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Biocompatible long-sustained release oil-core polyelectrolyte nanocarriers: From controlling physical state and stability to biological impact

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ABSTRACT

It has been generally expected that the most applicable drug delivery system (DDS) should be biodegradable, biocompatible and with incidental adverse effects. Among many micellar aggregates and their mediated polymeric systems, polyelectrolyte oil-core nanocarriers have been found to successfully encapsulate hydrophobic drugs in order to target cells and avoid drug degradation and toxicity as well as to improve drug efficacy, its stability, and better intracellular penetration. This paper reviews recent developments in the formation of polyelectrolyte oil-core nanocarriers by subsequent multilayer adsorption at micellar structures, their imaging, physical state and stability, drug encapsulation and applications, *in vitro* release profiles and *in vitro* biological evaluation (cellular uptake and internalization, biocompatibility). We summarize the recent results concerning polyelectrolyte/surfactant interactions at interfaces, fundamental to understand the mechanisms of formation of stable polyelectrolyte layered structures on liquid cores. The fabrication of emulsion droplets stabilized by synergetic surfactant/polyelectrolyte complexes, properties, and potential applications of each type of polyelectrolyte oil-core nanocarriers, including stealth nanocapsules with pegylated shell, are discussed and evaluated.

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1. Introduction

Structured and chemically functionalized surfaces have attracted attention for many technical or medical applications as, in principle, they represent a unique opportunity to construct at all possible interfaces a variety of biomolecular self-organizing materials, e.g., surfactant-mediated systems and nanostructures, nanoparticulate functional materials or functional nanostructures [1]. It is worth noting that structural design principles, mainly such as layering, applied to liquid droplets (e.g., oil droplets), solid particles (e.g., silica), polymers (e.g., proteins) or other substances (e.g., fibers, starch, granules, biological cells or crystals), make possible to create significantly improved forms of structured materials having specific physicochemical properties such as enhanced physical and/or chemical stability and surface functionality [2,3]. Since many therapeutic substances are lipophilic, in the past decades a large effort has been devoted to the development of functionalized nanoscale oil-core carriers (e.g., micro- and nanoemulsions, colloidosome particles, polymeric nanoparticles and nanocapsules) that selectively deliver biologically active compounds to diseased sites such as malignant cancers [4–6]. Therefore, the development of innovative chemical and physical methods for the optimization of the interface properties by means of, e.g., the specific adsorption or coupling of special structures or molecular groups on the surface, is a big challenge of current research. A beautiful example of the use of spontaneously self-organized ordering and structural design approaches towards the oil core (oil-in-water (o/w) emulsion, nanoemulsion, as well as microemulsion, liposome) to produce a variety of hydrophobic drug-loaded nanocarriers is the application of template-assisted processes. Recalling, the above mentioned micellar droplets can be used in nanotechnology as templates in two fundamentally different ways [6,7]. First approach, according to the concept of morphosynthesis, focuses on the use of the interface environment as a compartmentalized reaction space for the interface polymerization of amphiphilic monomers or surfmers. The other approach, in line with the concept of transcriptive synthesis, exploits the interface between the template and the solution as a specific site for adsorption of polyelectrolytes (PE), DNA, polymers, silica from precursor solutions or nanoparticles that leads to coating formation. Thus, the templates are used as directing and structuring agents. The key issues in surfactant-based nanoproducts are the structure-performance relationships along with surfactant–precursor interactions.

The development of novel types of micro- and nanocontainers is constantly one of the main topics in the scientific research and in the last few years the major progress in the synthesis and application of various methods of template mediated synthesis of drug vehicles has been achieved [8–10]. The key functions of the above mentioned nanocarriers are (i) to successfully encapsulate hydrophobic drugs in order to target cells; (ii) to improve drug efficacy and provide for its better intracellular penetration; and (iii) to serve as shields to protect a hydrophobic therapeutic or diagnostic cargo (e.g., photosensitizers and other NIR dyes, cytostatics, quantum dots, magnetic nanoparticles, PET or MRI contrasts) from degradation and various toxic interactions with the biological environment [8–16]. Sequential adsorption of polyelectrolytes (PE) called the layer-by-layer (LbL) technique is one of the most versatile methods of formation of nanostructured functional coatings on colloidal cores [17–23]. Application of various inorganic, polymer or hydrogel micro- and nanoparticles as cores for the preparation of polyelectrolyte multilayer capsules as drug delivery vehicles has been discussed in the numerous papers and recently reviewed in Ref. [24] (and references therein). Use of emulsions droplets as liquid cores for polymer encapsulation either by surface polymerization, polymer coacervation [25] or LbL adsorption [26] gives possibility to enclose oil soluble active components in micro- or nanosize containers with functionalized shells and that opens perspectives for application in many fields such as cosmetic, medicine, pharmacy and food industry [27–32]. The main issue during formation of polyelectrolyte structures on emulsion drops is their stability. Therefore, the effective technology of oil-core nanocarrier formation is based on gaining knowledge of fundamental problem of the surfactant–polymer (polyelectrolyte) interactions. The problem of surfactant and polyelectrolyte interactions in bulk and at interfaces was studied systematically by many groups [33–36]; however, it was the group of Reinhard Miller who investigated equilibrium and dynamic adsorption properties of polyelectrolyte/surfactant mixtures at both water/air and water/oil interfaces [37]. The latter is fundamental to understand the mechanisms of stabilization of emulsion drops and formation of polyelectrolyte layered structures on liquid cores.

The presented review paper will cover, first of all, the polyelectrolyte–surfactant interactions at interfaces leading to formation of stable micro- and nanoemulsion drops that allow buildup of polyelectrolyte shells for fabrication of physically stable multilayer oil-core nanocapsules. We discuss *in vitro* release of active cargoes from the mentioned nanoproducts, cellular uptake and internalization, stability, biocompatibility and other useful physicochemical features.

2. Physical state and stability of polyelectrolyte oil-core nanocarriers

2.1. Polyelectrolyte/surfactant interactions at interfaces

Polymer/surfactant mixtures have a wide range of technological applications due to their specific behavior at different interfaces. Surfactants reduce the surface and/or interfacial tension, whereas polymers provide viscoelastic properties to interfacial layers that cannot be provided by surfactants alone. Depending on the type of both surfactant and polymers they can interact by electrostatic, hydrophobic interactions, can form hydrogen bonds, while van der Waals interactions between them are of secondary importance.

Mixtures of surfactants and polymers are very common in many industrial formulations. With many suspension and emulsion systems stabilized with surfactants, polymers are added for several reasons, e.g. as suspending agents ("thickeners") to prevent sedimentation or creaming of these systems. In many other systems, such as in personal care and cosmetics, water-soluble polymers are added to enhance the function of the system, e.g. in shampoos, hair sprays, lotions and creams. Mixtures of ionic surfactants and polyelectrolytes bearing opposite charges are specifically interesting since they properties can be tuned by easy to control parameters like ratio of their concentrations, ionic strength and pH of their solution or hydrophobicity of surfactants. Although most polyelectrolytes themselves are not surface active, their aggregation with oppositely charge surfactants may lead to mixtures with high surface activity and interesting surface rheological properties. The thorough reviews are available, where the interaction of polyelectrolyte/surfactant mixtures was discussed in terms of complex formation, competitive adsorption between surface active polyelectrolyte/surfactant complexes and polymer/surfactant aggregation in solution [33–35,38–46]. Surfactant hydrophobicity determines the surface properties of polyelectrolyte/surfactant mixtures since their surface behavior can be explained by formation of surface active complexes, which compete with aggregation in bulk [47]. The group of Penfold and Thomas [33,46] proposed the macroscopic model of the surface tension of ionic surfactant/polyelectrolyte mixtures. They discerned two types of surface tension isotherms that depend on the strength of surfactant polyelectrolyte interactions. These isotherms are illustrated in Fig. 1. The Type 1 behavior is observed for the systems where surface active polyelectrolyte/surfactant complexes adsorb very strongly at the air/water interface and can form thick layers. Surface tension of the mixture decreases due to complex adsorption until it reaches plateau value at surfactant concentration termed as CAC (critical aggregation concentration). Further addition of surfactant produces only a small decrease in the surface tension until at the surfactant concentration equal to its CMC (critical micelle concentration) is reached. In that range of concentrations polyelectrolyte mediated formation of surfactant aggregates occurs and the surfactant surface coverage may exceed the monolayer. For

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