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Synthesis of hollow polydopamine nanoparticles using miniemulsion templating

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ABSTRACT

A soft templating method has been developed for the synthesis of hollow polydopamine nanocapsules with adjustable shell thickness. The method involves the use of an aqueous miniemulsion comprising submicron-size toluene droplets as templates. Dopamine polymerization is conducted at room temperature in the aqueous phase and/or at the droplet surfaces, thus forming hollow polydopamine nanocapsules. The core size is determined by the size of the initial toluene droplets, whereas the shell thickness can be readily tuned by adjusting the initial amount of dopamine. Nanocapsules of diameters as low as ~50 nm can be readily prepared using this novel approach. Dialysis was demonstrated to be an effective technique for removal of surfactant, hexadecane and unreacted monomer. This creative one-step method provides a new approach to the synthesis of hollow polydopamine nanocapsules, which has the potential to dramatically expand their commercial applications.

1. Introduction

Polymer nanocapsules represent an ideal universal carrier system, capable of being used in various areas including synthetic chemistry, biotechnology, cosmetics, food applications, pharmaceuticals and diagnostics. A range of substances can be loaded into polymer capsules, such as drugs, cells, as well as fluorescently, magnetically and biologically active materials [1,2]. Recently, hollow capsules have attracted increasing attention, especially in the drug delivery field [3]. A capsular system can increase drug solubility in aqueous physiological media, enhance drug stability in the physiological environment, reduce tissue damage on accidental extravasation, as well as enable drug targeting for specific cells and organs [4,5].

Inspired by the adhesive versatility of mussels, polydopamine was first investigated by Messersmith et al. [6] and has subsequently attracted significant attention in the polymer community. Polydopamine can be easily synthesized and forms thin coatings onto a wide range of surfaces including metal oxides, semiconductors, ceramics and other polymers *via* oxidative self-polymerization. As illustrated in Scheme 1, the mechanism of dopamine polymerization is similar to the formation of melanin [6]. Under slightly alkaline conditions, dopamine is oxidized and rearranges to form 5,6-dihydroxyindole, which subsequently undergoes polymerization to generate polydopamine. Polydopamine is not only capable of coating a wide range of substrate chemistries and geometries, but can also be easily modified by thiol and amine containing compounds through Michael addition and Schiff base reactions [6], thus making it an ideal coating for surface modifications. Furthermore, the cytotoxicity of polydopamine *in vitro* and *vivo* is negligible [7,8], which means that polydopamine has excellent biocompatibility features. As a result of these highly useful properties, polydopamine and its hybrid materials have been applied in various areas such as batteries [9,10], catalysis, water treatment [11,12], sensing [13–15], cell patterning [16], functional coatings [17–19] and tissue engineering [20–22]. Polydopamine has been considered an ideal material for capsules in drug delivery applications [23–25].

Templating is a commonly employed approach for the synthesis of polymeric capsules, often implemented as a layer-by-layer (LBL) technique, followed by removal of the template core [26]. The template can be a hard core material (*eg.* Ag core [27], carbon particles [28], SiO_2 [29,30], polymer particles [31] and bacteria [32]) which can be very stable and monodisperse, however removal of the core by thermal or chemical methods is complicated and energy consuming [33]. In order to circumvent this disadvantage, soft

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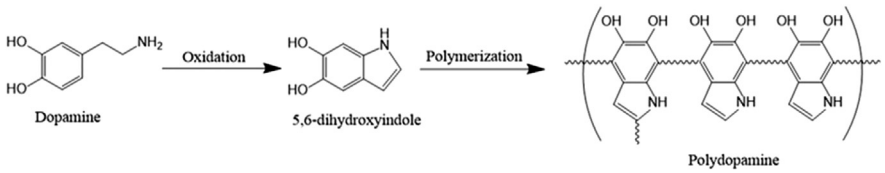

Scheme 1. Simplified reaction scheme for dopamine polymerization.

templating substances have been used by many researchers (*eg.* emulsion droplets [34], gas bubbles [35] and vesicles [36]), which can be removed under mild conditions. However, the stability and dispersity of soft template systems need to be considered as this may lead to several issues in the synthesis process [1]. For example, to obtain uniform capsules, the soft templates should be monodisperse at the reaction onset and sufficiently stable to retain their morphology during the entire polymerization. Polydopamine capsules have previously been fabricated by this method using either hard (silica [37] and polystyrene particles [38]) or soft (emulsion droplets [1]) substrates as sacrificial cores. However, these soft template approaches have resulted in polydopamine capsules with diameters greater than 100 nm. The Caruso group used dimethyldiethoxysilane (DMDES) emulsion droplets as templates to produce polydopamine capsules in the size range of 400 nm to 2.4 μm [1]. Wang et al. investigated pristine oil-in-water emulsion droplet templates to form polydopamine capsules, resulting in capsule sizes between 1.3 and 7.5 μm [39]. Recently, Ni et al. fabricated polydopamine capsules with a diameter of 200 nm and a shell thickness of 40 nm in a miscible tetrahydrofuran–buffer mixture capable of forming microscopically inhomogeneous domains acting as templates [40]. Nanoparticles with diameters below 100 nm can be employed for encapsulation of drugs for intravenous injection since they are sufficiently small to penetrate blood capillaries [4]. In a tumor microenvironment, the EPR (Enhanced Permeability and Retention) effect is also beneficial for nanoparticles to accumulate in the tumor and thus increase drug efficacy [41]. Considering the above, it appears worthwhile to develop methods for the synthesis of nanocapsules based on soft templates of nanometer size and high uniformity.

Considering the size constraint, miniemulsions [42] are the ideal soft templating systems. In general, miniemulsion polymerization is a versatile technique for the formation of a broad range of polymeric nanoparticles and structured materials [42–44]. Miniemulsions are thermodynamically unstable but kinetically stable emulsions usually generated by use of high-energy mixing (*e.g.* ultrasonication) comprising droplets typically in the diameter range of 50–300 nm. Miniemulsion formulations normally contain a conventional surfactant as well as an ultrahydrophobe (*e.g.* hexadecane), the latter to minimize droplet degradation *via* Ostwald ripening [42,43,45]. These small and sufficiently stable droplets can act as nanoreactors, whereby reactions can proceed within the droplets as in a regular miniemulsion polymerization, or on the droplet interface [46], the latter resulting in the formation of nanocapsules under suitable conditions. These properties make miniemulsion systems highly advantageous soft templates. In the research of Wu et al., miniemulsion droplets proved to be useful as a template to produce hollow silica spheres and nanocrystalline CdS hollow spheres of diameters below 100 nm [33,47].

In the present work, miniemulsion droplets have been used for the first time as soft templates for the direct coating of polydopamine to generate submicron-size polydopamine capsules. Miniemulsions of toluene droplets in water using the anionic surfactant sodium dodecyl sulfate (SDS) were generated *via* ultrasonication, and subsequently dopamine polymerization was conducted in the continuous aqueous phase to generate polydopamine shells around the toluene droplet templates. This novel approach is demonstrated to be a simple synthetic route to polydopamine capsules of adjustable diameter as low as 34 nm with potential applications in drug delivery.

2. Experimental

2.1. Materials

Toluene (RCI Labscan), dopamine hydrochloride (Sigma-Aldrich), TRIS (tris(hydroxymethyl) aminomethane) (Sigma-Aldrich), sodium dodecyl sulfate (SDS; Sigma-Aldrich) and hexadecane (HD; Sigma-Aldrich) were used as received without further purification. Distilled water was obtained from a Millipore purification system (Sartorius Arium 611VF).

2.2. Experimental procedures

2.2.1. Miniemulsion preparation

Miniemulsions were prepared using an ultrasonication process. In a typical experiment, the oil phase consisted of a mixture of 0.15 g (1.5 wt% to water) toluene with 0.024 g (16 wt% to toluene) hexadecane. The aqueous phase was made up of 0.024 g (16 wt% to toluene) SDS dissolved in 10 mL Milli-Q water. The two phases were then mixed together in a 25 mL glass vial and subsequently subjected to ultrasonication using an ultrasonic probe set to 50% amplitude for 10 min (Branson Digital Sonifier). The stability of the miniemulsion was investigated using dynamic light scattering (DLS) over a 24 h period.

2.2.2. Polydopamine nanocapsule synthesis (Method 1)

In a typical experiment, the oil phase consisted of 0.25 g (2.5 wt % to water) toluene and 0.04 g (16 wt% to toluene) hexadecane, and the aqueous phase was prepared by dissolving 0.04 g (16 wt% to toluene) SDS, 40 mg (4 mg mL^{-1}) dopamine and 24.2 mg (20 mM) TRIS in 10 mL Milli-Q water. The aqueous phase was then mixed with the oil phase and the resulting mixture was ultrasonicated for 10 min. Dopamine polymerization was conducted for 24 h at room temperature under constant magnetic stirring in an oil bath. Following this, the polymerized miniemulsion was transferred to a dialysis membrane (3500 MWCO) for dialysis against methanol for 24 h in a first step, followed by dialysis against water for another 24 h. A series of polymerizations were conducted using various dopamine concentrations (4, 6, 8, 10, 12 and 15 mg mL^{-1}) and TRIS concentrations (20, 30, 40, 50, 60 and 75 mM) (keeping the molar ratio TRIS:dopamine constant) at different toluene weight percentages against water (2.5, 5 and 10 wt% to water) (Table S1).

2.2.3. Polydopamine nanocapsule synthesis (Method 2)

According to this method, a toluene in water miniemulsion was prepared first prior to the addition of dopamine and TRIS. For a typical miniemulsion experiment by this methodology, the oil phase consisted of 0.15 g (1.5 wt% to water) toluene and 0.024 g (16 wt% to toluene) hexadecane. The aqueous phase consisted of