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Cellular uptake of poly(allylamine hydrochloride) microcapsules with different deformability and its influence on cell functions

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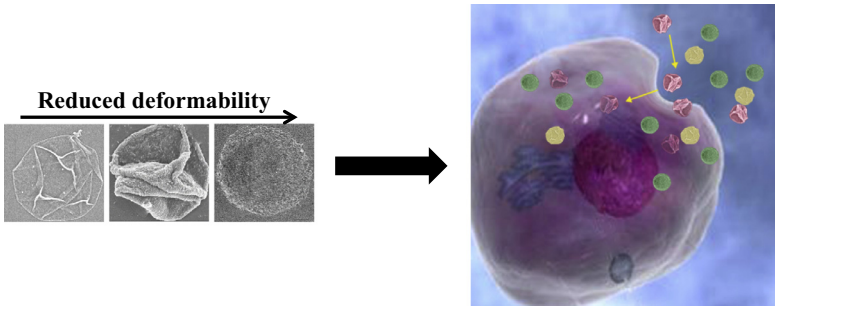
GRAPHICAL ABSTRACT

Cells showed faster uptake rate of microcapsules with lower deformability, leading to higher intracellular accumulation and subsequent higher impairment on cell functions.



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ABSTRACT

It is important to understand the safety issue and cell interaction pattern of polyelectrolyte microcapsules with different deformability before their use in biomedical applications. In this study, SiO_2, poly (sodium-p-styrenesulfonate) (PSS) doped $CaCO_3$ and porous $CaCO_3$ spheres, all about 4 μm in diameter, were used as templates to prepare microcapsules with different inner structure and subsequent deformability. As a result, three kinds of covalently assembled poly(allylaminehydrochloride)/glutaraldehyde (PAH/GA) microcapsules with similar size but different deformability under external osmotic pressure were prepared. The impact of different microcapsules on cell viability and functions are studied using smooth muscle cells (SMCs), endothelial cells (ECs) and HepG2 cells. The results demonstrated that viabilities of SMCs, ECs and HepG2 cells were not significantly influenced by either of the three kinds of microcapsules. However, the adhesion ability of SMCs and ECs as well as the mobility of SMCs, ECs and HepG2 cells were significantly impaired after treatment with microcapsules in a deformability dependent manner, especially the microcapsules with lower deformability caused higher impairment on cell functions. The cellular uptake kinetics, uptake pathways, intracellular distribution of microcapsules are further investigated in SMCs to reveal the potential mechanism. The SMCs showed faster uptake rate and exocytosis rate of microcapsules with lower deformability (Cap@$CaCO_3$/PSS and Cap@$CaCO_3$), leading to higher intracellular accumulation of microcapsules with lower deformability and possibly larger retardation of cell functions. The results pointed out that the deformability of microcapsules is an

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important factor governing the biological performance of microcapsules, which requires careful adjustment for further biomedical applications.

1. Introduction

Polyelectrolyte microcapsules, based on layer-by-layer (LbL) assembly and subsequent core removal, have been promising entities for disease diagnosis and drug delivery in recent years [1–15]. Due to the diversity of materials and tunable structure, the physiochemical properties of microcapsules can be well defined in terms of size, shape, wall composition and permeability [16–27].

During their applications in biomedical fields, the polyelectrolyte microcapsules have great chances to contact and interact with cells, the smallest units of living organisms [28]. Therefore, it would be important to understand their potential impact on cell functions which are normally generated during the internalization process. It is well known that the physiochemical properties of particles can influence the interaction between particles and cells. For example, Ai et al. demonstrated that microcapsules with positive surface tend to attach to negatively charged cell membrane through electrostatic interaction, resulting in enhanced uptake by cells [29]. Luo et al. showed that positive surface charge from microcapsules would destroy red blood cells and cause hemolysis [30]. Kreft et al. fabricated microcapsules with different shape and showed that hemispherical capsules were much easier to be uptaken by cells than spherical ones [31].

The mechanical property is another important factor of particles which plays a decisive role in cell uptake kinetics, pathways and intracellular transportation [32,33]. Based on theoretical modeling, Yi et al. suggested that cellular processing of deformable particles might be different to that of stiffer counterparts because these particles are less prone to membrane wrapping [34]. Banquy et al. found that nanoparticles with a Young's modulus between 30 and 140 kPa can be ingested by RAW 264.7 macrophages more efficiently than softer and stiffer ones [35]. However, this trend is also influenced by other parameters such as particle size and cell type. Liu et al. reported that the uptake rate of softer sub-micron size hydrogel particles (15–35 kPa) was higher than that of stiffer ones (75–160 kPa) by HepG2 cells [36]. Hartmann et al. prepared microcapsules with different modulus and encapsulated a pH-sensitive fluorescent dye. They demonstrated that the softer microcapsules entered into the lysosomes more rapidly than stiffer ones [37].

Besides cell uptake kinetics, particles' mechanical property might influence the interactions between particles and intracellular organs, and thereby influence cell viability and functions. Therefore, investigation of the intracellular fate of microcapsules with different mechanical properties and their influence on cell functions is of critical importance.

One possible method to control the deformability/mechanical property of microcapsules is to encapsulate a charged or neutral polymer inside capsules to increase the osmotic pressure from inside and thus capsule stiffness [38,39]. Another method is to control the inner structure of microcapsules using polyelectrolyte doped templates [40] or porous templates [41].

A method named glutaraldehyde (GA) mediated covalent LbL assembly has been used to fabricate single component polyelectrolyte microcapsules [42]. During this assembly process, GA can crosslink amino groups of polyelectrolytes and endow them with reactive aldehyde groups, by which another layer of polyelectrolytes can be assembled. The obtained microcapsules are stable in biological environments, i.e. in cell culture medium and inside cells, which is feasible for studying their uptake process and influences on cell functions. Herein, poly(allylaminehydrochloride) (PAH) is chosen as the single polyelectrolyte of the wall material because of its low cytotoxicity and wide application in capsule preparation.

In a current study, three kinds of templates with similar size (~4 μm in diameter) including silicon dioxide, porous calcium carbonate and poly(sodium-p-styrenesulfonate) (PSS) doped calcium carbonate are used to fabricate microcapsules with different

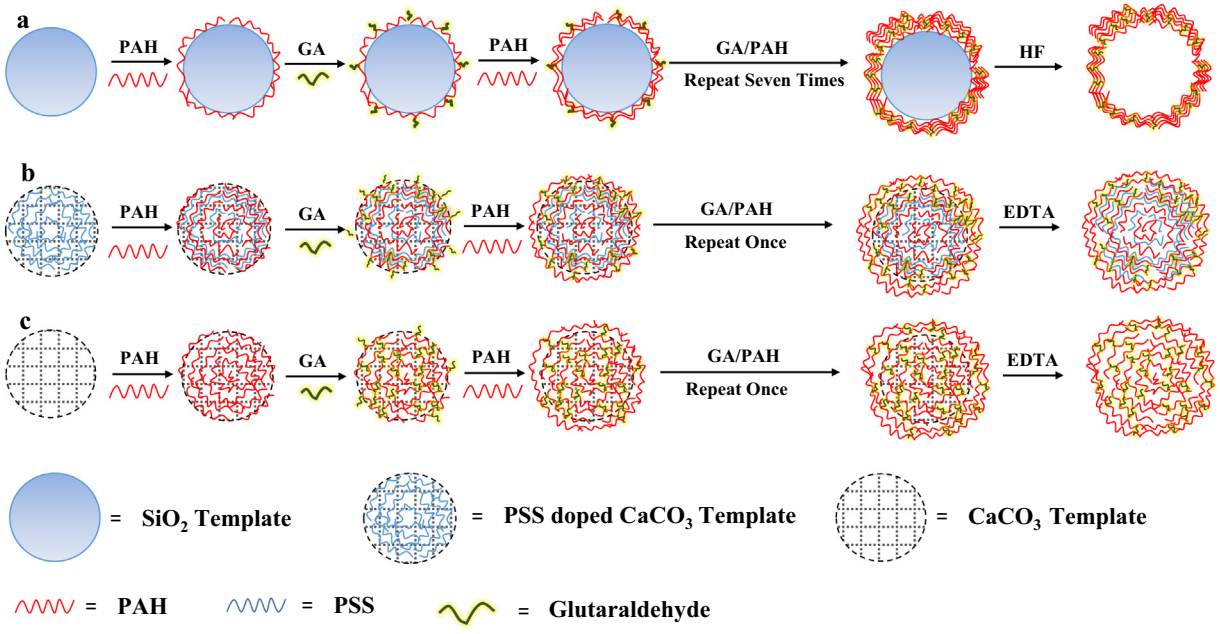

Fig. 1. Schematic illustration of the preparation of (a) $(PAH/GA)_7$/PAH microcapsules based on SiO_2 template, (b) $(PAH/GA)_2$/PAH microcapsules based on PSS/$CaCO_3$ template, and (c) $(PAH/GA)_2$/PAH microcapsules based on $CaCO_3$ template.