Current Opinion in Colloid & Interface Science 17 (2012) 281–289

Contents lists available at SciVerse ScienceDirect

Current Opinion in Colloid & Interface Science

journal homepage: www.elsevier.com/locate/cocis

Layer-by-layer coated emulsion microparticles as storage and delivery tool

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ARTICLE INFO

Article history:
Received 1 February 2012
Accepted 15 June 2012
Available online 30 June 2012

Keywords:
Layer-by-layer assembly
Emulsion
Pickering emulsion
Capsule
Polyelectrolyte multilayer
Ultrasonication
Drug delivery
Controlled release

ABSTRACT

Microencapsulation is an imperative technology in pharmacy, food industry and medicine. However, the current level of the development requires not only the fabrication of the emulsion systems, but also their functionalization in order to impart it multifunctional properties. One of the most perspective approaches to attain additional functionality to the emulsion particles is the use of the layer-by-layer modification of their surface. This technique permits the step-wise adsorption of various components (polyelectrolytes, nanoparticles, proteins, enzymes, etc.) as the layer growth is governed by their electrostatic, hydrogen bonding, hydrophobic, etc. forces and allows the formation of multilayer shells with nanometer (thickness) precision. The proposed review surveys the layer-by-layer approach for modification of both polymer and Pickering emulsions with polyelectrolyte or nanoparticle multilayers together with the demonstration of the application examples of the modified emulsion systems, where the emulsion particles play simultaneously the role of the template for layer-by-layer assembly as well as of the inner load.

1. Introduction

The use of the emulsions is enormous. They are known from many hundreds of years and employed nowadays in food industry, paintings, fertilizers, medicine, chemical industry and many other activity areas of the mankind. The main feature of the emulsion is the possibility to disperse immiscible liquids and, at the same time, separately dissolving immiscible reagents in each liquid allowing their interaction at the liquid-liquid interface. However, the current level of the development in the food industry and medicine requires not only the fabrication of the emulsion systems, but also their functionalization in order to impart it multifunctional properties. Microencapsulation is an imperative technology in pharmacy and medicine. This is particularly important for the novel drug-delivery concepts where the lipophilic drug has to be (i) dispersed on micro or submicro level, (ii) delivered to the damaged part of the body and (iii) released in a controlled way. The application of the emulsion systems here is indispensable, because they can (i) dissolve and disperse lipophilic drug, (ii) protect it by the emulsion shell and (iii) release the drug upon shell destruction. All these three steps need the additional functionalities of the emulsion particle. The dissolution/dispersion of the lipophilic drug can be achieved by tuning the oil phase of the emulsion; magnetic properties and specific guest-host interactions can be used for the targeted delivery while the most difficult characteristic to be achieved for the emulsion-based delivery system is the controllable release. A potential benefit of using emulsions as delivery systems is that they can be fabricated entirely from natural food grade ingredients (lipids, proteins, polysaccharides) using simple processing operations (homogenization, mixing). They could therefore be utilized in the development of pharmaceutical products or functional foods designed to combat diet-related diseases, such as obesity, heart disease, cancer, and hypertension.

There are several ways for triggering the release of the encapsulated drug employing either external or internal factors. First is the release triggered by the changes in pH (e.g. at pH~6.8 in the tumor interstitium, or at pH~5.0 in endosomes) or by action of enzymes in the emulsion shell [1]. Delivery systems designed to control the digestion, release, and absorption of encapsulated lipophilic components within the gastrointestinal tract are being developed for a variety of applications within the pharmaceutical, biopharmaceutical, and food industries [2]. They can be used to control the release of drugs and other bioactive components at specific locations within the gastrointestinal tract, such as the mouth, stomach, small intestine, or colon. Whilst such 'spontaneous' release is the most desirable since it functions solely inside the body and remotely without further intervention, it can still be slow. In order to produce more controlled, rapid, and complete release of the drug from a carrier, local intervention techniques can use temperature change (hyperthermia) [3], light (photodynamic therapy) or mechanical disruption (e.g. by ultrasound) to open the shell of delivery container [4].

One of the most perspective approaches to attain additional functionality to the emulsion particles is the use of the layer-by-layer (LbL) modification of their surface. This technique permits the step-wise adsorption of various components (polyelectrolytes, nanoparticles, proteins, enzymes, etc.) as the layer growth is governed by their electrostatic attraction and allows the formation of multilayer shells with nanometer

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doi:10.1016/j.cocis.2012.06.003

(thickness) precision [5,6]. Besides electrostatic attraction, the other forces like hydrogen bonding or hydrophobic interactions can be utilized for layer-by-layer assembly. The possibility of tailoring different functionalities, impregnating inorganic and organic substances both inside emulsion volume and in the shell, controlled release of encapsulated material provided continuous scientific and industrial interest for employing layer-by-layer approach for delivery of different compounds. This improved mechanic stability was achieved due to the differences in the thickness, electrical charge and packing of the interfacial layers surrounding the droplets. The LbL adsorption technique is widely used since early 90-s and further, the more detailed description of this approach can be found in reviews elsewhere [7,8].

The main goal of the proposed review is the demonstration of the recent achievements of the layer-by-layer assembly approach for the functionalization of the emulsions. The review surveys the LbL modification (by LbL deposition directly on the droplets of dispersed phase) of both polymer and Pickering emulsions with polyelectrolyte or nanoparticle multilayers together with the demonstration of the application examples of the modified emulsion systems. Herein, the emulsion particles play simultaneously the role of the template as well as of the container load.

2. LbL functionalization of polymer emulsions

A usual preparation method for LbL coated emulsion carriers involves several steps (Fig. 1) [9]. To stabilize the dispersed phase of initial emulsion, the oil phase (dodecane) was doped by small amount of cationic surfactant dioctadecyldimethylammonium bromide (DODAB). The colloidal stability of initial emulsion was achieved due to concentrated monolayer of strongly positively charged DODAB (z-potential was about +90 mV) at the surface of each droplet. Then, the subsequent LbL deposition was performed from concentrated (20 mg/mL) aqueous salt-free solutions of polyelectrolytes. The creamed upper layer of the strongly positively charged initial emulsion was added dropwise to 40 mL of the oppositely charged polyelectrolyte solution (poly(sodium 4-styrenesulfonate, PSS) upon continuous stirring at approximately 700 rpm. After this layer was completely brought into polyelectrolyte solution, the mixture was stirred for an additional hour to accomplish the binding of polyelectrolyte at the surfaces of the initial emulsion droplets and to ensure their overcharging. The second encapsulation step was done in an aqueous solution of positively charged polyelectrolyte (poly(diallyldimethylammonium chloride), PDADMAC or poly(allylamine hydrochloride), PAH) in the same manner (Fig. 1). The further repetition of the alternating adsorption steps leads to the formation of containers with desired shell thickness depending on the particular final demand. Centrifugation even at low rpm values cannot be considered as a reasonable alternative to accelerate the separation because of simultaneous deformation and strong coalescence of the disperse phase droplets in spite of strong electrostatic repulsion.

The further repetition of the alternating coating steps leads to the formation of capsules with desired shell thickness depending on the particular final demand. The oil core may be composed of different types of natural or artificial fats or oils like fish-oil soya-bean oil, triglycerides, hydrophobic vitamins (like vitamin B12) or drugs dissolved in oil etc. depending on the demands of the container application. Hence, the proposed approach to prepare loaded delivery systems via emulsion encapsulation can be envisaged is a general one that depends neither on the nature of the used oil nor on the specific behavior of an oil-soluble capsule load.

Biopolymers such as proteins in alternation with bioemulsifiers can be effectively used for the emulsion encapsulation as was shown on diverse food-relevant systems. The influence of the outer biopolymer layer on the electrical properties and physical stability of lipid droplets coated with biopolymers β-lactoglobulin (anionic) and chitosan (cationic) was studied by McClemens et al. [10]. The droplets, which had an outer protein coating, changed from positive to negative when the pH was increased from 3 to 7. As a result, these emulsions were unstable to droplet aggregation at intermediate pH values because of the low net charge on the droplets near the isoelectric point of the adsorbed proteins. The droplets, which had an outer chitosan coating, changed from highly positive to zero when the pH was increased from 3 to 7. These emulsions were stable to droplet aggregation from pH 3 to 6, but highly unstable at higher pH values because of the low net charge on the droplets at neutral pH. Emulsions, which had an outer alginate or pectin coating, changed from slightly negative to highly negative when the pH was increased from 3 to 7. These emulsions were unstable to droplet aggregation at pH 3 because of the low net negative charge on the droplets, but could be improved if higher anionic polysaccharide levels were used.

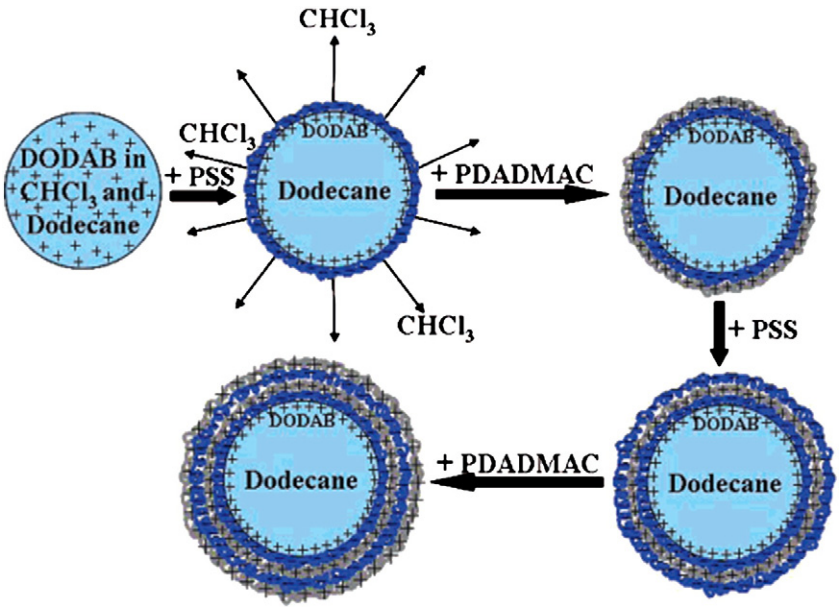

Fig. 1. Schematic representation of several steps during L-b-L polyelectrolyte emulsion encapsulation [9].