The relation between electrical conductivity versus water weight fraction.^[150]

and bulk viscosity, phase transition region and surfactant concentration and structure.^[154] In theory, the solvent diffusion nanoemulsification process can provide the same amount of O/W as W/O nanoemulsions, but most studies concern O/W as W/O nanoemulsions. This technique is based on the rapid diffusion of an organic solvent (e.g., acetone, ethanol...) from the oil phase to the aqueous phase. Evolution of the system is improved by diffusion of a solute into the phase in which it has greater solubility.^[17]

Nanoemulsions can be formed in the absence of surfactants and strong shearing, known as “diffusion and stranding” or the “Ouzo effect”.^[14,215] In Ouzo effect, oil droplets are produced and their diameter is a function of the ratio of excess oil to water-soluble solvent. In some studies related to this method, surfactants have been added to the system.^[14] The method to obtain nanoemulsion with surfactant has three steps: i) preparation of the organic phase and aqueous phase; organic phase consists of oil and a lipophilic surfactant in organic (water-miscible) solvent and aqueous phase consists of water and hydrophilic surfactant; ii) under magnetic stirring, the organic phase is injected in the aqueous phase; by diffusion of the organic solvent in the aqueous phase, oil

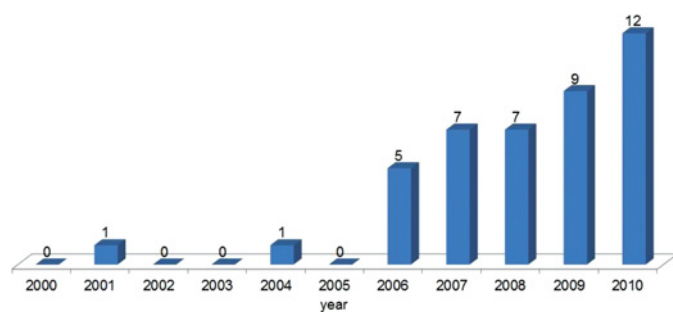


FIG. 15. The pattern of usage of PIC in the last decade. (Figure available in color online.)

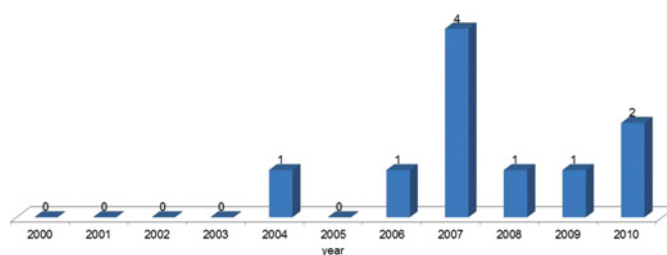


FIG. 16. The pattern of usage of solvent diffusion in the last decade. (Figure available in color online.)

nanodroplets instantaneously formed; for reaching the equilibrium system, stirring should maintain for about 30 minutes; iii) by evaporation under reduced pressure for 45 minutes, organic solvent is removed from the system and oil droplets dispersed in an aqueous phase.^[154]

The oil viscosity, the HLB of surfactant and the water solubility of the organic solvent are important parameters in determining the quality of the nanoemulsions obtained by solvent diffusion emulsification process. Based on the nature of the oil used, there is a large difference in the average size of droplets. The most viscous oil, gave drops with the smaller size. However, to obtain emulsions with small drops size the high viscosity of oil is not a sufficient condition.^[154] Some limitations of solvent diffusion method are as follows: i) low amount of oil which dispersed in aqueous phase (typically 1%); ii) selection of appropriate organic solvent that is soluble in water in all proportions; iii) removal of solvent.^[14]

The pattern of usage of solvent diffusion is illustrated in Figure 16.^[149,154,216–223]

5. APPLICATION OF NANOEMULSION

Nanoemulsions have various applications in the industrial field, such as personal care and cosmetics as well as health care, food, and agrochemicals. Nanoemulsions are appealing principally due to the following reasons:

- no creaming or sedimentation occurs on storage of nanoemulsion because of very small droplet size that reduces the gravity force and Brownian motion.
- no separation occurs in nanoemulsion because the small droplet size prevents any flocculation.
- in comparison to microemulsion, preparation of nanoemulsion need low concentration of surfactant. (5–10%).^[13,154]

As illustrated in Figure 17, the pharmaceutical and cosmetic application of nanoemulsion.^[27,30,37–41,43–48,51,53–62,64–73,75,77,78,81,86,93,95,97–109,111–118,122–127,129–137,139,140,142,145,164–167,169–172,177,178,182–186,188,189,191,192,194–206,208–211,213,216–224] in comparison to food industry.^[23,26,31,35,36,42,74,76,79,80,87,88,94,121,225] and other industry.^[84,110,144,176,181] is substantial.

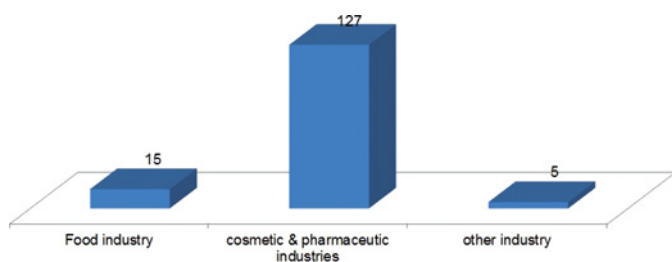


FIG. 17. Application of nanoemulsions in the last decade. (Figure available in color online.)

Nanoemulsions are used in the pharmaceutical field as drug delivery systems. This is due to the following reasons:

- Nanoemulsions can be formulated in variety of formulations such as foams, creams, liquids and sprays.
- Nanoemulsions have a much higher surface area than conventional emulsion and therefore it is suitable for delivery of active ingredients through the skin.
- Nanoemulsion deposit uniformly on skin and has high penetration, due to the small size of the droplet and low interfacial tension.
- The transparent and fluidity nature (at reasonable oil concentrations) of the system, may give nanoemulsion a pleasant aesthetic character and skin feel.
- Nanoemulsion can be applied for delivery of fragrant, which may be suitable in cosmetic and perfume products.
- Nanoemulsions may be applied as a substitute for liposomes and vesicles which are much less stable
- Nanoemulsions constitutes the first step in producing nanocapsules (encapsulated drug nanoparticles) and nanospheres (drug nanoparticles in polymer matrix).^[13,154]

The following are some examples of pharmaceutical application of nanoemulsion: cancer and tumor therapy,^[111–113,131,133,204] anti-inflammatory,^[97] malaria treatment,^[103,224] nonviral vectors for plasmid DNA delivery,^[123] treatment of coronary artery disease,^[132] ocular drug delivery.^[137] Celecoxib nanoemulsion for arthritis and osteoarthritis treatment,^[183,199–202] Carbamazepine nanoemulsion for anticonvulsant drug,^[189] Ramipril (antihypertensive drug) Nanoemulsion,^[182,194–196] and Calixarene-entrapped nanoemulsion for uranium skin decontamination.^[208,209]

Creams and lotions formulated with Buriti oil (*Mauritia flexuosa*),^[177,178] palm olesters-in-water, and virgin coconut oil-in-water,^[184] are examples of nanocosmeceuticals. With respect to agrochemical applications,^[181] O/W nanoemulsions are produced as solubilizing water-insoluble, β -cypermethrin. The system consists of water, polyoxy ethylene nonionic surfactant and methyl decanoate which serves as an oil phase. In this article spray formulations of

β -cypermethrin is achieved that in comparison to conventional O/W microemulsion pesticide has more economical and environmental friendly.

In Fallah and Falamaki,^[110] an application of nanoemulsion in catalyst engineering is considered. In this article a novel methods for production of rod shaped $2\text{Li}_2\text{O}/\text{MgO}$ catalyst nanoparticles on the internal surface of porous carriers ($\alpha\text{-Al}_2\text{O}_3$) for the Oxidative Coupling of methane reaction is disclosed. The required nanoemulsion for this technique is W/O nanoemulsion which is produced by ultrasonic probe.

In Choi and Kang,^[84] a new method to prepare a nanoemulsion system containing much smaller dye particles of nanosize in the range of 110 to 130 nm has been investigated. Six nano-disperse dyes were prepared using O/W nanoemulsions, which were produced by the microfluidizer.

There are potential applications of nanoemulsions in food technology, but there isn't much specific application in recent articles. As illustrated in Figure 17 application of nanoemulsion in food technology is limited to recent years. For example, Yuan et al.^[79,80] investigated the production of β -carotene (an important dietary antioxidant and precursor of vitamin A) nanoemulsion. In these articles β -carotene is considered as the dispersed phase.

As discussed above, pharmacy and cosmetic are fields where more direct applications of nanoemulsions are proposed. In pharmacy, most of the drugs are lipophilic and such drugs are preferably solubilized in O/W nanoemulsions.^[187] Therefore, as illustrated in Figure 18, the production of O/W nanoemulsions (in high-energy nanoemulsification)^[15,18,19,23,26–28,30–32,35–39,41–45,47,48,51,53,54,56–71,73,76,79,80,82–96,102–106,109,112,113,118–120,122,124,125,127,138,140,142,143,224] and low-energy nanoemulsification is^[10,12,15,16,146,148,150,152–154,162,163,165–179,181–186,188,190,191,193–195,197,198,202,203,205,208–214,216,222] very much than W/O nanoemulsion (in high-energy nanoemulsification^[110,116,145] and low-energy nanoemulsification.^[160,164,204,226])

With respect to Figure 19, in spite of requirement high-energy input, High-pressure homogenization,^[27,30,37–41,43–48,51,53–62,64–73,75,77,78,81] and ultrasonication^[102–109,111–118,122–127,129–137,139,140,142,145,224] methods are more attractive

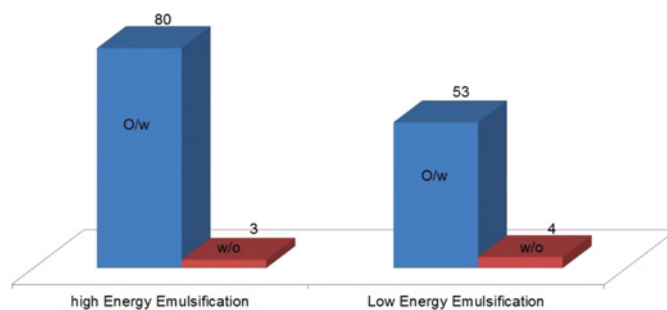


FIG. 18. The pattern of usage of two different methods in nanoemulsification and type of nanoemulsion in the last decade. (Figure available in color online.)

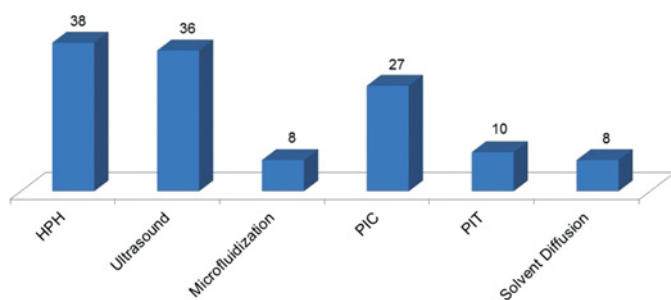


FIG. 19. The pattern of usage of different methods in nanoemulsification in pharmacy and cosmetic fields in the last decade. (Figure available in color online.)

methods in pharmacy and cosmetic field for nanoemulsion preparation because of low process time in comparison to other methods such as microfluidization,^[86,93,95,97–101] PIC,^[182–186,188,189,191,192,194–206,208–211,213] PIT,^[164–167,169–172,177,178] and solvent diffusion.^[216–223] HPH and ultrasonication are classified in high-energy methods as discussed earlier. Therefore, as illustrated in Figure 18, the high-energy nanoemulsification is more used than low-energy emulsification.

5. CONCLUSION

The small droplet size of nanoemulsion enhances emulsion stability and creaming or sedimentation should not occur even on prolonged storage, also the small size prevents flocculation of the droplets as well as their coalescence. Therefore, the production of nanoemulsion is increasing every year. For production of nanoemulsions, energy is needed. Based on the way this required energy is provided, nanoemulsification can be obtained with two general methods. i) high-energy emulsification in which mechanical device is used and ii) the low-energy method in which chemical potential of the components is used. In spite of high cost of high-energy method, this method is used widely in production of nanoemulsion especially in Pharmacy and cosmetic fields. This is because the process time is low.

The high-energy methods consist of high-pressure homogenization, ultrasonication, and microfluidization. In comparison to HPH and ultrasound, the microfluidizer is less used because of over processing. The low-energy emulsification consists of phase inversion temperature, phase inversion composition and solvent diffusion. Solvent diffusion is less used in comparison to other low-energy emulsification method. This is because of some limitation of this method, such as necessity of existence of an organic solvent which is soluble in water in all proportions.

Nanoemulsions have been widely used in many industries such as, personal care and cosmetics as well as health care, food and agrochemicals. Pharmacy and cosmetic are fields wherein which more direct applications of nanoemulsions

are proposed. In pharmacy, because of the lipophilic nature of drugs, production of O/W nanoemulsion is more than W/O nanoemulsion.

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