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Nanoemulsions: Formation, Stability and Applications

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***Abstract*: Nanoemulsions, kinetically stable, isotropic with mean droplet size in the range of 20-200 nm, have gained a lot of attention in various fields during last few decades. The major advantage of nanoemulsion technology is that the stability. It may remain stable for few hours to years depending upon the components used and process involved. Due to small droplet size, they do not suffer from problem such as creaming, sedimentation and flocculation. Destabilization in nanoemulsions occurs because of change in the droplet size by Ostwald ripening. This review paper explains the principle of nanoemulsion, low and high energy processes involved in the preparation of nanoemulsions. This article also focuses on Ostwald ripening, the main instability problems of nanoemulsions. It also gives various applications of nanoemulsions.**

***Keywords*:** Nanoemulsions, Stability.

I. Introduction

Nanoemulsion is one of the growing technologies especially in food and pharmaceutical industries as a novel delivery system for drugs and lipophilic materials such as flavours, colours, fatty acids etc. [1-3]. The potential benefits of nanoemulsions include optical clarity, good stability to separation, flocculation and coalescence. It also improves absorption and bioavailability of functional compounds [4-6]. A deeper understanding of the basic physiochemical properties of food nanoemulsions would, therefore, provide key information to better guide formulation and application of nanoemulsion to food products. Considering the significant commercial applications of food nanoemulsions, elucidating mechanisms that govern the formation and stability of flavour nanoemulsion would be useful.

Usually, an emulsion consists of two immiscible liquids with one of the liquid being dispersed as small droplets in the other. A number of different terms are commonly used to describe different types of emulsions and it is important to clarify these terms (Table 1). The range of droplet size for each type of emulsion is quite arbitrary and is defined in terms of the physical and thermodynamic properties of emulsions.

Type of Emulsion	Diameter	Thermodynamic Stability	Surface-to-mass ratio (m2/g)	Appearance
Macroemulsion	0.1-100 µm	Unstable	0.07-70	Turbid
Nanoemulsion	20-100 nm	Unstable	70-330	Transparent
Microemulsion	5-100 nm	Stable	330-1300	Transparent

Table 1. Different types of emulsion.

The aim of this review is to discuss the formation and physical properties of nanoemulsions. The review will start with the basic theories of nanoemulsion formation, characterization and stability and then discuss potential applications of them.

II. Formation of Nanoemulsions

Being non-equilibrium system, nanoemulsion cannot be formulated spontaneously. Energy input, generally from mechanical devices or from the chemical potential of compounds, is mandatory. Nanoemulsions consist of oil droplets in the nano-ranged size, between 10 to 100 nm dispersed within an aqueous continuous phase, with each oil droplet surrounded by surfactant molecules.

Nanoemulsions are formulated using different methods, which are classified as i) High energy approach ii) Low energy approach. High energy approaches utilize intense disruptive forces, generated by mechanical devices, to break the oil droplets while low energy approaches are based on spontaneous formation of oil droplets within mixed oil-water-surfactant systems when solution or environmental conditions are altered. Table 2 presents nanoemulsification techniques reported in the literature.

A. High Energy Approaches

The nanoemulsions are formed by high-energy methods which are based on selected composition, i.e. surfactant and functional compound, and on the quantity of energy supplied. The mechanical processes generating nanoemulsions are divided into three major groups based on the used devices.

1) High Pressure Homogenizer

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High pressure homogenizer is the most commonly used device to produce fine emulsions. In this method, the oil-water-surfactant mixture is subjected to very high pressure and is pumped through a resistive valve. A very high shear stress causes the formation of very fine emulsion droplets. The combination of two theories, turbulence and cavitation, explain the droplet size reduction during homogenization process. The high velocity gives the liquid high energy in the homogenizer valve generates intense turbulent eddies of the same size as the mean diameter droplet (MDD). Droplets ate thus torn apart by these eddie currents resulting in a reduction in droplet size. Simultaneously, due to considerable pressure drop across the valve, cavitation occurs and generates further eddies disruption droplets. Decreasing the gap size increases the pressure drop, which causes a greater degree of cavitation. Emulsion droplet diameters as small as 100 nm can be produced using this method if there is sufficient surfactant present to completely cover the oil-water interface formed and the adsorption kinetics is high enough to prevent droplet coalescence [7].

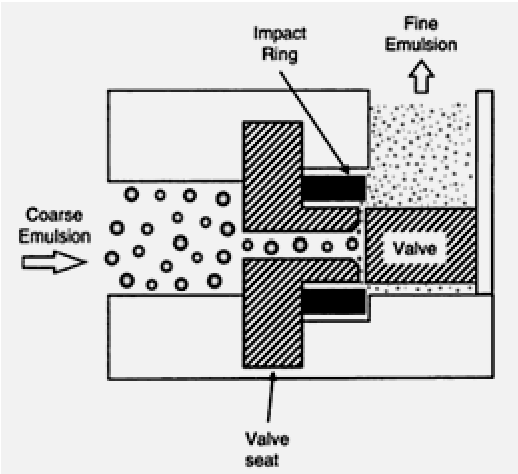

Figure 1. Schematic diagram of high pressure valve homogenizer.

2) *Ultrasonication*

One of the first applications of ultrasound was to make emulsions and the first patent on this technology is more than fifty years ago. Since then, different types of ultrasonic devices have been developed for emulsion applications. Cavitation is the main phenomenon of this method in which formation and collapse of vapour cavities, in flowing liquid, takes place. Two mechanisms are proposed for ultrasonic emulsification. First, the application of an acoustic field produces interfacial waves resulting in the dispersion of the oil phase in the continuous phase in the form of droplets. Secondly, the application of ultrasound causes acoustic cavitation causing the formation and subsequent collapse of microbubbles by the pressure fluctuations of the simple sound wave, which creates extreme levels of highly localized turbulence. Therefore, the turbulent micro-implosions break up primary droplets into sub-micron size. Since the emitted sound field is typically inhomogeneous in most ultrasonic devices, it is necessary to recirculate the emulsions through the region of high power so that all droplets experience the higher shear rate. The nanoemulsions produced by ultrasonication show wider and bimodal size distributions and greater dependence on coarse emulsion preparation methods than do those prepared using microfluidization [8, 9]. It is worth noting that all these researchers use small lab scale ultrasonic experimental set-ups. Commercial ultrasonic devices for nanoemulsion applications are not directly available since there are some design issues to be solved.

3) *High Speed Devices*

Nanoemulsions produced by these rotor/stator devices do not possess good dispersion, as compared to other high-energy approaches, in terms of droplet size. The energy provided gets dissipated generating heat [10].

B. *Low Energy Approaches*

In low energy approaches, nanoemulsions are obtained as a result of phase transition produced during the emulsification process which is carried out, usually, at constant temperature and changing the composition or at constant composition and changing the temperature.

1) *Phase Inversion Temperature (PIT)*

The phase inversion temperature is most extensively used in industry to form nanoemulsions. It is based on the changes in solubility of polyoxyethylene- type non-ionic surfactants with temperature. These types of surfactants become lipophilic with increasing temperature because of dehydration of the polyoxyethylene chains. At low temperature, the surfactant monolayer has a large positive spontaneous curvature forming oil-swollen micellar solution phases which may coexist with an excess oil phase. At high temperature, the spontaneous curvature becomes negative and water swollen micelles coexist with excess water phase. At intermediate temperature, the HLB temperature, the spontaneous curvature becomes close to zero and a bicontinuous, D phase microemulsion containing comparable amounts of water and oil phases coexists with both excess water and oil phases [11].

2) *Spontaneous Emulsification*

Spontaneous emulsification has been reported to occur upon pouring, into water, a solution consisting of a small concentration of oil in a water-miscible solvent without the presence of surfactant. Oils droplets are produced with their diameter being a function of the ration of excess oil to water-soluble solvent. This method can be used as an alternative to ultrasonic and high-shear methods. It has some limitations such as the low oil content that can be dispersed and the requirement that the solvent used to be soluble in water in all proportions [12]. The removal of solvent is difficult.

3) *Membrane Emulsification*

It is a low energy nanoemulsion process that requires less surfactant and produces emulsions with a narrow

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size distribution range. This method involves formation of a dispersed phase through a membrane into a continuous phase. Nevertheless, this method has an limitation the low flux of the dispersed phase through the membrane, this being an issue during scale-up [13]

4) *Emulsion Inversion Point*

This method consists in varting the composition of the system at a constant temperature. The structures are formed through a progressive dilution with water or oil in order to create kinetically stable nanoemulsions [10].

Methods	Solvent	Surfactant	Size distribution (nm)	Reference
High Pressure Homogenization	n-Hexane	Tween 20	-	14
Ultrasound	Sunflower oil	Tween 80, Span 80, Sodium dodecyl sulfate	40	15
Rotor/Stator	n-Hexane	Tween 20	150	16
Solvent displacement	MCT's and Lipoid E-80 dissoved in ethanol	Pluronic F18	185-208	17
Phase inversion temperature	Tetradecane	Brij 30	80-120	18
Spontaneous emulsification	Ethanol	Egg-lecithin	300	19

Table 2. Nanoemulsion methods reported in the literature.

III. Stability

Stability is one of the most important parameters in nanoemulsion system because of their small droplet size and large surface area. The small droplet size of nanoemulsions provides stability against sedimentation or creaming because of the Brownian motion and consequently the diffusion rate are higher than the sedimentation rate induced by the gravity force. Ostwald ripening or molecular diffusion, which arises from emulsion polydispersity and the difference in solubility between small and large droplets, is the main mechanism for nanoemulsion destabilization. The Lifshitz-Slezov [20] and Wagner [21] theory predicts a linear relationship between the cube of the radius r^3, and time, t, with the slop being the Ostwald ripening rate. The LSW theory assumes that the droplets of the dispersed phase are spherical, the distance between them is higher than the droplet diameter and the kinetics is controlled by molecular diffusion of the dispersed phase in the continuous phase. According to this theory, the Ostwald ripening rate in O/W emulsions is directly proportional to the solubility of the oil in the aqueous phase.

It is well known that Ostwald ripening rate increases with increase in surfactant concentration, however it has been observed that ripening rate get reduced with the increase of surfactant concentration, because the increase in the quantity of micelles in the continuous phase which prevents oil molecules to diffuse into continuous phase. On increasing the surfactant concentration below the critical micelle concentration (CMC), small drops are formed with low interfacial tension having monodisperse distribution which decreases Ostwald ripening process [22]. Using polymeric surfactants in o/w nanoemulsions has been used to reduce Ostwald ripening by getting strongly adsorbed at the O/W interface and modifying interfacial tension and increasing Gibbs dilatational elasticity. By addition of an insoluble surfactant in the dispersed phase, nanoemulsions can be stabilized against Ostwald ripening. It has been reported that for an ethoxylated nonionic surfactant system, addition of a second surfactant with the same alkyl chain length and higher degree of ethoxylation than the primary surfactant led to a reduction in Ostwald ripening rate [23].

The rate of Ostwald ripening can be retarded by storing the nanoemulsions at optimum temperature as it follows Arhenius law of the reverse of temperature. Addition of a secondcomponent(e.g. squalane) to dispersed phase that is insoluble in the continuous phase can reduce Ostwald ripening. Nanoemulsions prepared by using highpressure homogenisation have shown improved stability than those prepared by using the PIT method against Ostwald ripening. Further, literature reports that Ostwald ripening of W/O emulsions is slower as compared to O/W emulsions using the same hydrocarbon. The physical properties of the components, mutual solubility of the phases, nature and concentration of surfactant used, method of preparation, storage conditions can thus play a significant role in protecting nanoemulsions against Ostwald ripening.

IV. Applications of Nanoemulsions

Nanoemulsions containing pharmaceutically active agents can be utilized for the production of pharmaceutical preparations. If desired a special galenic form can be imparted to the mixture. Ampoules, especially sterile injection and infusion solutions; solutions, especially oral liquids, eye drops and nose drops which can contain various auxiliary substances can be formulated in the form of nanoemulsion; aerosols without metering feature and dosing aerosois, which can contain propellant gas and stabilizers besides the nanoemulsion; hydrophilic and hydrophobic gels and ointments containing the nanoemulsion; o/w or w/o creams containing the nanoemulsion; lotions and pastes containing the nanoemulsion are available in the market.

A. Ocular Delivery

Oil in water emulsions are being explored for improved topical lipophilic drug delivery to the eye. Examples: Piroxicam, Pilocarpine, Indomethacin, cyclosporine A.

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B. Nasal Route

The nasal route has received great attention due to number of advantages over parenteral and oral administration especially by bypassing the liver. Nanoemulsions increase absorption by solubilizing the drug in the inner phase of an emulsion and prolonging contact time between emulsion droplets and nasal mucosa. Examples: Lipid soluble renin inhibitor was incorporated into an O/W emulsion, insulin and testosterone can also be delivered by this route.

C. Nanoemulsion Polymerization [24, 25]

The small droplet size, high kinetic stability and optical transparency of nano-emulsions compared to conventional emulsions, give them advantages for their use in many technological applications. The majority of publications on nano-emulsion applications deal with the preparation of polymeric nanoparticles using a monomer as the disperse phase (the so-called miniemulsion polymerization method). In contrast to emulsion and microemulsion polymerization, in nano-emulsion polymerization droplet nucleation is reported to be the dominant mechanism, making possible the preservation of size and composition of each droplet during the formation of latex particles (Fig. 2). Consequently, nano-emulsion droplets can be considered as small nanoreactors.

Surfactants containing a polymerizable group (surfmers) are used in nano-emulsion polymerization to protect, stabilize and functionalize the polymer particles. In this context, it is reported that nano-emulsion polymerization of methylmethacrylate or styrene in the presence of acrylic surfmers which gave the latexes good stability. However, a non-polymerizable surfactant was required to obtain stable nanoemulsions. Recently, fluoro-containing nanoparticles are obtained by nanoemulsion polymerization of different monomers in the presence of a fluorinated monomer-sulfimer.
Nanoemulsion polymerization has been used recently to combine the properties of different polymers or materials in the same particle. An interesting use of nanoemulsion polymerization is in the specific synthesis of complex particles that cannot be obtained by the classical polymerization methods. Magnetic polymeric nanospheres are prepared by nanoemulsion polymerization in presence of iron oxide particles. Core-shell SiO_2/polystyrene nanocomposite particles and particles with other morphologies can also be prepared using nanoemulsion polymerization.

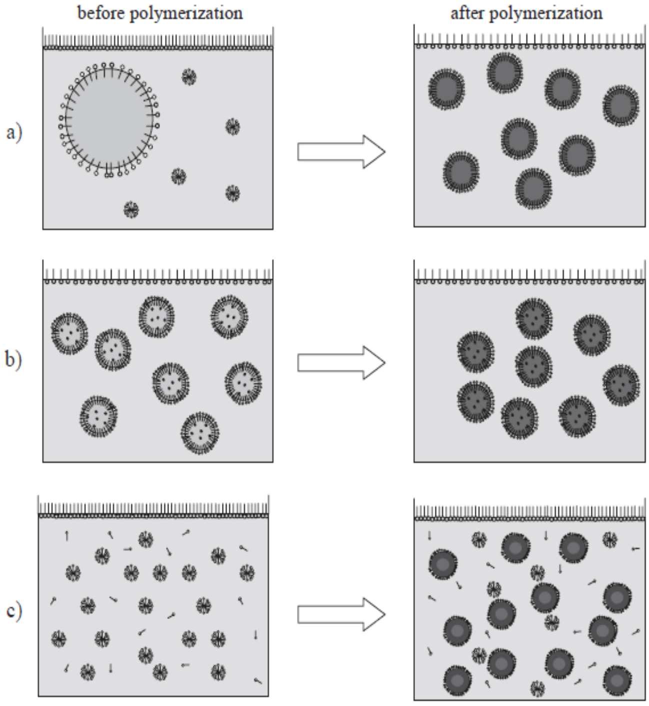

Figure 2. Schematic representation of heterophase polymerization processes: a) emulsion polymerization; b) nanoemulsion polymerization; c) microemulsion polymerization [24].

The production of polymeric particles that contain fluorescent dyes, interesting for their applications as tracers, has been also achieved using nano-emulsions. The preparation of liquid-core capsules which have applications in efficient encapsulation and controlled delivery of a wide range of drugs, dyes, etc. has also been achieved in nano-emulsions.

D. Nanoemulsion in Cosmetics

Nanoemulsions are recently becoming increasingly important as potential vehicles for the controlled delivery of cosmetics and for optimized dispersion of active ingredients into skin.
Nanoemulsion gain increasing interest due to their bioactive effects. Nanoemulsions are acceptable in cosmetics because there is no inherent creaming, sedimentation, flocculation or coalescence observed with macroemulsions.

E. Antimicrobial Nanoemulsion

Antimicrobial nanoemulsions are oil in water droplets with size range from 200-600 nm. The nanoemulsion particles are thermodynamically driven to fuse with lipid containing organisms. When enough nanoparticles fuse with the pathogens, they release part of the energy trapped within the emulsion. Both the active ingredient and the energy released destabilize the pathogen lipid membrane, resulting in cell lysis and death. Nanoemulsion has broad spectrum activity against bacteria (e.g. E. Coli, Salmonella, S. aureus) enveloped viruses (e.g. HIV, Herpes Simplex), Fungi (e.g. Candida, Dermatophytes) and spores (e.g. anthrax).

F. Nanoemulsion in Printing

In the printing and data storage industries, one may imagine the resolution of using zeptolitre droplets instead of picolitre droplets. The precise manipulation and deposition of such tiny droplets pose many technological hurdles, but the potential exists for creating piezodriven and thermally-driven printers using nanoemulsion inks.

V. Conclusions

This review has captured much of the current activity surrounding the formation, stability, and application of nanoemulsions. The study of basic and applied aspects of nanoemulsions is receiving increasing attention in recent years. Dispersion or high-energy emulsification methods are traditionally used for nanoemulsion formation. However, nanoemulsions are also efficiently formed by condensation or low-energy methods. Stability of formulation may be enhanced by controlling factors such as type and concentration of surfactant and cosurfactant, type of oil phase, methods used, process variables and addition of additives. With the advent of new instruments, competition amongst various manufacturers, the cost of production of nanoemulsions is likely to decrease soon. Thus, nanoemulsions hold promise in revolutionising the future of pharmaceuticals, cosmetics, food technology, agricultural and biotechnological field.

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