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Historical perspective

Layer-by-Layer polyelectrolyte assemblies for encapsulation and release of active compounds

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ABSTRACT

Soft assemblies obtained following the Layer-by-Layer (LbL) approach are accounted among the most interesting systems for designing biomaterials and drug delivery platforms. This is due to the extraordinary versatility and flexibility offered by the LbL method, allowing for the fabrication of supramolecular multifunctional materials using a wide range of building blocks through different types of interactions (electrostatic, hydrogen bonds, acid-base or coordination interactions, or even covalent bonds). This provides the bases for the building of materials with different sizes, shapes, compositions and morphologies, gathering important possibilities for tuning and controlling the physico-chemical properties of the assembled materials with precision in the nanometer scale, and consequently creating important perspective for the application of these multifunctional materials as cargo systems in many areas of technological interest. This review studies different physico – chemical aspects associated with the assembly of supramolecular materials by the LbL method, paying special attention to the description of these aspects playing a central role in the application of these materials as cargo platforms for encapsulation and release of active compounds.

1. Introduction

The design and fabrication of soft nano/micro-sized assemblies for encapsulation and controlled release of active compounds has been a very active field in the past few decades. The extensive development of this field has been due mainly to its important implications in many areas of science and technology, from functional foods to pest control, and from cosmetics to drug delivery. The growing interest on the application of supramolecular functional materials in the aforementioned applications has led to a strong development of different techniques to self-assembly materials in a controlled way. The building blocks can be chosen so that they have the appropriate properties and structures to fulfill the requirements associated with the different application fields. Different methods have been developed for manufacturing materials with tunable composition, structure and dimensionality, among which the Layer-by-Layer (LbL) technique is one of the most remarkable due to its extraordinary simplicity and versatility [1].

The LbL method was firstly introduced by Iler [2] more than 50 year ago, and then revisited by Decher et al. [3,4] in the earliest 90s of the past century. The LbL method initially consisted on the alternate deposition of oppositely charged materials, mainly polyelectrolytes, onto flat macroscopic solid charged substrate through electrostatic interactions [3]. Therefore, the LbL method can be considered as a template assisted methodology, which needs a precursor structure, sacrificial or not, to build the final supramolecular material. Beyond the use of macroscopic flat solid substrates, other types of substrates with multiple chemical natures, shapes and sizes are frequently used as templates, including colloidal particles [5], liposomes or vesicles [6], and fluid interfaces [7]. In addition to the classical LbL assembly mediated through electrostatic interactions, it is also possible to build materials by the LbL method taking advantage of other types of interactions, including hydrogen bonds, chemical bonds (click chemistry), host-guest interactions or acid-base reactions [8–10]. This has expanded the range of materials used as building blocks, beyond simple polyelectrolytes and currently the list of potential materials includes different chemical compounds, and nano- and micro-objects, ranging from simple molecules to carbon nanotubes or nano- or microparticles, and from synthetic polymers to different types of biomolecules (nucleic acids, proteins, peptides or lipids) [9,11–18]. The final structure of the materials built ranges from particles with onion-like structures to sponges, membranes or nanotubes [19], which offer many possibilities for the use of LbL materials as platforms for the encapsulation and

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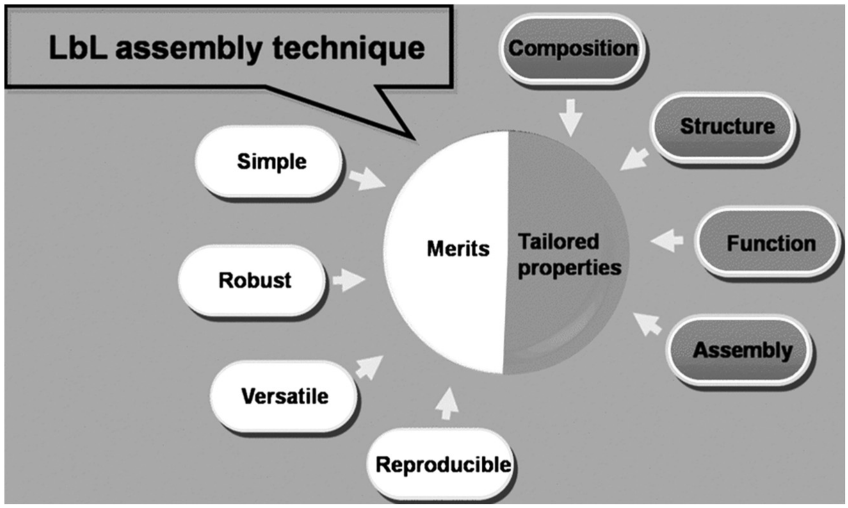

Fig. 1. Main advantages and characteristics of the LbL approach on the fabrication of functional materials.
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controlled delivery of active compounds [20,21]. Furthermore, the LbL method provides the bases to tailor the optical, electrical, mechanical and many other physico-chemical properties of the fabricated materials. This allows one to tune the delivery process using external stimuli [22]. Fig. 1 summarizes the main advantages and characteristics of the LbL method for the fabrication of functional materials. Therefore from the seminal works in this field, the fabrication of LbL materials for encapsulation and controlled release of active compounds has become a challenge in which the research efforts of different areas of the interfacial nanoengineering, e.g. chemistry, physics, materials and life sciences, have converged to provide a coordinated response to different questions raised for the progress of the modern society.

In addition to the variables above mentioned (nature of the building blocks, interactions involved, templates used), there are other many variables having an important impact on the fabrication of functional materials, (charge density of the molecules, concentration, ionic strength and type of ions, solvent quality for the molecules, pH, and temperature) [23–29]. The precise understanding of their role is essential for the fabrication of supramolecular materials with controlled and tunable structures and physico-chemical properties. The knowledge of the effect of these variables is important for determining the properties of any material. However, in the case of the LbL films, their control is even more important. This review intend to afford a complete overview of some of the most relevant physico-chemical aspects related to the building of LbL films, paying special attention to the aspects relevant for the fabrication of functional materials with applications as platform for the encapsulation and controlled release of active molecules.

2. LbL assembly methodology

The assembly methodologies used for the fabrication of LbL materials has not changed so much since the seminal works by Decher el al. [3], and only slight modifications due to the particular characteristics of the templates have been introduced. Fig. 2 illustrates the most extended protocol: the alternate dipping of flat macroscopic substrates into solutions [30], including intermediate rinsing cycles for removing the material not strongly adsorbed. This is most necessary in the case of polyelectrolytes because undesirable interpolyelectrolyte complexes can precipitate, thus modifying the composition, structure and properties of the final material [30].

Fig. 3 shows two more methods [31] for deposing LbL films onto flat macroscopic templates: spin coating and spraying. They will not be discussed in this review because they can only be used for flat substrates, that have a limited use as cargo systems [31].

Most interesting from the practical point of view for the fabrication of platforms for encapsulation and controlled release of active compounds is the use of colloidal particles, vesicles and liposomes, or micelles, as templates for the LbL deposition [5,32]. In general, the fabrication method has to be modified because the substrate is dissolved or suspended in the solvent. The simplest approach for the fabrication of capsules by the LbL method was the one introduced by Sukhorukov et al. [5,32] who coated microparticles with a multilayer of two polyelectrolytes. This can lead to the formation of both core-shell capsules and hollow capsules, in the latter case the particle act as a sacrificial template that after the adequate chemical treatment is removed. The classical approach is based on the alternate deposition of the polyelectrolytes onto the particles surface in aqueous media with intermediate cleaning and centrifugation steps in order to remove the excess of non-adsorbed polyelectrolyte, thus avoiding the formation of interpolyelectrolyte complexes in the media during the addition of the subsequent oppositely charged polyelectrolytes [33]. Once the desired number of layers is reached, the hollow capsules can be obtained by a chemical dissolution of the core using an appropriate agent that does not affect the integrity of the shell, while being able to dissolve the core. This treatment depends on the chemical nature of the template, and some classical examples used are diluted hydrochloride acid for melamine formaldehyde resin particles, fluoride acid for silicon oxide particles and tetrahydrofuran when polystyrene latex is used as template [33]. Fig. 4 shows a scheme of the most frequent protocol used for the assembly of polyelectrolyte onto colloidal templates.

The methodology described for the fabrication of LbL films onto colloidal templates is tricky due to the introduction of intermediate centrifugation cycles, which are difficult to perform when microparticles are replaced by nanoparticles. This problem can be overcome using other separation methods to separate the excess of polyelectrolyte from the dispersion of coated nanoparticles. Among these techniques, the most successful is probably serum replacement [34,35] that also allows for the preparation of concentrate dispersions of capsules. Voigt et al. [35] showed that the use of filtration-based methodologies allows speeding up the coating process in relation to conventional methods for capsule fabrication, enhancing the recovery yield. This is especially important because the preparation of highly concentrated suspensions of capsules by the LbL method is one of the main drawbacks for the industrial application. Scaling up at industrial level is an important difficulty associated with the use of the LbL method both with flat templates or colloidal particles. In the case of LbL materials onto flat templates, this limitation has been partially overcome with the devel-