REVIEW ARTICLE

Nanoemulsions *versus* lyotropic liquid crystals

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Nanoemulsions have gained great accolade in pharmaceutical and food industries, because of integer features, such as optical clarity, ease of preparation, thermodynamic stability, and increased surface area. They are isotropic, non-equilibrium, kinetically stable system of oil, defined blend of surfactant and co-surfactant and water, which serve as vehicles for the delivery of active pharmaceutical ingredients as well as other bio-actives. Both high and low-energy methods have already been exploited to design this system. This review clarify the recurrent confusions found in the literature regarding the difference between nanoemulsions and lyotropic liquid crystals, components, method of preparation, evaluation parameters, and stability issues, which have been described and also the significance of pseudo-ternary phase diagram has been addressed.

Key words: *Energy methods, lyotropic liquid crystals, nanoemulsions, phase diagram*

INTRODUCTION

To deliver a drug candidate in order to attain maximum therapeutic effect is the first priority in any formulation. The selection of the most appropriate methodology in drug delivery is based on numerous factors including physicochemical characteristics of the model drug candidate ease of preparation, patient acceptability, cost effectiveness and so on.[1-3] Presently, micro/nano-scale techniques are available to provide remarkable effects by overcoming some of the common problems associated with drug molecule such as, low solubility, enzymatic degradation, high first pass metabolism, shorter half-life and so on. In this pool, "*Nanoemulsions*" (NE) has been gaining an accolade not only in the pharmaceutical world but also in the food industry, nano engineering and cosmoceuticals.[4-6] NE's are non-equilibrium, optically transparent, metastable dispersion of nano-sized particles having defined surface tension formed by certain shear.[7] Nanoemulsions comprises of a suitable oil and definite blend of surfactants and co-surfactants. Their capacity to dissolve large quantities of hydrophobic drugs, and their ability to protect the drugs from hydrolysis and enzymatic degradation make them ideal vehicles for drug delivery. Furthermore, the frequency and dosage of injections can be reduced throughout the drug therapy period as they assure the release of drugs in a sustained and controlled mode over long periods of time.[8] Moreover, the lack of flocculation, creaming and high kinetic stability offers obvious benefits over emulsions of larger particle size. Some very interesting physical properties, such as optical transparency and unusual elastic behavior are obtained due to the reduced droplet size in nano range.

The researchers in the field of modern material science are attracted the synthesis of materials at nano level to the control shape, and chemical and physical properties of supra molecular materials. There are various nanoparticles, hollow spheres, vesicles and mesoporous bulk that materials have been prepared with the use of surfactant as reaction carriage, one of the most promising approaches towards the synthesis of functional inorganic and organic nano materials.[9-13] NE's are often misinterpreted as "*lyotropic liquid crystals/micro-emulsions*". Although nanoemulsions are non-equilibrium structures, they do not form spontaneously without any shear as compared with lyotropic crystals.[14] There were many conflicts regarding suitable method of preparation of nanoemulsions and later on it was proved that nanoemulsions can be formulated easily even by "*low-energy emulsification method*" along with high shear method. This review focuses on the merits, trends, achievements and difference between micro-emulsions and nanoemulsions as drug delivery tool.

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NANOEMULSIONS

The experimental point-of-view on nanoemulsion [Figure 1] investigations (mechanistic/kinetic); there has been a comprehensive work accomplished which provides enhanced broad considerate of complex mechanisms in self-organized media and enables the prediction of kinetics/molecular weight/particle size distributions of nanoemulsions.[15] After nucleation with-in the initial nanoemulsion, additional monomer and surfactants (to nourish nanoemulsion polymerization) are added to the lattices produced with a particle (approx. 80 nm) and differ by different polymer/surfactant ratios.[16] The small droplet size leads to the reduction in the gravity force (prevents settling down of particles or lack of creaming\sedimentation). Also, small and elastic nature of the droplets prevented flocculation (weak and surface) and coalescence respectively, which enables the system to remain, dispersed with no separation. Hence, nanoemulsion is suitable for efficient delivery (enhance bioavailability) of active ingredients (lipophilic drugs) due to easy solubilization; large surface area allows rapid absorption rate/penetration of substances, transparent nature and ease in fluidity.[17]

Misinterpretation of nanoemulsions

Sometimes lyotropic liquid crystalline phases\micro-emulsions appear to be similar to nanoemulsions in composition and structure but lyotropic crystals are equilibrium structures that can be formed spontaneously through self-emulsification rather than nanoemulsions which are non-equilibrium system that cannot be formed spontaneously without the application of an external shear which can rupture the larger droplets into smaller ones.[18] There is high surface tension in case of nanoemulsions but in case of lyotropic structures surface tension effectively vanishes and the droplets are formed by spontaneous self-assembly. In most microemulsions surfactants are highly soluble in both dispersed phase and continuous phase but in case of nanoemulsions surfactant is soluble in continuous phase only. In micro-emulsions of lyotropic crystals both immiscible liquid phases show mutual solubility in each other, whereas the relative solubility of both phases is very low in case of Nanoemulsions.[19] Systems such as lyotropic phases having such low surface tensions convert back into other types of microemulsions by changing the temperature to original one but nanoemulsions don't have such minute surface tension that only with a change in temperature they can be converted into other types of emulsion. Micro-scale emulsions are turbid white in appearance and show multiple scattering of white light but the particles of dispersed phase in nanoemulsions [Table 1] are much smaller than visible wavelengths, so they appear optically transparent. Nanoemulsions have a much larger surface area to volume ration than any other emulsion, so chances of deformation of the droplets due to Laplace pressure is more in this case.[20,21]

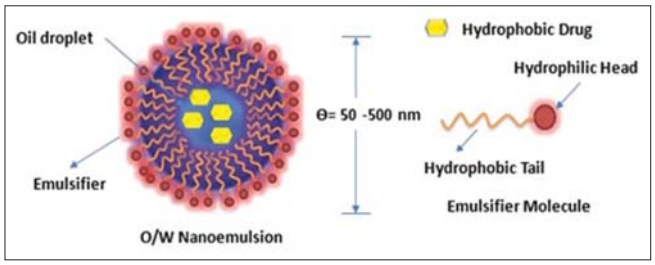

Figure 1: Nanoemulsion Structure

COMPONENTS

In formulation of nanoemulsions, three fundamental components are required, that is, an "*oil*" (solubilize the drug candidate), "*surfactants*" (lower the surface tension) and "*co-surfactants*" (reduce the interfacial tension, increase the fluidity of the interface and also provide better penetration of oil phase). A significant decisive factor in the formulation of nanoemulsions is selection of oil (drug has to be completely solubilized in the oil) and drug loading is a significant step in the development of nanoemulsions for poorly soluble lipophilic drugs. Mostly lipophilic drugs favor small/medium molar volume oils, such as medium-chain mono, di- and triglycerides. Oils of natural origin or edible in nature are not frequently used due to poor solubility profile and hence large amount of drug has to be incorporated, which in turn require even much higher surfactant concentration to achieve oil solubilization thereby increasing risk of toxicity associated with it. A list of commercial oils used along with their general class and names are given in Table 2. To decrease the surface tension and solubilization of drug loaded oil to form an acceptable and stable formulation; surfactants are required [Table 3]. Because, toxicity is a problem associated with surfactants, lesser quantity should be used accordingly. Non-ionic surfactants are relatively less toxic than ionic ones and have lower critical micelle concentration. Their selection is based on their hydrophilic-lipophilic balance (HLB) values. The appropriate blend of low quantity of surfactants with more HLB value leads to the formation of stable nanoemulsions. It is generally observed that higher HLB surfactants are much suitable for oil-in-water emulsions (O/W) and that of lower HLB values are for water-in-oil emulsions (W/O).[22,23] Unlike microemulsions, nanoemulsions can be formulated using surfactants which are enlisted as "*Generally recognized as safe*" by the United-Food Drug Administration and hence can be exploited for oral route. To lower the concentration of surfactants, co-surfactants are added. Moreover they reduce the interfacial tension and increase the fluidity of the interface. They enhance permeability of oil and improve miscibility of oil and aqueous phase due to partition between the phases. Short-to-medium chain length alcohols are commonly added as co-surfactants, for example ethanol, isopropyl alcohol, polyethylene glycol (PEG-400), 1-butanol, propylene glycol (PG), carbitol, transcutol P, and others.

Table 1: Different types of emulsions

Emulsion type	Diameter	Thermodynamic Stability	Surface-to-mass ratio (m^2/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 2: Oils used in nanoemulsion formulation

General class	Oils	Commercial name
Fixed oils	Soybean/Castor/Almond oil	-
Mono\di\triglycerides	Mono\di\tri-glycerides of capric or caprylic acids; triacetin, glycerylmonooleate	Miglyol 810, 812, Labrafac CC Crodamol GTCC, Captex 300, 355, 500, Capmul, Imwitor 742, Akoline, Peceol, Capmul-GMO
Fatty acid esters	Propylene glycolmonocaprylate\laurate\ di-laurate\caprylate\caprate, ethyloleate; isopropyl myristate\palmitate	Capryol 90, Capmul PG-8, Sefsol 218, Lauroglycol 90, Capmul PG-12, Lauroglycol FCC, Miglyol 840, Captex 200, Crodamol EO
Fatty acids	Oleic acid, caprylic acid	Crossential O94
Vitamins	Vitamin E	
Glyceryl monolinoleate	Maisine-35	

Table 3: Examples of commercially available surfactants used in nanoemulsion formulation

General class	Surfactants	Commercial name
Polysorbates	POE-20-sorbitan mono-oleate/laurate	Tween® 80/20 (Crillet 4/1)
Sorbitan esters	Sorbitan mono-oleate/laurate/stearate	Span® 80/60/20 (Crill 4/3/1)
PEO-PPO-Block Co-polymers	Poloxamer 407/188	Pluronic®/Lutrol F 127/68
POE castor oil	POE-35-castor oil, POE-40/60-hydro-genated castor oil	Cremphor® EL, Etocas 35 HV Cremophor RH 40/60, HCO-40/60, Croduret™ 40 LD
POE-stearate	PEG-660-12-hydroxystearate	Solutol HS 15®
POE-vitamin E	Tocopheryl-PEG 1000-succinate	Vitamin E TPGS
Sucrose esters	Sucrose laurate/palmitate	
Polyglycolyzed glycerides	Linoleoyl/oleoyl/caprylocaproyl/lauroyl/stearoyl macrogol glycerides, polyglyceryl oleate	Labrafil® 2125/1944 CS, Labrasol® Plurol® oleique CC 497 Gelucire® 44/14 Gelucire 50/13
Phospholipids	Soybean lecithin	

PEO: Polyethylene oxide, PPO: Polypropylene oxide, POE: Polyolefin elastomer, Croduret™ 40 LD: Trade-name (Chemical description-Polyethylene glycol-40 hydrogenated caster oil),TOGS: D -α-Tocopherol polyethylene glycol succinate, HCO: Hydrogenated caster oil

METHODS/PREPARATION

Being non-equilibrium systems of structured liquids their preparation involves the input of a large amount of energy and surfactants/combination. Hence, both the high- and low-energy methods [Figure 2] can be used in their formulation.[24] Although high-energy method uses mechanical devices such as ultra-sonicators, micro-fluidizer, and high-pressure homogenizers to create strongly disruptive forces which break up the oil and water phases to form nano-sized droplets.[25-27] Although high-energy emulsification methods produce nanoemulsions with the expected properties, they may not be suitable for thermo labile drugs such as retinoid and macromolecules, including proteins, enzymes and nucleic acids.[8] On the contary, low-energy emulsification method, which has been recently developed according to the phase behavior and properties of the constituents,[7] which include self-emulsification, phase transition and phase inversion temperature methods.[28,29] The low energy method utilizes

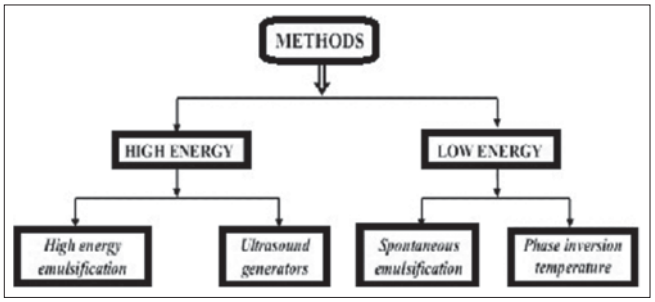

Figure 2: Energy methodæs flow chart

the stored energy of the system to form small droplets and can be obtained by changing the parameters such as temperature, composition, and so on, which would affect the HLB of the system.[30-32] Moreover, the presence of surfactants lowers the surface tensions between oil and water and prevents the shear-induced coalescence during emulsification. Continuous phase should have significant additional surfactant which

enables new surface area of the nano-scale droplets, thereby inhibiting shear-induced coalescence.[33]

High pressure homogenization

Any process that reduces the relative heterogeneity of a system can be called homogenization [Figure 3]. This process is applied to liquid by devices that consist of a positive displacement pump and one or more restrictions to flow (stages) created by valves or nozzles. High-pressure homogenization pumps are able to deliver at least 100 MPa hydrostatic pressure to a liquid before a restriction to flow is imposed, regardless of the flow rate. This technique produces nanoemulsions of extremely low particle size (up to 1 nm) due to action of forces, such as hydraulic shear, intense turbulence, cavitation and others.[34] Among several procedures applied to enhance the efficiency of emulsification while producing nanoemulsions, it was observed that the emulsion is preferably prepared at high volume fraction of the disperse phase and diluted afterwards.[35] However, sometimes it may result in coalescence during emulsification, but more surfactant could be added to create a smaller reduction in effective surface tension. Surfactant mixtures that show more reduction in surface tension than the individual components could also be used.

Ultra-sonication

Another method for producing NEs is by ultrasonic agitation [Figure 4] of an emulsion of micro sized droplets. In this method, a vibrating solid surface agitates the premixed emulsion at ultra-sonic frequencies of approximately 20 kHz or larger, which produces extreme shear and cavitation that breaks up droplets to nano-scale. The devices contain focusing horns and pointing tips. In most of the ultrasonic devices, recirculation of high-pressure homogenizers is necessary because the emitted sound field is normally inhomogeneous. Practically uniform droplet size distributions at dilute concentrations can be obtained if the emulsion is recirculating many times through the region of high shear.[14] The efficiency of the dispersion process is strongly dependent on the ultra-sonication time at different amplitudes.[33] And also it was found that the more hydrophobic the monomer, the longer will be the sonication time required.[23,36,37] *Tiwari and associates*[35] formulated oral NE formulations for enhancing bioavailability of hydrophobic drugs by sonication method which had the particle size range between 90 and 120 nm and zeta- potential values ranging from −56 mV to +34 mV. Oral bioavailability enhancement of paclitaxel (hydrophobic drug; relative to administration in aqueous solution) shown by NEs formulation.[38,39] A formulation prepared by ultrasonic technique was more stable for longer duration when compared with emulsions prepared by mechanical agitation, which can be attributed to the small droplet size that is thermodynamically stabilized.[40,41]

Micro-fluidization

Micro-fluidization [Figure 5] is mixing technology, which makes use of a device called micro-fluidizer, having a high-pressure positive displacement pump (500-20,000 psi), which forces the product through the interaction chamber, consisting of small channels called "*micro-channels*". The product flows through the micro-channels on to an impingement area resulting in very fine particles of submicron range. The two solutions (aqueous phase and oily phase) are combined together and processed in an inline homogenizer to yield a coarse emulsion.[17] The coarse emulsion is introduced into a micro-fluidizer repeatedly until the desired particle size is obtained. The bulk emulsion is then filtered under nitrogen to remove large droplets to get a uniform nanoemulsion. To create a very strong extensional flow, fast flowing streams of a premixed emulsion of droplet sizes typically less than 10 μm are forced through rigid stainless steel micro-channels

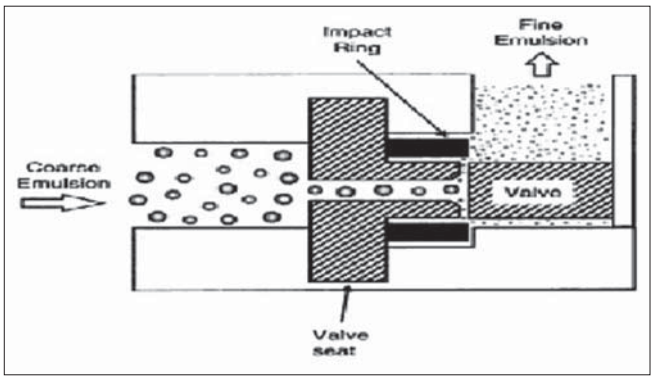

Figure 3: Schematic representation of pressure homogenization

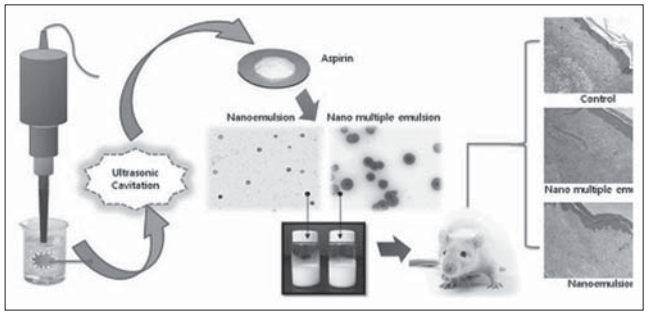

Figure 4: Ultrasonic agitation

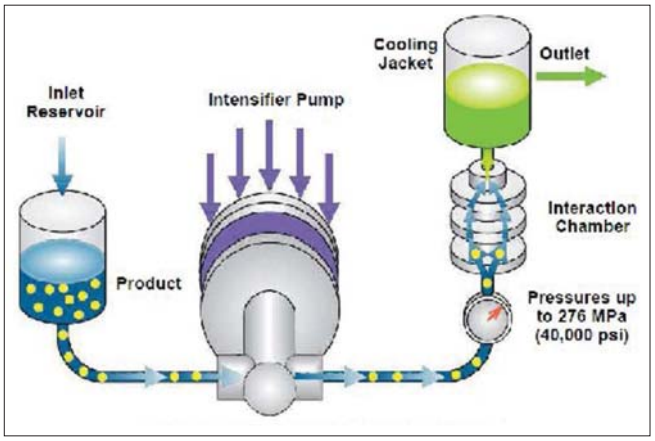

Figure 5: Schematic of micro-fludizer processer[44]

of about 100 µm.[20] High-pressure air around (100 psi) is mechanically augmented by a piston to produce liquid pressures that can reach as high as about 30,000 psi. Micro-scale emulsion droplets are taken at a rate of about 3 mL/s into the channel and routed into an interaction area where an extreme extensional shear flow is created.[42,43] After emulsification of this portion, the remainder of the external phase is added to the emulsion concentrate. In emulsions having phase inversion temperature (PIT), this blending of two portions should be carried out above the PIT, which results in the formation of extremely small-sized nanoemulsions utilizing internal energy stored within the molecules of the compound can also lead to nanoemulsions formulation which is termed as phase inversion composition technique (PIC).

Phase inversion temperature/composition

The principle of low-energy emulsification is that all of the internal phase, but only small portion of external phase, is heated.[45,46] The emulsifier concentration taken into consideration at the temperature where inversion occurs is called phase inversion temperature. Emulsions prepared by this technique [Figure 6] are generally table and contain a finely dispersed internal phase. It is also referred to as HLB temperature; the hydrophilic and lipophilic properties of the emulsifiers are in balance. Owing to their small droplet size nanoemulsions possess stability against sedimentation or creaming with ostwald ripening forming the main mechanism of nanoemulsion break down.[7] Phase inversion in emulsions can be one of two types: Transitional inversion induced by changing factors which affect the HLB of the system, for example temperature and/or electrolyte concentration, and catastrophic inversion, which can also be induced by changing the HLB number of the surfactant at constant temperature using surfactant mixtures.[47] In the PIT method, oil, water and nonionic surfactants are mixed together at room temperature. This mixture typically comprises o/w micro-emulsions coexisting with excess oil, and the surfactant monolayer shows positive curvature. When this macro-emulsion is heated gradually, the poly-ethoxylated surfactant becomes lipophilic

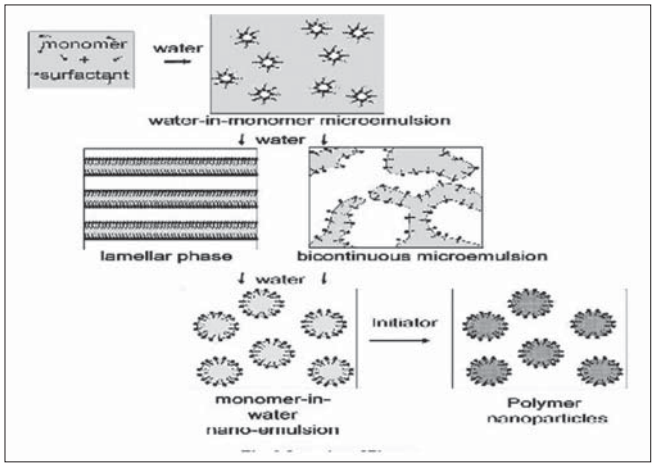

Figure 6: Inversion of Phase

and at higher temperatures, the surfactant gets completely solubilized in the oily phase and the initial O/W emulsion undergoes phase inversion to W/O emulsion.[8] The PIC method has drawn a great deal of attention from scientists in various fields (including pharmaceutical sciences) as it generates nanoemulsions at room temperature without the use of any organic solvent and heat involving the change in composition at constant temperature. Kinetically stable nanoemulsions with small droplet size (~50 nm) can be generated by the stepwise addition of water into solution of surfactant in oil, with gentle stirring or vortexing.[48] The influence studied of the phase behavior on the properties of ionic nanoemulsions prepared by the phase inversion composition method was studied and it is concluded that through this method, the surfactants can be "trapped" in a lower curvature than the spontaneous one.[49] The stability of O/W nanoemulsions prepared by PIC was observed and concluded that no flocculation occurred to cause instability of nanoemulsions. Many researchers proved the efficiency of PIC by exploring various categories of drugs to formulate into nanoemulsion and obtained stable nanoemulsion with low Poly-dispersity index.[50-52]

Solvent displacement

In this method, an oily phase is dissolved in water-miscible organic solvents, such as acetone, ethanol, or ethyl methyl ketone and poured into an aqueous phase containing surfactant to yield spontaneous nanoemulsion by the rapid diffusion of the organic solvent.[53-58] The organic solvent is removed from the nanoemulsion by a suitable means, such as vacuum evaporation. Solvent displacement methods can yield nanoemulsions at room temperature and require simple stirring for the production. Hence, this technique is also being exploited for fabricating nanoemulsions mainly for parenteral use. However, the major drawback of this method is the use of organic solvents, which require extra contributions for their removal from nano-emulsion. Furthermore, a high ratio of solvent to oil is required to obtain a nanoemulsion with a desirable droplet size; this may be a limiting factor in certain cases.[54,55]

PHASE'S SIGNIFICANCE

After the screening and selection of various components of nanoemulsion, that is, oil, surfactant and co-surfactant,[22] it is necessary to find out the minimum concentration to be used for a stable formulation. To find out the concentration range of components for the nanoemulsions, pseudo-ternary phase diagrams are constructed using water titration method at ambient temperature.[42,56,57] Different phase diagrams are prepared with varying weight ratios of surfactant to co-surfactant. These ratios are chosen in increasing the concentration of surfactant with respect to co-surfactant and increasing concentration of co-surfactant with respect to surfactant for a detailed study of the phase diagrams. For each phase diagram at a specific surfactant: Co-surfactant weight ratio (S_{mix}), the ratios of oil to the mixture of surfactant and

co-surfactant are varied.[42] The mixtures of oil, surfactant and co-surfactant at certain weight ratios are diluted with water drop-wise, under moderate magnetic stirring or vortexing.[7,58] Visual observations are made for transparent and easily flow able nanoemulsions. The physical state of the nanoemulsions are marked on a pseudo-ternary phase diagram with one axis representing the aqueous phase, the second one representing oil and the third representing a mixture of surfactant and co-surfactant at a fixed weight ratio.[59,60] To select the optimized concentration is directly proportional to the area covered by the points. Larger nanoemulsion area gives the best result and can be selected for formulation.

CHARACTERIZATION

To provide/evidence about the actual nanoemulsion morphologies formed using sophisticated techniques, such as dynamic light scattering (DLS), transmission electron microscopy (TEM), and others, are typically required exploring the structure and behavior of nanoemulsions.[61] Nano-emulsions have some interesting physical properties that distinguish them from ordinary microemulsions. The structures in nanoemulsions are much smaller than visible wavelengths, so most nanoemulsions appear optically transparent, even at large phase volume ratio and for large difference in refractive index. Nanoemulsions may lose their transparency with time as a result of increase in droplet size. Nanoemulsions have a much larger surface area to volume ratio than ordinary emulsions, so phenomena related to deformation of the droplets, such as the elastic modulus, are typically larger for nanoemulsions than ordinary emulsions. Due to the large surface to volume ratio of droplet interfaces in nanoemulsions, the concentration of surfactant required to stabilize them is larger than for micro-emulsions. Different characterization parameters for nanoemulsions are as given in the following sections.

Particle size

After synthesis, nanoemulsions are required for evaluation for their particle size and poly-dispersity index by using a sophisticated instrument, such as Malvern Zetasizer. Polydispersity is defined as the ratio of standard deviation to volume-weighted mean and for amonodispersed nanoemulsion its value should be less than 0.2. DLS measurements are taken at 90° to determine the size distribution profile in a dynamic light scattering spectrophotometer, which uses a neon laser of wavelength 632 nm.

Viscosity

Nanoemulsions viscosity of several compositions can be measured at different shear ratesat different temperatures using Brookfield type rotary viscometer. The sample room of the instrument must be maintained at 37°C ± 0.2°C by a thermo bath, and the samples for the measurement are to be immersed in it before testing.

Dilutability

O/W nanoemulsions can be evaluated by diluting with water whereas W/O are not and undergo phase inversion into O/W nanoemulsion. O/W nanoemulsion where the external phase is water, are highly conducting whereas W/O are not, because water is the internal or dispersal phase. A sharp increase in conductivity in certain W/O nanoemulsion systems was observed at low volume fractions and such behavior was interpreted as an indication of a "*percolative behavior*" or exchange of ions between droplets before the formation of bi-continuous structures [Figure 7].

Morphology

The morphology of nanoemulsions can be determined by TEM and scanning electron microscopy (SEM). SEM gives a three-dimensional image of the globules. The samples are examined at suitable accelerating voltage, usually 20 kV, at different magnifications. A good analysis of surface morphology of disperse phase in the formulation is obtained through SEM. In TEM, higher resolution images of the disperse phase can be obtained. The sample is negatively stained with one percentage aqueous solution of phosphotungstic acid or by dropping two percentage uranyl acetate solutions onto a 200 mi. mesh size Pioloform™ coated copper grid ora microscopic car- bon-coated grid using a micropipette and the sample can be examined under the transmission electron microscope at 80 kV.

Refractive Index

The net value of the components of nanoemulsion and indicates the isotropic nature of the formulation and gives the optical clarity of the emulsion.

Internal morphology

Nanoemulsion characteristics can be studied including internal morphology (confocal microscopy), crystallinity by X-ray diffraction and encapsulation efficiency and stability using spectro-fluorometry of chosen drugs.[48]

Drug content

Drug content can be evaluated by taking small amount of formulation and measure it's spectrometrically by suitable

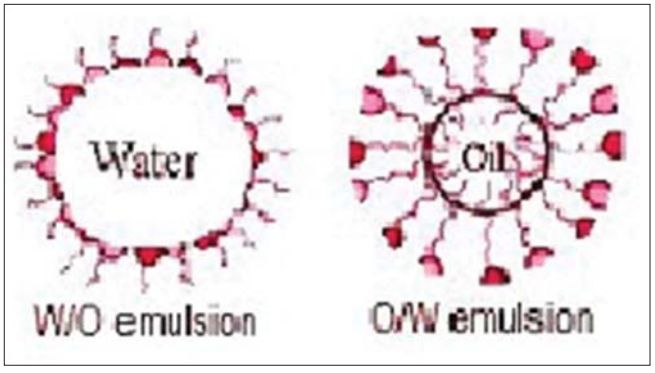

Figure 7: Bi-continuous structure of w/o emulsion and o/w emulsion

dilution. Cumulative percentage release of the drug from the formulation can be calculated using dialysis or cellulos membrane filled with it and dipped in a suitable medium.

STABILITY

The issues of stability of dosage form refer to the chemical and physical integrity of the dosage unit and when appropriate, the ability of the dosage unit to maintain protection against microbiological contamination.[62-64] Stability of drug product is one of the problems associated with the development of emulsions, microemulsions and nanoemulsions. Nanoemulsions have been known to enhance the physical as well as chemical stability of drugs.[65,66] Stability studies are performed on nanoemulsions by storing them at refrigerator and room temperatures over a number of months. The viscosity, refractive index and droplet size are determined during this period of storage. Insignificant changes in these parameters indicate formulation stability. Accelerated stability studies can also be performed. In this instance, nanoemulsion formulation are kept at accelerated temperatures and samples withdrawn at regular intervals and analyzed for drug content by stability indicating high-pressure liquid chromatography.[67,68] The amount of drug degraded and remaining in nanoemulsion formulation is determined at each time interval. There are two main mechanisms that can destabilize the nanoemulsions and cause the droplet size distribution to change.[69] The first is coalescence, caused by the breaking of films of the continuous phase and the fusion of two droplets into a single larger droplet. By choosing a surfactant that provides a strong repulsion between droplet interfaces, coarsening through coalescence can also be effectively eliminated even at large molar volume of dispersed phase provided that critical adjoining pressure for rupturing is not exceeded. The second mechanism leading to destabilization of the nanoemulsions is higher solubility of dispersed phase in continuous phase. If molecules of the dispersed phase have a relatively high solubility in the continuous phase, this may lead to the diffusive passage of individual dispersed phase molecules that are driven from smaller droplets, which have a higher Laplace pressure, to larger droplets, which have a lower Laplace pressure, and the phenomenon is known as "*Ostwald ripening*".[70] By selecting molecules of the dispersed phase that have very low solubility in the continuous phase, the "*Ostwald ripening*" can be prevented. Thus, for an emulsion formulation, choosing an appropriate composition cans essentially remove both the destabilization mechanisms. By contrast, it is very difficult to eliminate "*Ostwald ripening*" in gaseous foams[71] because the gas molecules inside the bubbles dissolve readily in common liquid phases.

CONCLUSION

Through this review, the misconception of taking nanoemulsions as lyotropic liquid crystalline micro-emulsion phases has been clarified. It has also shed light on various methods of preparation of nanoemulsions. Selection of the best method for the preparation of nanoemulsions has been a topic of conflict till now, although both the methods regarding energy usage are well accepted. Hence, this review exhibits a better understanding to highlight the significance and merits of the methods along with their characterizing parameters, which will allow and improve systematical approaches towards the design of nanoemulsions. The stability concern of nanoemulsions, significant basic causes for instability issues in nanoemulsions or any emulsions with such a small sized droplets have also been discussed. Some portion of this review deals with various components along with their relevant classification and examples, evaluation parameters and briefly justified the importance of pseudo-ternary phase diagram in the formulation of nanoemulsions which is an essential tool to select the nanoemulsion region from mixture of three different liquids. This exciting field of research will gain more attention and provide deeper insight into nanoemulsion formation.

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