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# Templated globules — applications and perspectives

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ABSTRACT

Polyelectrolyte capsules represent a class of particles composed of an internal core and an external polymer matrix shell. In recent years, it has become clear that the manufacture of polyelectrolyte capsule is likely to have a significant role in several areas including medicine and biology. Many distinct methodologies for the fabrications of templated globules have been reported. Despite the huge availability of knowledge used to obtain such globules, the choice of the appropriate technology for the desired applications demands a deeper appreciation of this issue. Furthermore, the extent to which the applications of polyelectrolyte capsule may be actively involved in the practical biomedical field is still a fascinating challenge.

Here, we review the recipes for the globule assembly with their own benefits and limitations and how different templates could affect the final globule features, with a particular focus on the Layer by Layer (LbL) procedure. The latest applications in biological, therapeutical and diagnostic areas are also discussed and some outlooks for the strategic development of polymer globule are highlighted.



**Contents**



## 1. Introduction

Material Science in the last decades is providing a number of strategies enabling the deep development of high-tech applications [1–3]. The progress induced in various fields, including the sensors and biosensors [4], synthetic chemistry [5], pharmacology [6], regenerative medicine [7] and so forth, is sufficient to have an idea of the revolution generated by the research on material engineering. The design of functional systems is achieved by the combination of different components which is a strategic approach to overcome the limitations arising from single components and meets a number of features that can enrich the various devices with several properties brought about by the *cocktail* of constituents.

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Significant advances have been made in the development of stable multicompartmental tools with well defined shape and size gaining responsive features especially in the field of Medicine and Biology. A large amount of different colloid assemblies, like liposomes [8–10], vesicles [11–14], polymer micelles [15,16] and non-polymeric micelles [17], has been and is still being studied and deeply characterized for developing drug delivery systems.

The request of new engineered delivery tools is proven by the increasing number of research teams involved in this topic and, after all, the need of manufacturing devices able to provide highly specific therapeutic treatments is hardly surprising considering that these systems are critical for saving lives around the world. The value of these multi-compartmental drug delivery devices, for instance, relies on the possibility of driving the cargos toward specific cells. Since the steering of the desired cargo depends on the administration route the selection of appropriate strategies is a crucial aspect.

Among the emerging materials the polymer capsules are drawing tremendous attention. They are considered as challenging devices because of their unique structural properties and because they offer the opportunity to design multi-component devices.

Polymer capsules are basically structures with the shape of a globule produced by coating a spherical template made of different materials, like for instance, colloidal inorganic or organic particles, latex particles and emulsion droplet, with one or more polymer layers. A system assembled in this way is a core–shell structure which can already be considered as a device for several applications [18]. In many cases the template is removed by dissolution or calcination to leave hollow polymer capsules. Hollow polymer spheres are recognized as interesting vessels to be employed as microreactors [19], catalytic systems [20], environmental defense [21], drug delivery carriers [22], and so on. Building up polymer globules offers the opportunity to choose, according to the application purpose, the most appropriate procedure and the ingredients among templates and polymers. Since the late nineties, the use of Layer by Layer (LbL) technique, which entails the alternate deposition of interacting polymers onto a surface, has been extended to the fabrication of polymer capsules by coating polystyrene (PS) latex particles with poly(dimethyldiallylammonium chloride) and silica particles [23], and from then on a huge amount of capsules has been produced with the same approach. Several templates and pairs of polyelectrolyte have been assembled in the ordered fashion provided by the LbL method [24,25]. In this context the deep chemical knowledge on polymer systems provides a significant help in this topic [26–30].

The major chance offered by LbL is the fabrication of new materials made by the complexes of polyelectrolytes which, in many cases, give different performances from those offered by the single polymers [31]. Additionally, in combination with the polymers, the templates also provide supplementary opportunities for the control of globule structures [32]. Keeping this in mind, pH responsive, temperature sensitive, light activated and engineered materials functionalized with several molecules for specific “targets” can be designed. Among the numerous applications, however, the most challenging concerns the innovation in the biomedical area for both diagnostic and therapeutical uses. In order to succeed in these fields of application, the polymer capsules should be designed with dimension in the nanometer range which makes them effective during the interaction with cells. This characteristic is consequently beckoning an intense investigation for the assembly of engineered nano-capsule [33–37]. The LbL method, in addition, is a way to assemble nano-devices with a polymer multishell functionalized with several features which represent a more effective tool compared to a combination of nanoparticles where each possesses a different feature.

This review will describe the strategies employed for the assembly of polymer globules, in particular the LbL method and the importance of the size of globules will be underpinned according to the use they are oriented to. Besides the significance of the multishell engineering the impact of the type of core material will be underlined together with the advantages and the drawbacks derived by each of them. Despite the availability of a huge number of possible types of capsules we do not intend to cover the complete area. Some meaningful applications and future development of this smart material will be discussed.

## 2. Manufacturing globules

Polymer capsules are prepared according to several procedures whose characteristics will affect the properties and the features of the assembled globules. Among the proposed procedures, the most employed are the emulsion polymerization, the flow focusing method, the internal phase separation and the Layer by Layer assembly (LbL). Here we will focus on the latter technique, whereas the general lines of the other cited methods will be briefly described. A representative illustration of the main routes of fabrication is reported in Fig. 1.

### *2.1. Emulsion polymerization*

The production of polymer capsules through the emulsion polymerization occurs at the interface of the emulsion droplets where the monomer units react to produce the polyelectrolyte generally from condensation reactions. The polymer formed at the interface will coat the surface of the droplet thus allowing the formation of a core–shell structure. The shell thickness of the globule wall will depend on the number of polymerization cycles [38]. An alternative route to the emulsion polymerization is the Pickering emulsion polymerization. According to this method the liquid–liquid interface of the emulsion is stabilized by solid particles used as polymerization vessels to fabricate hybrid polymer globules [39,40].

### *2.2. Flow focusing*

In hydrodynamic flow focusing method a double emulsion is generated, containing a single internal droplet encased in a layer of a second fluid dispersed in turn into another fluid. The second fluid, containing a polymer, through cross-linking agents or by solvent evaporation, provides the wall of a core–shell structure. The formation of the double emulsion is realized thanks to the device dedicated to the flow focusing technique which allows two or more fluids to be co-axially focused and forced through an orifice. The flow rate of the outer fluid is higher than the others and generates a pressure drop on the inner phase which is induced to break up into droplets once passed the orifice [41].

### *2.3. Internal phase separation*

The capsule formation by internal phase separation envisages an oil-in-water emulsion. The shell-forming polymer is dissolved in the oil phase made of a mixture of low-boiling and high-boiling solvents. The mixture should ensure suitable solubilization of the polymer. This solution is then dispersed into a water/stabilizer mixture to produce an oil-in-water emulsion and the volatile solvent is then gradually removed by heating. As a consequence of the composition modification of the oil dispersed phase, the polymer precipitates and migrates toward the oil/water interface where a polymer shell surrounding the oil droplet is formed [42].

### *2.4. Layer by Layer*

LbL assembly is employed to prepare a variety of materials and has attracted increasing interest as a simple and versatile approach. Typically, assembly process onto various templates is based on the ordered and alternated deposition of oppositely charged polyelectrolytes. The template material is then removed, thus generating a free-standing multilayer whose properties depend on the type of polyelectrolytes adsorbed, on the number of shells and on the template dissolution methods. In addition to the electrostatic interaction, other assembly forces such as hydrogen bonding [43], covalent bonding [44], base-pair interactions [45] and