PREPARATION OF NANOEMULSIONS BY HIGH-ENERGY AND LOW-ENERGY EMULSIFICATION METHODS

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Abstract. High energy methods include high pressure homogenization, microfluidization, sonication, method in jet disperser, high-amplitude ultrasonic method. The droplet size of the dispersed phase in nanoemulsions produced in a high pressure homogenizer declines with increasing of the number of homogenization cycles its, lowering of surface tension, the increasing the rate of surfactant adsorption and decreasing the ratio of viscosity of the dispersed and continuous phase to some extent. The droplet size of the dispersed phase of nanoemulsions produced in microfluidizer decreases with the increase of homogenization pressure, the increase of the number of passages of nanoemulsion through microchannels, the increase of the concentration of surfactant and decrease of the ratio of the dispersed and continuous phases's viscosities. The droplet size of the dispersed phase in nanoemulsions produced by sonication decreases with increasing duration of ultrasonic homogenization, power levels and concentration of surfactant. Only small amounts of nanoemulsion formulations can be prepared by this method.

The low-energy methods are: spontaneous emulsification, phase inversion methods, and solvent displacement method. Phase transition in the phase inversion methods, occures when the temperature is changed while the composition is constant or the temperature is kept constant with changing composition. The mixture of oil, water and nonionic surfactant at room temperature shows a positive curvature. In the phase inversion temperature method rapid temperature changes prevent coalescence and produce stable nanoemulsions. A large ratio of solvent and oil is required for the production of small diameter droplets of the disperse phase by solvent displacement method.

High-energy methods, such as homogenization under pressure, can be prepared with the nanoemulsion droplet sizes up to 1 nm, and nanoemulsion with uniform droplet size of the disperse phase. Low energy methods are more acceptable for manufacturers because they do not require expensive equipment.

Keywords: nanoemulsions, high-energy methods, low-energy methods

1 Introduction

Nanoemulsions are therapeutic systems whose characteristics (biocompatible and biodegradable components and the possibility of formulation in different pharmaceutical forms) make them suitable for pharmaceutical preparations for the oral, parenteral, transdermal, dermal, nasal, ocular, and pulmonary delivery of active substances [1-4]. Nanoemulsions are nanodispersed systems because of the relatively high physical stability and acceptable aesthetic appearance that can be a safe choice for the development of new formulations of pharmaceutical and cosmetic products [1,5].

Kinetically stable nanoemulsions are formulated with the appropriate choice of the oil phase, controlled size of dispersed droplets, relatively low concentration of suitable surfactants (usually nonionic surfactants), cosurfactants and satisfactory conditions of manufacturing [1,6]. Droplet size of the inner phase [1,7] of a nanoemulsion is less than 300 nm, but size range can vary, depending on the author. The surfactants (for oil/water (O/W) type, in concentrations of 5-10%) reduce interfacial tension between the mutually immiscible phases and Laplace's pressure [1,8]. By addition of a suitable cosurfactant (propylene glycol, glycerol, polyethylene glycol, lecithin, ethanol, propanol, polyglyceryl-3-oleate, propylene glycol monolaurate, and others) the flexibility of the interfacial film is improved which has a positive impact on physical stability of nanoemulsions [1]. Cosurfactants are required, because single-chain surfactants themselves can not sufficiently reduce the oil/water interfacial tension to produce nanoemulsions [1,5]. By reducing the concentrations of surfactant and cosurfactant the interfacial tension between water and oil increases which lead to increase in viscosity. On the other hand, increased content of the aqueous phase

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cause decrease in the viscosity of the nanoemulsion [3]. The use of polymeric surfactants in the O/W nanoemulsions leads to the reduction in Ostwald's ripening, as a consequence of strong adsorption of the O/W surface, alteration of interfacial tension and growth of Gibbs's dilatation elasticity [9]. Ostwald's ripening is reduced when nanoemulsions are stored at the optimal temperature. Addition of the second component (eg. squalane) to the dispersed phase, which is insoluble in the continuous phase [10,11], the long chain triglyceride oils [12], insoluble components in the core of nanoemulsion's droplets [12,13], or small amounts of other oils with low viscosity in the water phase [14] reduce of Ostwald's ripening. If the concentration of surfactant is increased above the critical micelle concentration, small droplets with low interfacial tension will be formed. These droplets have monodisperse distribution, resulting in the reduction of Ostwald's ripening [15]. Apart from surfactans and cosurfactans, quality nanoemulsions require energy, thus for their production high-energy and low-energy methods are used.

In this paper the high-energy and low-energy methods for preparation of nanoemulsions, applicable both to the industry and in laboratories of smaller capacity, are described. The preparation method is very important for the formation and stability of nanoemulsions. These systems can be prepared by high or low emulsification energy methods [16-19]. High-energy approaches utilize mechanical devices (microfluidizers, high pressure homogenizers or ultrasonic methods) that generate intense forces capable of forming very fine oil droplets. Low-energy methods involve complex interfacial hydrodynamic phenomena and depend on the system composition properties [20]. The low-energy method includes spontaneous emulsification, phase inversion methods, and solvent displacement method [9,21].

2 Methods of preparation of nanoemulsions

2.1. High-energy methods for preparation of nanoemulsions

In high-energy methods, large disruptive forces are provided by the use of mechanical devices such as ultrasonicators, microfuidisers and high pressure homogenizers which produce droplets of small size. The droplet size depends on the equipment, production conditions, such as temperature and time, as well as the properties and composition of sample. High-energy methods require sophisticated equipment and consume large amount of energy, therefore, they are very expensive. Their positive side is that they allow good control of droplet size and large selection of integral components. These methods are not applicable for thermolabile active ingredients such as retinoids and macromolecules including proteins, enzymes and nucleic acids [22-24].

2.1.1. High pressure homogenisation

This method is widely used for the production of nanoemulsions it utilizes several forces such as hydraulic shear, intense turbulence and cavitation. In this method, two liquids including surfactants and cosurfactants are passed through a small orifice of piston homogeniser under high pressure (500-5000 psi) to produce nanoemulsions [1,25]. At first, emulsion is formed with large volume fraction of dispersed phase, which may be diluted later on. The problem of coalescence can be reduced by adding surfactants in excess amount. High pressure homogenisation is a highly efficient method, available at both laboratory and large scale, but consumes a large amount of energy and the temperature usually increases during processing which might deteriorate the components [1].

This technique use high-pressure homogenizer/piston homogenizer to produce nanoemulsions of extremely low particle size (up to 1 nm). The droplet size depends on the number of homogenization cycles. More homogenization cycles lead to smaller droplet size. The droplet size of the nanoemulsion produced by this method decreases with decreasing the ratio of dispersed and continuous phase viscosities to certain extent ($0{,}05 < \frac{n_D}{n_c} < 5$), where n_D is the viscosity of the dispersed phase, and n_c is the viscosity of the continuous phase [5,25]. With this method only O/W (oil in water) liquid nanoemulsion of less than 20% oil phase can be prepared [26]. Some problems associated with homogenizer are poor productivity, component deterioration due to generation of substantial amount of heat. Nevertheless, this is the most used frequently method for preparation of nanoemulsions [27].

2.1.2. Microfluidization

This mixing technique utilise high pressure displacement pump (3,45-137,89 MPa) to produce fine nanoemulsions. Liquids (oil and water) from two opposite microchannels collide with each other at a common impingement area,

developing high pressure resulting in tremendous shear. Crude emulsion passes repeatedly through the interaction chamber microfluidizer until the desired size of droplets is obtained [1]. To obtain a uniform size of the droplets of the nanoemulsions inner phase, crude emulsion is filtered in nitrogen atmosphere to remove larger droplets [26].

The droplet size of the dispersed phase of nanoemulsions produced in microfluidizer decreases as the pressure of homogenization increases, or by increasing the number of passages through microchannel devices, increasing the concentration of surfactant and decreasing the ratio of dispersed and continuous phase viscosities [28]. Microfluidization is not suitable for the preparation of large amounts of nanoemulsions and it is very expensive [21,29].

2.1.3. Sonication

Sonication or ultrasonic homogenization can be used to produce kinetically stable nanoemulsions. Sonicator probe (of ultrasonic homogenizer) is brought in contact with dispersion of liquids with surfactants and cosurfactants to generate mechanical vibration and cavitation, which provides the energy input necessary for formation of small sized droplets.

Sonication or ultrasound processing is widely used in small scale production of nanoemulsions. However, care must be taken to prevent shear induced coalescence [13,30]. The particle size of the dispersed phase in nanoemulsions produced by sonication decreases with increasing duration of ultrasonic homogenization, power levels and concentration of surfactant [28]. In order to achieve a droplet size of the dispersed phase of 20 nm, it is necessary to optimize the design of ultrasonic reaction chambers, operating conditions and the formulation of the product (eg. the concentration of surfactant and the type and content of the oil phase) [31]. The main disadvantage of sonication is that it is not suitable for preparation of large volumes of nanoemulsions [27].

2.1.4. Jet disperser

In the jet disperser two or more jets of crude emulsion, each from opposing bores, collide with each other, but at a different way than in microfluidizer. The diameter of the bores in jet dispersers is typically 0,3 - 0,5 mm. Finally, an “orifice plate” is the simplest construction form for a homogenizing nozzle whose role is to coordinate energy dispersion of emulsion jet. Droplets are disrupted predominantly due to laminar elongation flow ahead in front of the bores. Unlike radial diffusers, the nozzle is microfludizer; jet dispersers and orifice plate contain no moving parts, so they can be used at high pressures up to 300-400 MPa [2,30].

2.1.5. High-amplitude ultrasonic method

This method is an alternative to high-pressure homogenization. Forces necessary for the production of nanoemulsions are generated by ultrasonic cavitation. Ultrasonic cavitation produces violent and asymmetric imploding vacuum bubbles. Micro-nozzles disperse and break up droplets to nanometer size. This method is successfully used in production of small quantities of pharmaceutical nanoemulsions and liposomes. Conventional ultrasonic technology processes to operate on the principle *small amount - high amplitude* or *high levels - low amplitude* without the possibility of combining processes like *large amount - high amplitude*. Despite the potential of the method, ultrasonic method is limited to the laboratory use [27].

2.2. Low-energy methods for preparation of nanoemulsions

Low energy methods use internal physical properties of the system such as temperature or composition to produce nanoemulsions [1].

2.2.1. Phase inversion methods

Phase inversion or condensation method, is based on transition of phases during the emulsification process. These phase transitions are result of changes in the spontaneous curvature of the surfactant and can be achieved a) at constant composition, by changing the spontaneous curvature of nonionic surfactants with temperature, (the well-known phase inversion temperature (PIT) method widely used in industry) or b) at constant temperature, by varying the composition of the system employing the emulsion inversion point (EIP) method. Limitations of these methods are: complexity, requisites for precision and use of synthetic surfactants [32,33]. Phase transition is conducted either by increase in temperature at constant composition or for keeping the temperature constant by altering the composition [1].

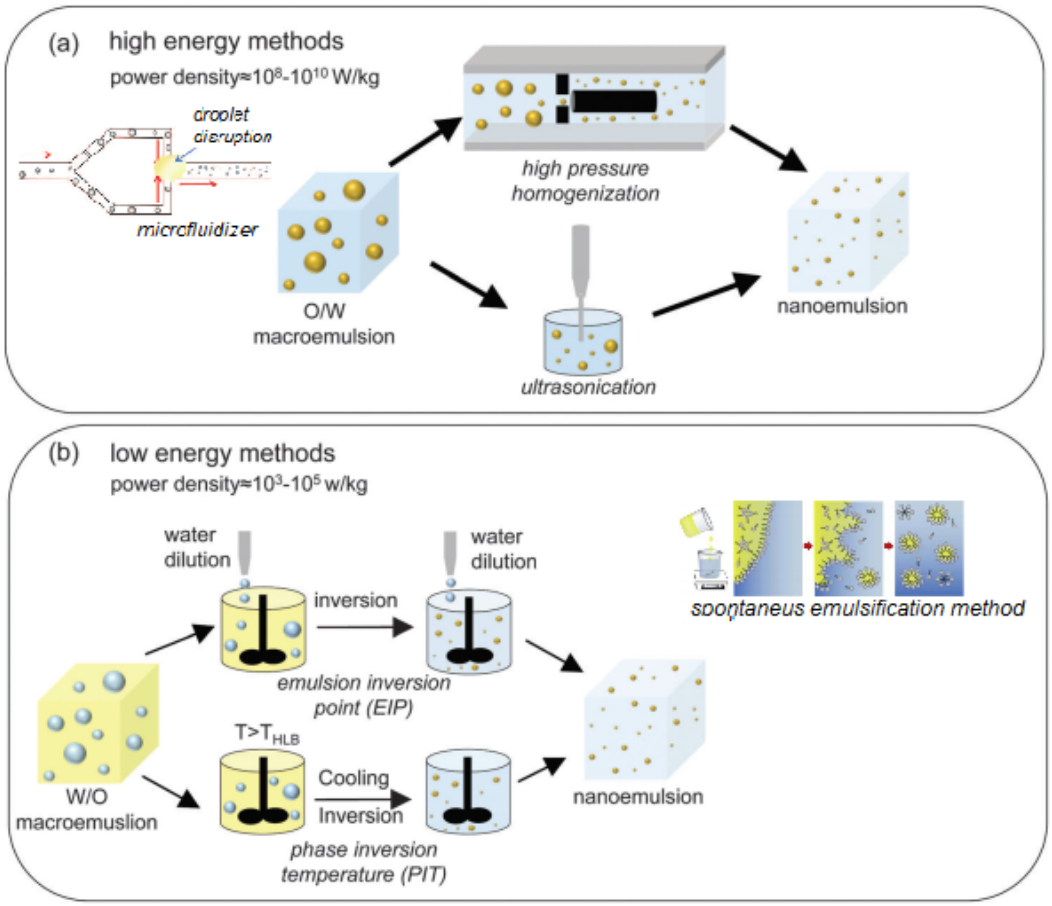

Fig. 1. Overview of high energy and low energy methods for preparing O/W nanoemulsions [20]

Phase inversion temperature method uses a mixture of oil, water and nonionic surfactants at room temperature exhibiting a positive curvature with increase in temperature, the polyethoxylated surfactant becomes lipophilic (due to dehydration) and gets solubilized in the oily phase. This results in the phase inversion and O/W emulsion changes to W/O emulsion, exhibiting a negative curvature. It must be noted here that at intermediate temperature, so-called HLB temperature (when the hydrophilic and lipophilic properties of the surfactant are balanced), highly unstable emulsions are formed as the curvature approaches zero. A quick change in temperature (increase or decrease in HLB temperature by 25-30 ^{o}C) prevents coalescence and produce stable nanoemulsions [1,2]. The main limitation of the PIT method in the preparation of nanoemulsions is that they become more prone to coalescence as the temperature of the dispersed phase droplets increases (in the food and beverage industry). Therefore, a new approach was developed in making nanoemulsions by using nonionic surfactants with relatively low phase inversion temperature (such as Brij® 30) with dilution using a solution containing another surfactant (sodium dodecyl sulfate or Tween® 80) with a high phase inversion temperature [34].

The disadvantages of PIT method are: it is limited to the nonionic surfactants, necessity of thermal energy requirement of the presence of phases such as liquid crystal (LC) or midrange microemulsion (ME) [21,29,35]. In the PIT method the change from one type of an emulsion to another involves a transitional phase inversion, whereas in the EIP method the change from one type of an emulsion to another involves a catastrophic phase inversion. A catastrophic phase inversion occurs when the ratio of the oil-to-water phase is altere with constant surfactant properties [36].

2.2.2. Spontaneous emulsification

Spontaneous emulsification is a low energy method for the preparation of nanoemulsions. Nanoemulsions can be produced by this method at room temperature without the use of any special equipment. Water is added into solution of oil and surfactant stepwise, at constant temperature while gently stirr in order to produce O/W nanoemulsions. The spontaneity of the emulsification process depends mainly on: interfacial tension, interfacial and bulk viscosity, phase transition region, surfactant structure and its concentration [37]. The main disadvantage of this method is the limited amount of the oil phase and the presence of the solvent [21,29,35].

2.2.3. Solvent displacement method

Nanoemulsions can be produced employing this method at room temperature by pouring the organic phase containing oil dissolved in a solvent, like ethanol or acetone, into aqueous phase containing surfactants. Emulsification occurs spontaneously during with due to diffusion of organic solvent, which may be removed later by vacuum evaporation. A high ratio of solvent to oil is needed to prepare small sized droplets [1,38].

There are many factors that affect the selection of emulsifying device, and some of them are volume of emulsion, the viscosities of the emulsion and its phases, surfactant type and concentration, temperature, size and size distribution of the droplets of the disperse phase. To achieve the desired nanoemulsions formulation parameters of emulsification must be optimized. Those parameters include: flow rate, pressure, density of interface, temperature and time of emulsification, and speed of rotation [8].

Schematic representation of various methods that can be used to produce nanoemulsions are summarized in Figure 1.

3 Conclusions

Nanoemulsions are attractive systems for use in the cosmetic, pharmaceutical, food and other industries, due to low amount of surfactant, they require higher stability against coalescence, lack of toxicity or irritant characteristics, low viscosity, good appearance, and adaptability of formulations as foams, creams, liquids and sprays. High pressure homogenization can be applied to production of nanoemulsions if the optimized composition of the system is ensured, as well as the device capable of generating intense disruptive forces. The advantages of this method are flexibility in the choice of surfactant and the internal structure, as well as possibility of preparing nanoemulsions in a short time. Large energy costs during the development is a disadvantage of this method as it is not suitable for thermosensitive substances and substances sensitive the shear. As nanoemulsions have very small particle size range, it is still the most frequently used method for preparation of nanoemulsions. Benefits of microfluidization are controlled droplet size of dispersed phase, and possibility of creation of multiple nanoemulsions. It is an expensive method. It is not suitable for the production of large amounts of nanoemulsions as well as the high-amplitude ultrasonic method. Sonication can be used to produce small amounts of kinetically stable nanoemulsions. Spontaneous emulsification is a low energy method by which nanoemulsions are made at room temperature without the use of special equipment. Solvent displacement method requires no heating, nor the presence of an organic solvent and LC or ME as a phase. Disadvantages of low-energy methods are: limited amount of oil phase and the presence of the solvent (spontaneous emulsification); limitition to nonionic surfactants, requirement the presence of LC or ME phases and heat (PIT method); the need of a large ratio of solvent and oil for the production of small sized droplets of the disperse phase (solvent displacement method). Although high energy emulsification methods are traditionally used for the preparation of nanoemulsion formulation, low energy emulsification methods are attractive nowadays, due to their wide application and advantages, such as the formulation and stability aspects.

References

1. Setya S., Talegaonkar S., Razdan B.K. Nanoemulsions: formulation methods and stability aspects. World J. Pharm. Pharm. Sci. 2014; 3(2): 2214-2228
2. Kumar S. Role of nano-emulsion in pharmaceutical sciences - a review. AJRPSB. 2014; 2(1): 1-15
3. Charles L., Attama A.A. Current state of nanoemulsions in drug delivery. J. Biomat. Nanobiotech. 2011; 2(5A): 626-639
4. Chen H., Du D., Mao C.M.D., Wan J., Xu H., Yang X. Hydrogel-thickened nanoemulsion system for topical delivery of lipophilic drugs. Int. J. Pharm. 2008; 353(1-2): 270-276
5. Tadros T., Izquierdo P., Esquena J., Solans C. Formation and stability of nano-emulsions. Adv. Colloid Interface Sci. 2004; 108-109: 303-318

6. Maruno M., Rocha-Filho P.A. O/W nanoemulsion after 15 years of preparation: a suitable vehicle for pharmaceutical and cosmetic applications. J. Dispers. Sci. Technol. 2010; 31(1): 17-22
7. Zhang L.W., Al-Suwayeh S.A., Hung C.F., Chen C.C., Fang J.Y. Oil components modulate the skin delivery of 5-aminolevulinic acid and its ester prodrug from oil-in-water and water in-oil nanoemulsions. Int. J. Nanomedicine. 2011; 6: 693-704
8. Jaiswal M., Dudhe R., Sharma P.K. Nanoemulsion: an advanced mode of drug delivery system. 3 Biotech. 2015; 5(2):123-127
9. Solans C., Izquierdo P., Nolla J., Azemar N., Garcia C.M.J. Nano-emulsions. Current Opinion in Colloid and Interface. Science. 2005; 10(3-4): 102-110
10. Liu W., Sun D., Li C., Liu Q., Xu J. Formation and stability of paraffin oil-in-water nanoemulsions prepared by the emulsion inversion point method. J Colloid Interface Sci.2006; 303(2): 557-563
11. Ee S.L., Duan X., Liew J., Nguyen Q.D. Droplet size and stability of nano-emulsions produced by the temperature phase inversion method. Chem. Eng. J. 2008; 140(1): 626-631
12. Wooster T.J., Golding M., Sanguansari P. Impact of oil type on nanoemulsion formation and Ostwald ripening stability. Langmuir. 2008; 24(22): 12758-12765
13. Delmas T., Piraux H., Couffin A.C., Texier I., Vinet F., Poulin P., Cates M.E., Bibette J. How to prepare and stabilize very small nanoemulsions. 2011; 27(5):1683-1692
14. Reza A. Nanometric-scaled emulsions (nanoemulsions). Iran. J. Pharm. Res. 2010; 9(4): 325-326
15. Tadros T. Polymeric surfactants in disperse systems. Adv. Colloid Interface Sci. 2009; 147-148: 281-299
16. Gianeti M.D., Wagemaker T.A.L., Seixas V.C., Maia Campos P.M.B.G. The use of nanotechnology in cosmetic formulations: the influence of vehicle in the vitamin a skin penetration. Curr. Nanosci. 2011; 8(4): 526-534
17. Adjonu R., Doran G., Torley P., Agboola S. Whey protein peptides as components of nanoemulsions: a review of emulsifying and biological functionalities. J. Food Eng. 2014; 122(1): 15-27
18. Mason T.G., Wilking J.N., Meleson K., Chang C.B., Graves S.M. Nanoemulsions: formation, structure, and physical properties. J. Phys. Condens. Matter. 2006;18(41): 635-666
19. Abbas S., Bashari M., Akhtar W., Li W.W., Zhang, X. Process optimization of ultrasound-assisted curcumin nanoemulsions stabilized by OSA-modified starch. Ultrason. Sonochem. 2014, 21(4): 1265-1274
20. Piorkowaski D.T., McClements D.J. Beverage emulsions: recent developments in formulation, production, and applications. Food Hydrocolloides, 2013; 42: 5-41
21. Koroleva M.Y., Yurtov E.V. Nanoemulsions: the properties, methods of preparation and promising applications. Russ. Chem. Rev. 2012; 81(1): 21-43
22. Graves S., Meleson K., Wilking J., Lin M.Y., Mason T.G. Structure of concentrated nanoemulsions. J. Chem. Phys. 2005; 122(13): 134703
23. Jafari S.M., He Y., Bhandari B. Optimization of nanoemulsion production by microfluidization. Eur. Food Res. Tech. 2007; 225 (5-6): 733-741
24. Quin C., McClement D.J. Formation of nanoemulsions stabilized by model food grade emulsifiers using high pressure homogenization: factors affecting particle size. Food Hydrocolloids. 2011; 25(5): 1000-1008
25. Thakur N., Garg G., Sharma P.K., Kumar N. Nanoemulsions: a review on various pharmaceutical application. Global J. Pharmacol. 2012; 6(3): 222-225
26. Jincy J., Krishnakumar K., Anish J., Dineshkumar B. Nanoemulsion in pharmaceuticals: a review. Current Research in Drug Targeting. 2015; 5(1): 1-4
27. Kumari Ch.T.L., Sowjanya G.N., Bandhavi P. Nanoemulsions an emerging trend: a review. IJPRD. 2012; 4(6): 137-152
28. Kentish S., Wooster T., Ashokkumar M., Balachandran S., Mawson R.L., Simons L. The use of ultrasonics for nanoemulsion preparation. Innovative Food Sci. Emerging Technol. 2008; 9(2): 170-175
29. Maali A., Mosavian Hamed M.T. Preparation and application of nanoemulsions in the last decade (2000-2010). J. Dispersion Sci. Technol. 2013; 34(1): 92-105
30. Leong T.S.H., Wooster T.J., Kentish S.E., Ashokkumar M. Minimising oil droplet size using ultrasonic emulsification. Ultrason. Sonochem. 2009; 16(6): 721-727
31. Kumar H.S.L., Singh V. Nanoemulsification - a novel targeted drug delivery tool. JDDT. 2012; 2(4): 40-45
32. Izquierdo P., Feng J., Esquena J., Tadros T.F., Dederen J.C., Garcia M.J. The influence of surfactant mixing ratio on nanoemulsion formation by the pit method. J. Colloid Interf. Sci. 2005; 285(1): 388-394
33. Forgiarini A., Esquena J., Gonzalez C., Solans C. Formation of nano-emulsions by low-energy emulsification methods at constant temperature. Langmuir. 2001; 17(7): 2076-2083
34. Rao J.J., McClements D.J. Stabilization of phase inversion temperature nanoemulsions by surfactant displacement. J. Agric. Food Chem. 2010; 58(11): 7059-7066
35. Anton N., Benoit J.P., Saulnier P. Design and production of nanoparticles formulated from nano-emulsion templates - a review. J. Controlled Release. 2008; 128(3):185-199
36. Thakur R.K., Villette C., Aubry J. M., Delaplace G. Dynamic emulsification and catastrophic phase inversion of lecithin-based emulsions. Colloids and Surfaces A: Physicochemical and engineering aspects. 2008; 315(1-3): 285-293
37. Bouchemal K., Briancon S., Perrier E., Fessi H. Nanoemulsion formulation using spontaneous emulsification: solvent, oil and surfactant optimization. Int. J. Pharm. 2004; 280(1-2): 241-251
38. Fryd M.M., Mason T.G. Advanced nanoemulsions. Annu. Rev. Phys. Chem. 2012; 63: 493-518