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Evaluation of short cycles of ultrasound application in nanoemulsions to obtain nanocapsules

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ABSTRACT

Ultrasound is widely used in several chemical reactions and other process, including production of nanocapsules by *in situ* polymerization. In this work, the main objective was to evaluate the impacts and viability of successive ultrasound application in nanoemulsions to obtain nanocapsules. Initiator potassium persulfate (KPS) concentration, number of ultrasound cycles and reaction time influences on polymerization efficiency and droplet size were evaluated. This work revealed the successful *in situ* production of nanocapsules using successive shorts cycles of ultrasound. Number of cycles was the only parameter that not exerted significant influence in polymerization yield. Particle size decay was observed in all nanoemulsions after the first ultrasound application, the same was not observed in further cycles. Gravimetric assessment showed remarkable increase of monomer conversion, indicating that once started polymerization continued at least until 28 days after ultrasound application. Concluding, ultrasound short cycles can be used with no harm to formulation, if carefully performed and, furthermore is a potential cost-effective route for polymerization reactions.

1. Introduction

Nanoemulsions can be defined as colloidal systems in which a lipid phase is dispersed in an aqueous continuous phase, as small droplets, stabilized by a thin interfacial layer of surfactant molecules [1,2]. Their nanometric size, frequently in the range of 10–200 nm, is an intrinsic characteristic giving them a variety of exclusives properties [3,4], one of which is the improved stability. Nanoemulsions are kinetically stable and are prepared with low amounts of surfactants (4–10%) [5,6] when compared with microemulsions, which are thermodynamically stable and require much higher concentration of surfactants. Due to the small droplet size of nanoemulsions, instability events, e.g. creaming, sedimentation and coalescence, tend to not occur as the gravity force is overcome by the Brownian motion of the droplets, allied to surface charge that inhibit droplets proximity and further aggregation [1,3,4,7,8].

All of these advantages make nanoemulsions suitable for applications in personal care, agrochemical, cosmetics, food and pharmaceutical industries. They have also been used as reaction media for polymerization [8,9].

Nanoemulsions are prepared by numerous methods. High-energy emulsification methods require high mechanical energy-input, generally provided by high shear forces to achieve small droplet sizes [4,7]. Emulsification is also achieved by low-energy methods that are based on physicochemical behavior of the system by altering the spontaneous curvature of surfactants. For example, the phase inverse temperature (PIT) method [10] consists of heating an oil-in-water (O/W) emulsion, prepared with nonionic ethoxylated surfactants. These surfactants are temperature sensitive molecules and undergo dehydration at elevated temperatures becoming more hydrophobic and resulting in a water-in-oil (W/O) emulsion. When the system is cooled, it goes through a point of zero curvature of the surfactant layer with minimum interfacial tension, promoting a phase inversion from W/O to O/W emulsion with nanometric droplet size [3,8]. Another method of changing spontaneous curvature of surfactants is by altering the water volume fraction. This approach is called the Emulsion Inversion Point (EIP) method. Adding water to an oil phase, initially, droplets are formed consisting in a W/O emulsion wherein becomes an O/W emulsion as the volume of water is progressively increased and overcomes oil volume fraction. The hydration of polyethoxylated surfactant chains also increases and, at the inversion point, it reaches a zero spontaneous curvature as well as minimum interfacial tension, forming small droplets [11,12].

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One use of nanoemulsion is as a template to obtain nanocapsules. Hydrophobic monomers are introduced in the oil internal phase and polymerization of these nanoemulsions leads to formation of nanoparticles with the oil entrapped within the polymer particles. The particle size of these solid colloidal systems ranges from 10 to 1000 nm [13]. Depending on their composition and structure, they are named: nanocapsules or nanospheres. Nanocapsules are vesicular systems composed of a cavity with an inner liquid core, usually lipophilic, surrounded by a polymeric membrane. Encapsulated material is dissolved in the inner core or adsorbed or dispersed in the polymeric shell. Nanospheres are devoid of a nucleus and consist of a polymeric matrix, in which drug is encapsulated in the matrix or adsorbed on the surface [7,14]. Nanocapsules and nanospheres are prepared using similar methods. They are used as carrier systems for targeted and controlled drug delivery as such or with surface modifications [15–17].

A potential application of nanocapsules in pharmaceutical field is as nanocarriers to lipophilic drugs. Anton and coworkers [7] described three main advantages of nanocapsules for this use: high encapsulation efficiency, lowered tissue irritation at the administration site and protection against drug degradation; all of them are due to the great drug solubility in nanoparticle oily core while the solubility on the external phase is kept low. Another potential utilization as carrier is in cosmetic field, focusing in topical administration, once their nanometric size and larger superficial area favor drug penetration through the complex skin structure [4].

One way to perform *in situ* polymerization of nanoemulsions is using Atom Transfer Radical Polymerization (ATRP) technique. It is based on chain reaction caused by formation of a radical initiator and subsequent reaction with monomers. Potassium persulfate ($K_2S_2O_8$ or KPS) is described as one of the most common initiators [9]. Its characteristics of being hydrosoluble direct polymerization from the external phase toward the internal hydrophobic phase, inducing the formation of the polymeric shell. KPS undergoes an homolytic break forming radicals $[SO_4^-]^{\cdot}$ and starting a chain reaction [18]. Fig. 1 illustrates step by step of nanocapsule formation by *in situ* polymerization of monomers in an oil droplet.

The method suggested by Spernath and Magdassi [19] to produce polymeric nanoparticles requires heating and stirring of a nanoemulsion previously prepared by PIT method, using a solution of $FeSO_4$/KPS in a ratio of 1:1 to initiate polymerization. The Fe^{2+} ions cause the dissociation of KPS, activating the initiator. However Fe^{2+} ions can lead to undesirable complexes with other components present in formulation. Moreover, this process takes around 4 h to finish.

Ultrasound is used as another method to supply the energy required to start polymerization [20–22]. It is characterized as sonic waves of frequency between 2×10^4 and 10^7 Hz [23]. Many theories about its mechanism in chemical reactions are suggested, but they all propose acoustic cavitations, which occur when ultrasound waves propagate through a liquid media creating bubbles that grow and collapse. The temperature estimated during bubbles formation is in range of 750–6000 K and the breaking process emits pressures over 1000 atm. These conditions promote the rupture of initiator bonds, starting the polymerization reaction [21,24,25]. Since ultrasound is a high-energy method, the process time is in general faster than common methods. It is known that most of traditional methods used to supply mechanical energy to obtain nanostructured carriers frequently present an unsuccessful control of particle size distribution and, consequently, poor dispersion stability [26]. In this context, ultrasound cavitation has been pointed as a promisor method, once cavitation is able to provide a reliable and simple route for the control of both synthetic process and nanostructure. This method is also reported as feasible to afford chemical homogeneity and reactivity through atomic level [27].

In order to avoid long exposures to high energy provided by continuous ultrasound application but still assuring a fast method to obtain nanocapsules, we suggested the employment of successive short cycles. The present work is an initial step of development of proposed method and aimed to evaluate physicochemical impacts, behavior and viability of these successive ultrasound applications in nanoemulsions.

2. Experimental section

2.1. Materials

2-Ethylhexyl acrylate (2-EHA) (analytical grade) monomer was kindly provided by BASF. It was previously filtered with activated charcoal to remove the polymerization inhibitor (Hydroquinone Mono-Methyl Ether). Soybean oil was supplied by Cargill. Surfactants were Sorbitan Monooleate (Span 80 – Croda do Brasil – Campinas-Brazil) and PEG-40 Hydrogenated Castor Oil (Croduret® 50 Special – Croda do Brasil – Campinas-Brazil). KPS (analytical grade) was purchased from Merck.

2.2. Nanoemulsion production

Formulation was constituted of an oil and an aqueous phases. Oil phase was composed by 3.0% (w/v) of PEG-40 Hydrogenated Castor Oil, 2.0% (w/v) of Span 80 (both as surfactants), 5.0% (w/v) of Soybean oil and 5.0% (v/v) of monomer (2-EHA). Distilled water was used as aqueous phase. The O/W nanoemulsion was prepared using a method that combines PIT and EIP techniques. Oil and aqueous phases were heated separately to 80 ± 2 °C, thus aqueous phase was slowly added into oil phase under constant mechanical agitation of 600 rpm (Fisaton 713D) until cooling at room temperature (22 ± 2 °C) [28]. The monomer was added to oil phase during heating.

2.3. Nanocapsule production

Nanocapsules were obtained from polymerization of nanoemulsions containing monomers. Polymerization was carried out by two methods: by successive ultrasound applications and by heating. The second one was mainly used as comparison.

2.3.1. Ultrasonic polymerization

Nanoemulsions were divided in 5.0 ml aliquots and 0.3 or 0.9 ml of 10% (w/v) KPS solution (respectively 6 and 18 mg/ml as final concentration) were added. Each aliquot was submitted four times to sonication using 25% of amplitude ultrasonic in processor (Vibra cell™ VC750 – Sonics-USA) with a metal rod titanium probe, 13 mm tip diameter, at 300 W for different cycle times: 0.5, 1.0, 2.0, 3.0 and 5.0 min.

2.3.2. Heating polymerization

The method was adapted from Spernath and Magdassi [19] and described by Goto et al. [27]. Different quantities of a 10% (w/v) KPS solution (corresponding to a final concentration of 6 or 18 mg/ml respectively) were added in the previously obtained nanoemulsions and kept in water bath Thermomix® (B. Braun Biotech International, model 18BU) at 40 °C under magnetic stirring. After 2 h of reaction, the same quantity of KPS was added to each formulation and mixed for 4 h.

2.4. Characterization of the formulations

2.4.1. Particle size measurements

Particles size distribution was obtained by Dynamic Light Scattering using Nanosizer® N5 Submicron Particle Size Analyzer

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