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ScienceDirect

Resource-Efficient Technologies 2 (2016) 233–239

www.elsevier.com/locate/reffit

Research paper

Nano- and microcapsules as drug-delivery systems

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Received 24 July 2016; received in revised form 29 October 2016; accepted 31 October 2016

Available online 1 December 2016

Abstract

Preparation of nano- and micrometer-size capsules with lipid core might have several biomedical applications for delivery of lipophilic drugs. Successful usage of these nano- and microcarriers depends on their colloidal stability. Emulsion based carriers for drug delivery: nanoemulsions, colloidosomes, and solid lipid particles have been investigated in this work. Diameters of oil droplets in nanoemulsions are equal to 15 and 20 nm, however they are not stable to phase separation. In spite of large droplet diameters (several tens of micrometer), colloidosomes stabilized by heteroaggregates of oppositely charged SiO_2 nanoparticles are stable toward creaming. Paraffin emulsions stabilized by Carbopol 940 have particles 190 nm in size and are also stable to creaming during several months. Encapsulation of lipophilic drugs tocopherol, hydrocortisone, nimesulide or curcumin does not cause changing diameters of nanoemulsion based nanocapsules. Incorporation of these drugs in paraffin particles leads to decreased or increased particle sizes, but in all specimens the sizes are equal or less than 700 nm and such particles can be used as microcapsules for lipophilic drug delivery.

Keywords: Nanocapsules; Microcapsules; Nanoemulsions; Colloidosomes; Solid liquid particles; Drug delivery

1. Introduction

The nano- and microcapsules are currently promising systems for drug delivery in the treatment of many types of diseases [1]. Nano- and microcarriers have also been employed as imaging tools that makes possible to increase imaging resolution and highlights small lesions which are undetectable with traditional methods [2,3].

In the case of the administration of drugs using nano- and microcapsules a prolonged drug release with controlled rate may be achieved. Many of pharmacologically active compounds exhibit poor water solubility that requires the creation of new carriers for their administration and delivery. One of the most promising approaches is using appropriate lipid vehicles. Rational design of delivery system can lead to the success of lipid based drug delivery systems [4,5].

A variety of lipid-based systems can be obtained based on the type of excipients and formulation variables [6]. Colloidal systems such as nanoemulsions, solid lipid nanoparticles, nanostructured lipid carriers, liposomes, niosomes, and colloidosomes have materialized great means toward improved targeted delivery of drug cargoes [7].

Emulsion based carriers: nanoemulsions, solid lipid particles, and colloidosomes were investigated in this paper. Nanoemulsions are emulsions with oil or water droplets that sizes are at most 100 nm. They can encapsulate either lipophilic and hydrophilic drugs or imaging agents in the oil or in the aqueous phase [8,9]. Nanoemulsions can be prepared by high-energy stirring, ultrasonic emulsification, high-pressure homogenization, microfluidics, and membrane emulsification [10] or by low-energy methods, e.g., phase inversion temperature or composition methods [11], spontaneous emulsification [12].

Low-energy methods of nanoemulsion preparation such as phase inversion temperature and phase inversion composition methods are of particular interest recently because they are non-destructive for encapsulated molecules, energy-saving and attractive for large-scale production [11]. Molecules of surfactant, especially nonionic ethoxylated surfactants, show appreciable affinity for aqueous phase at low temperatures due to hydration of polar groups and affinity for oil phase at elevated temperatures because of dehydration of oxyethylene groups. If a W/O emulsion stabilized by ethoxylated surfactant is prepared at elevated temperature and then rapidly cooled, an O/W nanoemulsion is formed through the phase inversion.

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http://dx.doi.org/10.1016/j.reffit.2016.10.013

Solid lipid particles are obtained from nanoemulsions or macroemulsions. Emulsions are prepared at temperatures higher than the melting point of the lipid and cooled to ambient temperature which causes crystallization of the lipid and, as a result, solid lipid particle formation [10].

Colloidosomes are hollow-porous microcapsules which are formed because of self-assembling colloidal particles of different sizes and shapes on the surface of emulsion droplets [13,14]. The self-assembled shell of colloidosomes differs from the shells of other carriers since it consists of the particles and voids between them, and so it is penetrable for drugs encapsulated in the core [15].

Nanoemulsions, solid lipid particles, and colloidosomes are thermodynamically unstable systems. The main mechanism of nanoemulsion coarsening is Ostwald ripening [16], i.e., the dissolution of smaller oil droplets and the growth of larger ones.

Droplet aggregation takes place if the attractive forces between oil droplets exceed the repulsion ones. If aggregation occurs, the tendency of subsequent coalescence of liquid droplets increases. Solid lipid particles are free from these limitations but these systems are usually unstable toward creaming.

Stability toward creaming can be achieved by steric stabilization of emulsions and the formation of hydrogel in the aqueous phase. For this purpose cross-linked polyacrylate polymers are usually used. Solid lipid nanoparticles in such hydrogel are stable for a period of six months [17].

In colloidosomes templated from Pickering emulsions, the adsorption of particles on the oil–water interface provides steric hindrance to drop–drop coalescence. However Pickering emulsions are much less stable to creaming also.

Solid particles with diameters more than 100 nm can form monolayer on the surface of emulsion droplets. Nanoparticles are adsorbed mainly as aggregates at the water/oil interface [18]. Aggregation of solid stabilizers may be caused by the introduction of electrolytes, surfactants or by change of pH of the aqueous phase in emulsions [19,20]. Colloidosomes can be functionalized with magnetic, semiconductor and other particles [21–23], that increases the fields of these colloidosome applications.

The aim of the present study is to examine the impact of various stabilizers on particle sizes and stability of emulsion based colloid systems such as nanoemulsions, solid lipid particles, and colloidosomes. The effect of lipophilic drugs encapsulation on droplet diameters in nanoemulsion and paraffin particle sizes has been investigated.

2. Materials and methods

2.1. Chemicals

Nonionic surfactants: polyethylene(4)glycol dodecyl ether (Brij 30, HLB 9.7 to 20 °C), polyoxyehylene(20)sorbitan monooleate (Tween 80, HLB 15.0), sorbitan monooleate (Span 80, HLB 4.3) (≥60%), polyoxyethylene sorbitan monostearate (Tween 60, HLB 14.9), sorbitane monostearate (Span 60, HLB 4.7) (45–55%) were purchased from Sigma-Aldrich, cetyl/oleyl acohol ethoxylate EO 10 (Eumulgin O10, HLB 12.5) was purchased from BASF (Germany). **Poly(vinyl alcohol)** Mowiol® 8–88 (PVA, Mw ~ 67 000 was received from Sigma-Aldrich (Steinheim, Germany) and used as polymer stabilizer. Cross-linked polyacrylate Carbopol 940 (Acros organics, USA) was used as gelling agent.

NaCl (extra pure) and NaOH (analytical grade) were provided by Merck (USA).

Liquid paraffin (Britol 20 USP) was obtained from Sonneborn and used as oil phase in nanoemulsions. Paraffin wax was purchased from Lukoil (Russia).

Negatively charged silica particles Ludox HS-30 and positively charged alumina-coated silica particles Ludox CL were purchased from Sigma-Aldrich as 30 wt.% aqueous dispersions at pH 9.8 and 4.5, respectively. The average particle diameter is 10 nm for Ludox HS-30 and 30 nm for Ludox CL as determined by dynamic light scattering. Silica nanoparticles were used as solid stabilizers.

(+)-α-Tocopherol, hydrocortisone (≥98%), nimesulide, curcumin (≥65%) were obtained from Sigma-Aldrich and used as model drugs.

All materials were used as received without further purifications. Bidistilled water was used throughout the study.

2.2. Preparation on nano- and microcapsules

2.2.1. Preparation of nanoemulsions

Oil-in-water nanoemulsions were prepared by the phase inversion temperature method [11]. W/O emulsion was prepared as follows. Liquid paraffin (0.5–4.3 ml), Brij 30 (0.1–0.8 ml) or mixture of Tween 80 and Span 80 (0.5–1.3 ml), and aqueous solution (5.0–8.8 ml) of NaCl (0.15 M) were heated to 80 °C and dispersed for 15 min at 1000 rpm in magnetic stirrer (IKA RCT Basic, Germany). Obtained W/O emulsion was immediately cooled in an ice bath under stirring at 1000 rpm until 5–10 °C temperature was reached. O/W nanoemulsion was formed because of phase inversion.

2.2.2. Preparation of colloidosomes

O/W Pickering emulsions stabilized by heteroaggregates of oppositely charged SiO_2 nanoparticles were prepared as follows. Aqueous dispersions of silica particles Ludox HS-30 or Ludox CL were diluted to the required concentrations by bidistilled water and mixed. The pH value was adjusted to 6 with 0.1 M HCl or NaOH aqueous solution. Aqueous dispersion of heteroaggregates (15 ml) was added to liquid paraffin (15 ml) and pre-homogenized in a magnetic stirrer at 1000 rpm for 2 min. The primary emulsion was then further homogenized using in a high shear mixer (Ultra-Turrax T 25, IKA, Germany) at 11 000 rpm for 2 min.

2.2.3. Preparation of paraffin emulsions

Paraffin emulsions were prepared by the high-share homogenization method. Three grams of paraffin was melted and heated at 75 °C. Aqueous solution (27 ml) of Eumulgin O10 (0.3 g), and PVA (0.03–0.15 g) or Carbopol 940 (0.01–0.10 g) was previously heated to 75 °C and added to melted paraffin. Concentration of paraffin and Eumulgin O10 in next prepared emulsions was fixed and equal to 10 and 1 wt.%, respectively. This mixture was homogenized in Ultra-Turrax T 25 for 10 min.