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REVIEW

Food-grade nanoencapsulation of vitamins

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Abstract
Vitamin deficiency arises when the dietary intake of essential vitamins is too low. Insufficient levels of vitamin weaken the body and induce diseases. Although the dietary intake of essential vitamins has increased through food fortification, there are still major issues of vitamin deficiency. Moreover, consumption of vitamins in classical food supplements presents drawbacks such as poor bioavailability and low stability, notably in the gastrointestinal tract conditions. To overcome such issues, vitamin nanoemulsions have been recently developed. Here, we review the design of vitamin nanoemulsions with various oils to meet specific needs; actual research and markets for vitamin nanoemulsions; and techniques for nanoemulsion characterization.

Keywords Vitamin deficiency · Vitamin nanoemulsion · Poor bioavailability · Novel characterization · Dietary intake

Introduction

Nanotechnology has been explored extensively as the next revolution, notably in the field of agriculture and food industry (Donsì 2018). Nanotechnology can also enhance water solubility, thermal stability, gastrointestinal stability and oral bioavailability of bioactive compounds and vitamins like A, D, E and K (Ezhilarasi et al. 2013). This is achieved by encapsulating essential vitamins, using various types of wall materials. In food and pharmaceutical industries, encapsulation allows to protect bioactive compounds and vitamins within a wall material in the form of capsules (Bartusik et al. 2016; Borthakur et al. 2016). Emulsification, coacervation, inclusion complexation, emulsification-solvent evaporation, nanoprecipitation, and supercritical fluid techniques are used to produce nanocapsules in the range of 10–1000 nm (Ezhilarasi et al. 2013). Figure 1 shows the different types of emulsion forms. This review majorly focuses on the use of oils as a carrier material to protect vitamins from temperature, light, and controlled release in the human body. Various researchers have extensively studied the production of nanoemulsions using different vitamins and carrier materials (oils). Table 1 presents the studies conducted by various researchers pertaining to vitamin nanoemulsions. This article is an abridged version of the chapter published by Dasgupta and Ranjan (2018) in the series Environmental Chemistry for a Sustainable World (http://www.springer.com/series/11480).

Nanoemulsion-based delivery systems and functional properties

Vitamin E is one of the nutraceutical compounds that have been a major research area for the researchers. Vitamin E is one of the nutraceutical compounds that have been one of the potent attention seekers of research. The most nutritionally imperative form of vitamin E is α-tocopherol, so there has been more interest of incorporating it into various food products. However, while incorporating the α-tocopherol into functional food products, there are various challenges associated with incorporation: poor water solubility, chemical instability (to oxygen, light, and heat), and variable oral bioavailability (Ozturk et al. 2015a). Researchers have studied the natural emulsifiers to develop the vitamin E acetate

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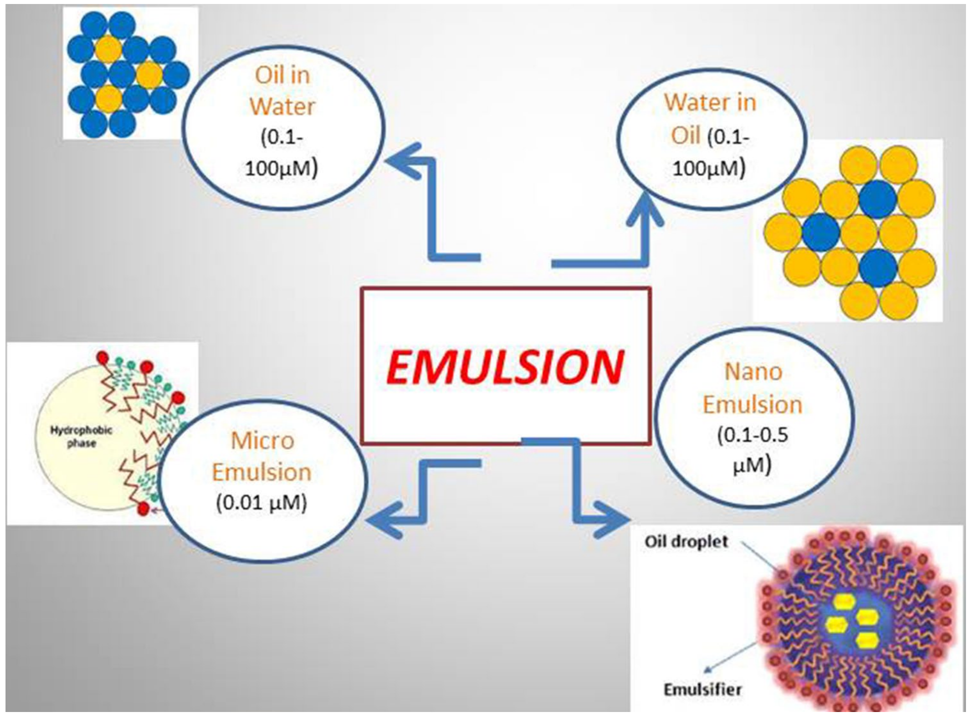

Fig. 1 Different forms of emulsions. The broad categories are further described with their specifications

emulsion-based delivery system. Natural emulsifiers like protein (whey protein isolate) and polysaccharides (gum Arabic) have been used to formulate vitamin E acetate emulsions, and they observed that the protein emulsifier was more effective in producing smaller size droplets in the range of 110 nm, as compared to polysaccharide emulsifier (380 nm). On the other hand, emulsion prepared with gum Arabic has been found to be more stable, especially at elevated temperatures compared to whey protein isolate. This may be due to the protein surfactants that get denatured in protein-based emulsions (Ozturk et al. 2015a).

Ozturk et al. (2015b) studied the influence of different carrier oils on the bioaccessibility of vitamin D_3-encapsulated nanoemulsion in simulated gastrointestinal conditions. Stable nanoemulsions in the range of 140–190 nm were synthesized using natural surfactants by high-pressure homogenization technique. Researchers have observed that the medium-chain triglycerides (MCT), carrier oil enabled better free fatty acid release during lipid digestion of vitamin D_3, compared to other carrier oils like corn oil, fish oil, orange oil and mineral oil, whereas long-chain triglycerides (LCT) effectively increased bioaccessibility of vitamin D_3. This can be attributed to the fact that long-chain free fatty acids protectively surround lipid droplets and thus prevent them from lipase action (Ozturk et al. 2015b).

A study has been conducted by Mehmood (2015) where response surface methodology was used to optimize the formulation of nanoemulsion (Mehmood 2015). In his work, he used canola oil, as a carrier oil to encapsulate the vitamin E acetate using high-energy approach to understand the changes in nanoemulsion with edible mustard oil as carrier oil. Researchers have used low-energy approach to formulate vitamin E nanoemulsion with edible mustard oil as carrier oil. Analysis such as stability test, antioxidant analysis, and HPLC is done/performed for measuring encapsulation efficiency, and antimicrobial test in order to synthesize an effective emulsion system for vitamin E. The prepared nanoemulsion was found to be much stable, for nearly more than 15 days with significantly higher antioxidant activity of 62.55%. It has higher antibacterial property, making it a suitable additive for enhancing the shelf life of health drinks. High encapsulating efficiency (99.65%) proves that the synthesized nanoemulsion is highly effective in encapsulating and protecting vitamin E from unfavourable conditions (Dasgupta et al. 2016b). This study is a supportive evidence for the advantages of using nanoemulsion system as a health supplement in beverage industries (Figs. 2, 3).

Characterization of nanoemulsions

Separation techniques

Chromatography technique

In colloidal food science, separation technology is mainly used for identification and quantification of the different bioactive compounds. Many researchers have established the use of these separation techniques in nanocolloidal food science, i.e., food-grade nanoemulsions or nanoencapsulated

Table 1 Nanoemulsion of various vitamins and carrier oils. The table depicts the active compound encapsulation, the encapsulating materials, the emulsifier used and the preparation method used. The following abbreviations denote: whey protein isolates (WPI); gum arabic (GA); short-chain triglycerides (SCT); medium-chain triglycerides (MCT); long-chain triglycerides (LCT); polyethylene glycol (PEG); reverse-phase high-performance liquid chromatography (RP-HPLC); hydrogenated castor oil (HCO); and polyoxoethylene and polypropylene (EOPO)

Encapsulated compound	Encapsulating material	Emulsifier	Preparation method	Droplet size	Brief summary	References
Vitamin E	Orange oil	Natural surfactant: (a) whey protein isolate (WPI) (b) gum Arabic (GA)	High-pressure homogenization	(a) 0.11 µm (b) 0.38 µm	WPI was successful in producing small droplets at low emulsifier concentration and GA was more stable to environmental stress	Ozturk et al. (2015a)
Vitamin D_3	Corn oil, fish oil, orange oil and mineral oil	Tween 80; Natural surfactant: Quillajasaponin	Ultrasonication; High-pressure homogenization	140–190 nm	Long-chain fatty acids serve as better delivery system for nutrients	Walia et al. (2017); Ozturk et al. (2015b)
Vitamin E	Short chain triglycerides (SCT): glycerol tributyrate Medium-chain triglyceride (MCT): caprylic triglyceride Long-chain triglyceride (LCT): olive oil	Non-ionic synthetic surfactant: tween 80	Emulsion phase inversion	83–110 nm	Synthesized nanoemulsions were found stable to heat, pH and salt, but significant degradation was seen when exposed to heat shock and long storage conditions	Hategekimana et al. (2015)
Vitamin E	Canola oil	Synthetic and natural surfactant mixture: Tween 80/soya lecithin (3:1)	High-pressure homogenization	132–160 nm	Response surface methodology was used to optimize nanoemulsion synthesis process. The effect of emulsifying conditions on droplet size and stability of nanoemulsions was studied	Mehmood (2015)
Vitamin D	Medium-chain triglyceride (MCT)	Non-ionic synthetic surfactant: Tween	Spontaneous emulsification	<200 nm	Effect of emulsifying conditions on the stability of synthesized vitamin D nanoemulsion was analyzed. In this study, it has been concluded that the thermal stability of nanoemulsions can be increased by adding a co-surfactant	Guttoff et al. (2015)

Table 1 (continued)

Encapsulated compound	Encapsulating material	Emulsifier	Preparation method	Droplet size	Brief summary	References
Vitamin D	Cinnamon oil	Tween 80	Ultrasonic technique	40–50 nm	Nanoemulsions were studied and portrayed cytotoxic, genotoxic, antibacterial potential, and hence its usage in food industry could be ensured wherein they can be used as a carrier for lipophilic nutraceutical	Meghani et al. (2018)
Vitamin D	Corn oil	Quillajasaponin	High-pressure homogenization	Vehicle: 0.30 µm Coarse: 1.60 µm Nanoemulsion: 0.30 µm	Study proved that the coarse emulsion increased the bioaccessibility by 36%, whereas nanoemulsion increased it by 73%	Kadappan et al. (2018)
Vitamin E	Orange oil	Natural surfactants: Quillajasaponin and lecithin	High-pressure homogenization	≈ 120–130 nm	The effect of emulsifying conditions (surfactant concentration, oil concentration) and environmental conditions (temperature, ph or ionic strength) on the formation and stabilization of nanoemulsion has been demonstrated	Ozturk et al. (2014)
Vitamin E	Canola oil	PEG-40 hydrogenated castor oil and Sorbitan-monoleate	Mechanical stirring	–	The release rate of nanoemulsion system was measured and compared via dialysis sac, reverse dialysis sac and USP apparatus 4 fitted with dialysis adapter	Morais and Burgess (2014b)
Vitamin E	Bupivacaine HCl	PEG 400 Castor oil Olive oil Soya oil Sunflower oil Tween 20	Mechanical stirring	111–400 nm	Temperature was kept as available for different systems; influence of oil for the formation of nanoemulsion was studied with different variables	Rachmawati et al. (2018)

Table 1 (continued)

Encapsulated compound	Encapsulating material	Emulsifier	Preparation method	Droplet size	Brief summary	References
Vitamin E	Medium-chain triglyceride (MCT)	Non-ionic synthetic surfactant: Tween 80	Spontaneous emulsification	≈ 50–100 nm	With increasing concentration of glycerol, the amount of surfactant required to fabricate vitamin E nanoemulsion could be reduced	Saberi et al. (2013)
Vitamin E	Palm olein	Brij 30	Homogenizer	20–500 nm	Antioxidant-based nanoemulsions were studied with pH range of 6–7, hence could be applied on human skin	Ramli et al. (2017)
Vitamin E	Medium-chain triglyceride (MCT)	Non-ionic synthetic surfactant: Tween 80 and Brij 35	Membrane emulsification	106 nm	Membrane emulsification technique has been successfully chosen as an alternative for the formation of vitamin E nanoemulsion	Laouini et al. (2012)
Vitamin D	Canola oil Pea protein isolate	–	Sonication pH shifting	–	Comparison study of nanoemulsion-based vitamin D and conventional vitamin D for histopathological studies	Sherbiny et al. (2018)
Lipophilic compounds	MCT, flavour oil, LCT	Tween 80	Spontaneous emulsification	–	To understand the influence of emulsifying conditions on the formation and stability of nanoemulsion	Komaiko and McClements (2014)
Vitamin E and paclitaxel drug	Chloroform	Soy lecithin and sodium deoxycholate	High-pressure homogenization	≈89-217 nm	In this study, drug encapsulation has been demonstrated by incorporating the paclitaxel drug into vitamin E nanoemulsion to improve its efficiency against breast cancer	Pawar et al. (2014)
Vitamin E	Canola oil	PEG-40 hydrogenated castor oil and Sorbitan-monoleate	Low-energy method: Washout method	87–103 nm	In this study, a practical RP-HPLC method was developed for vitamin E acetate estimation in lipid-based nanoemulsions	Morais and Burgess (2014a)

Table 1 (continued)

Encapsulated compound	Encapsulating material	Emulsifier	Preparation method	Droplet size	Brief summary	References
Vitamin A	Polyoxyethylene hydrogenated castor oil	Non-ionic surfactant and liquid paraffin	–	–	The stability of vitamin A in different emulsion systems (simple and complex) was studied and compared	Yoshida et al. (1999)
Lipophilic vitamin Retinol palmitate	Vitamin E	HCO (hydrogenated castor oil) EOPO	Stirrer	20–80 nm	Nanoemulsion based on polyoxoethylene and polypropylene showed superior efficacy compared to polyoxoethylene hydrogenated caster oil Their mechanistic pathway was studied	Miyake et al. (2018)
β-Carotene	Olive oil	Tween 80 Soya lecithin	Ultrasonic homogenization	89–130 nm	The study investigated the effect of independent variable on response variables	Mehmood et al. (2018)
Vitamin E	Mustard oil	Non-ionic surfactant: Tween 80	Washout method	86.45 ± 3.61 nm	Researchers formulated vitamin E nanoemulsion and performed its activity analysis	(Dasgupta et al. 2016b)
Vitamin E	MCT and orange oil	Tween series, whey protein isolate, sucrose monopalmitate, casein and Quillajasaponin	Emulsion phase inversion (EPI) and microfluidization	< 200 nm	This research was done to demonstrate the effect of surfactant to oil ratio (SOR) on the formation of nanoemulsion and specifically on its particle size. A detailed comparison of low- and high-energy methods has also been done	Mayer et al. (2013)
Docetaxel drug	Sunflower weed oil Soya oil Coconut oil Olive oil	Non-ionic hydrophobic surfactant; Tween 20, 60, 60 80, 85 mixed with lecithin with selected mixtures of oil	High-energy emulsification using homogeniser	90–110 nm	Research accounted the various parameters incorporating the nanoemulsion formulation in order to enhance the bioavailability and solubility issues	Asmawi et al. (2018)

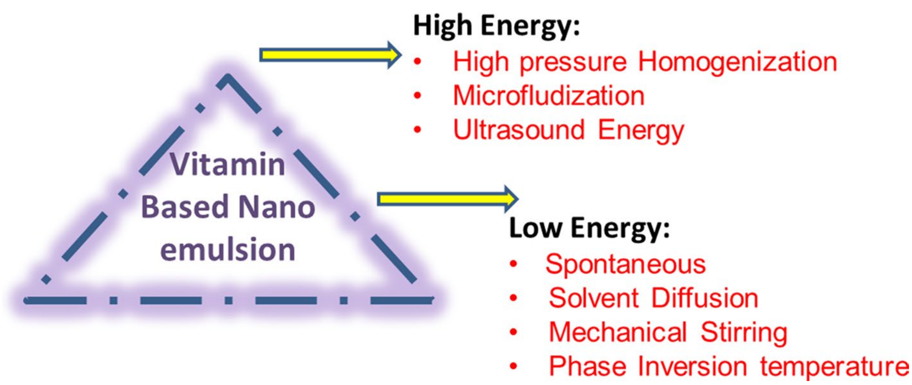

Fig. 2 Methods for the preparation of nanoemulsions

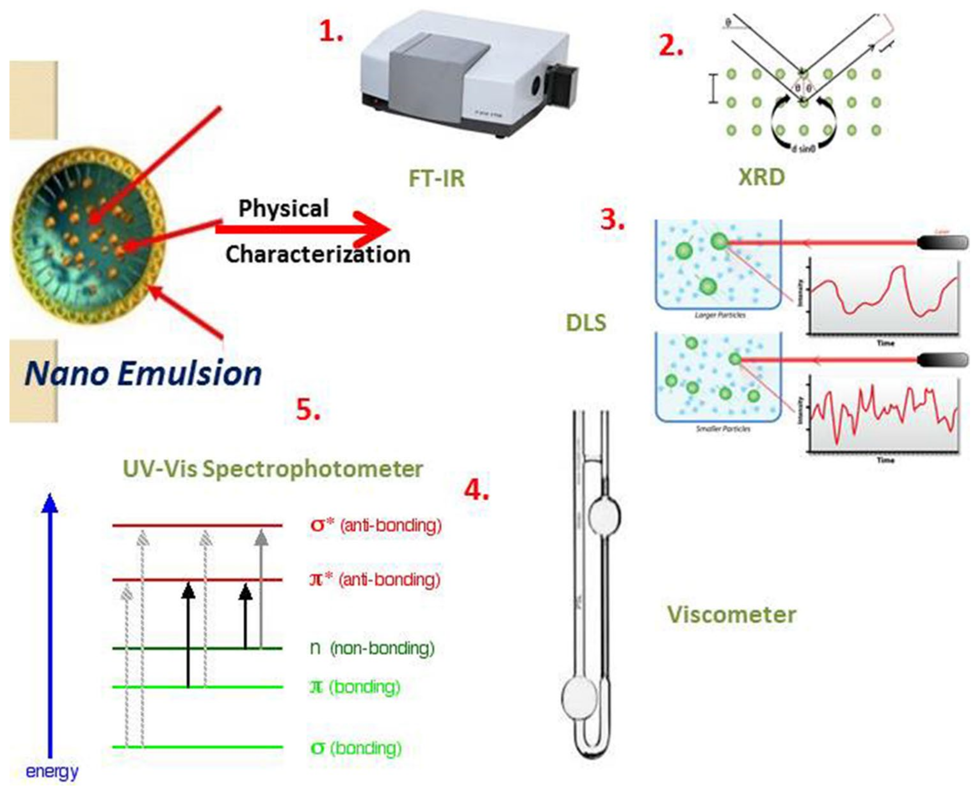

Fig. 3 Methods of physical characterization of nanoemulsion. The FTIR (Fourier transformation infrared radiation), XRD (X-ray diffraction), DLS (dynamic light scattering), viscometer, UV–Vis spectrophotometer. The mentioned techniques are described elaborately in the running text given below

products. The main challenge for food-grade nanoemulsion is the in situ characterization of them; nevertheless, in most cases it is not possible to detect them in the food matrixes. Therefore, separation techniques are mandatory/utmost important to isolate the nanoemulsion from food prior to their characterization.

Size exclusion chromatography

It is one of the chromatographic methods which accounts for size exclusion wherein molecules are separated on the basis of their size and molecular weight. It is usually applied to larger molecules or macromolecular complexes such as proteins and industrial polymers. It can be noted that size is the main characteristic of nanoemulsions, so it is the most suitable type of liquid chromatography for the separation of nanoemulsions from food matrix (Saifullah et al. 2016). It has been used in nanoemulsion-based drug delivery analysis.

Development of a nanoemulsion should focus on droplets with a well-defined size, i.e., with a narrow size distribution. Otherwise, contaminations with droplets of large size might be taken up more efficiently and/or carry a higher which leads to carrying of higher perfluorocarbon load, affecting both the specificity and quantity of the perfluorocarbon label. Grapentin and co-workers generated perfluorocarbon nanoemulsion by using phospholipids that usually show a broad size distribution—a challenge which cannot be overcome by the conventional manufacturing process. However, the formation of well-defined perfluorocarbon nanoemulsion is feasible by combining centrifugation with size exclusion chromatography.

Size exclusion chromatographic technique was able to separate effectively well-defined fractions of a perfluorodecalin emulsion via a Toyopearl HW-75S column (Grapentin et al. 2014). Similarly, this technique has been used for characterization of nanoemulsion-based drug delivery by ketene-based polyester synthesized using electron rich carbon/silica composite surface (Swarnalatha et al. 2008). The use of size exclusion chromatographic technique in nanoemulsion characterization is quite rare nowadays and can be employed in drug delivery system (Bae and Chung 2014; Vezocnik et al. 2015).

Ion exchange chromatography

Ion exchange chromatography separates ions and polar molecules based on their affinity to the ion exchanger. It works on wide variety of charged molecule—including large proteins, small nucleotides, and amino acids. Simultaneously, as charge size is also one among the main characteristics of nanoemulsions, so it is also the most suitable type of liquid chromatography for the separation of nanoemulsions from food matrix (Saifullah et al. 2016). Ion exchange chromatography has been reported in a purifier for nanoemulsion which includes sucrose fatty acid ester (Bromley 2011).

High-performance liquid chromatography (HPLC)

HPLC method has also been highly explored to identify the presence of some unidentified compounds in natural/real extracts, e.g., leaf, fruit, or stem samples including environmental samples such as soil, water, and other samples. It mainly works on the principle of separation-based technique.

Recently, Dasgupta and co-workers have employed HPLC to quantify non-encapsulated vitamin E and have calculated the encapsulation efficiency for food-grade mustard oil nanoemulsion. It was for the first of its kind, an article in the field of food-grade nanoemulsions (Dasgupta et al. 2016b). During the similar time period, many other researchers have also reported/employed/practiced/explored/used HPLC for characterization of different nanoemulsions, calculating encapsulation efficiency and in analyzing the stability of selective/target molecule in nanoemulsion (Li et al. 2015; Panatieri et al. 2016; Youssof et al. 2016). Overall, similar to other chromatographic techniques, HPLC was also used to identify and quantify the active compounds and was found more precise, easier and efficient for nanoemulsions characterization.

Physical characterization

UV–Vis spectrophotometer

UV–visible spectrophotometer analysis can be performed to identify and quantify the concentration of the compounds based on their optical density and the amount of light transmitted or refracted. The UV–visible spectrophotometer cannot give absolute structural confirmation, and the quantification and identification of the particular sample result should also be calibrated with the controls. Earlier researchers have used this method for various estimations, e.g., detection of oil content in the final nanoemulsion (Costa et al. 2013), to estimate the encapsulated curcumin (Rachmawati et al. 2014) and to measure the transmittance percentage of nanoemulsions (Jaiswal et al. 2015).

Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC)

FTIR and DSC are the commonly used instrumental techniques for analyzing the structural identity of the selective molecule or mixture of compounds. These techniques were performed to identify the structural identity of active compound present in food materials. FTIR and DSC are normally used for assessing structure, encapsulating active compound, analyzing their integrity, and further ensuring their compatibility among other ingredients (Pathan and Mallikarjuna Setty 2011, 2012; Ahmad et al. 2014).

X-ray diffraction (XRD)

XRD is used to determine the crystal structure of any compound. Researchers have analyzed the crystalline structure of electrospinned nanofibre from nanoemulsion (Gordon et al. 2015; Sugumar et al. 2015). Other researchers also analyzed the crystal structure of specifically designed nanoparticles from nanoemulsions (Shams and Ahi 2013; Filipović et al. 2015; Soltani et al. 2016). Further extending the applications of XRD in core-nanoemulsion characterization, few researchers have used it on derived forms of nanoemulsions by using several food engineering steps (Ahmad et al. 2014; Zhou et al. 2014). Additionally, the protocol has been established to analyze the presence of ions in nanoemulsions (Mahendran and Philip 2013). Other X-ray-based technologies are also being used to identify/study lipid-based nanoparticles or nanoemulsion-based solid nanomaterials—small-angle X-ray scattering (Jenning et al. 2000; Alaimo et al. 2015; Truong et al. 2015; Uzun et al. 2016).

The other physical perspective of the nanoemulsion characterization techniques has been described in the later section—e.g., size distribution, zeta potential, crystallinity, viscosity, stability, etc., of the nanoemulsions.

Dynamic light scattering (DLS)

DLS is commonly used technique for determining the size distribution profile of small particles in suspension or polymeric solutions. In this technique, the temporal fluctuations are usually analyzed/examined/studied by means of the intensity or photon autocorrelation function; hence, DLS is also termed as photon correlation spectroscopy or quasi-elastic light scattering spectroscopy. Recently, DLS analysis has become a basic but compulsory methodology to measure the hydrodynamic size of nanoemulsion droplets. This is so because of one-step process of DLS size measurement and precise estimation of hydrodynamic size range of nanoemulsion droplets. Many food-grade nanoemulsions have been fabricated recently; almost all of them have used DLS size measurement in their research (Dasgupta et al. 2014, 2016b; Guttoff et al. 2015; Komaiko and McClements 2015; Ma et al. 2016). It has been reviewed and summarized in many recent scientific articles (Azeem et al. 2009; Rajpoot et al. 2011; Shakeel et al. 2012; Ranjan et al. 2014, 2016a, b, Dasgupta et al. 2015, 2016a; Jain et al. 2017). Nowadays, DLS is getting integrated with the zeta potential analyzer which is changing the normal DLS cuvette to the double-electrode integrated cuvette, which further helps to analyze the zeta potential of the nanoemulsion (Dasgupta et al. 2016b; Jain et al. 2017).

Viscometer

Viscometer is an instrument used to measure the viscosity of a fluid. Nanoemulsions are mainly characterized by using rotational viscometer. Rotational viscometers use the idea of torque required to turn an object into a fluid as a function of its viscosity. They measure the torque required to rotate a disk or bob in a fluid at a known speed. It is very important to know the viscosity of the food-grade nanoemulsions if ingested or passed through gastrointestinal tract or applied transdermally. Positively charged nanoemulsion-based steroidal drug for transdermal application has been analyzed using rotary viscometer (Da Costa et al. 2014). Similarly, many researchers have used rotary viscometer for analyzing the food- and drug-grade nanoemulsions (Tsai et al. 2014). Recently, few reviews have also highlighted the recent characterization technologies for nanoemulsions (Jaiswal et al. 2015; Jain et al. 2017).

Stability and pH analysis of nanoemulsion

Stability of the nanoemulsion can be analyzed only visually, and the main forms of instability of nanoemulsions are due to gravitational separation, flocculation, coalescence and phase separation. It can be noted that one has to be very precise while analyzing stability through naked eyes or the magnifying glasses. Similarly, stability and pH analysis are a need/requirement to be determined for food- and drug-grade nanoemulsions, because these emulsions will interact with the biological matrices which ultimately depend upon the pH (Jain et al. 2017).

Imaging techniques

Atomic force microscopy (AFM)

Atomic force microscopy technique is used for the nanoemulsions which is present in the colloidal film on slides. AFM images will provide a clear idea about the shape and size of the nanoemulsions droplets.

Recently, many researchers have focused on AFM imaging technique confirmed using dynamic light scattering (Makidon et al. 2008; Ghosh et al. 2013; Dasgupta et al. 2016b; Ma et al. 2016), whereas others researchers have confirmed that AFM results with other imaging techniques (Salvia-Trujillo et al. 2013; Neeru et al. 2014; Singh et al. 2015b; Song et al. 2016).

Transmission electron microscopy (TEM) and scanning electron microscopy (SEM)

TEM is a microscopy technique in which a beam of electrons is transmitted through an ultra-thin specimen interacting with the specimen as it passes through it. An image is formed from the interaction of the electrons transmitted through the specimen; the image is magnified and focused onto an imaging device. In the case of SEM, the scanned electrons are responsible for image formation. TEM and SEM are efficiently used for nanoparticles from early decade of the twenty-first century, but recently after several instrumental advancements now researchers are performing TEM and SEM images for nanoemulsions too (Klang et al. 2012; Jaiswal et al. 2015). In the current decade, several protocols have been established for SEM and TEM analyses of nanoemulsions and many food-grade and drug nanoemulsions have been characterized by SEM and TEM (Da Costa et al. 2014; Singh et al. 2015a, b; Lee et al. 2016).

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