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Dynamic assembly of molecularly imprinted polymer nanoparticles

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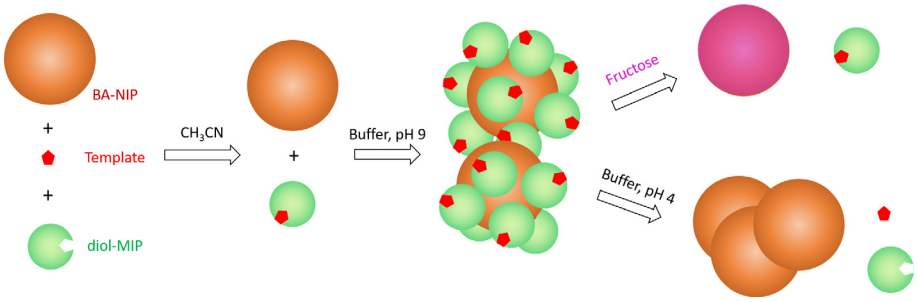
GRAPHICAL ABSTRACT



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ABSTRACT

Manipulation of specific binding and recycling of materials are two important aspects for practical applications of molecularly imprinted polymers. In this work, we developed a new approach to control the dynamic assembly of molecularly imprinted nanoparticles by surface functionalization. Molecularly imprinted polymer nanoparticles with a well-controlled core-shell structure were synthesized using precipitation polymerization. The specific binding sites were created in the core during the first step imprinting reaction. In the second polymerization step, epoxide groups were introduced into the particle shell to act as an intermediate linker to immobilize phenylboronic acids, as well as to introduce *cis*-diol structures on surface. The imprinted polymer nanoparticles modified with boronic acid and *cis*-diol structures maintained high molecular binding specificity, and the nanoparticles could be induced to form dynamic particle aggregation that responded to pH variation and chemical stimuli. The possibility of modulating molecular binding and nanoparticle assembly in a mutually independent fashion can be exploited in a number of applications where repeated use of precious nanoparticles is needed.

1. Introduction

Molecularly imprinted polymers (MIPs) are synthesized through a process of template-guided co-polymerization of functional monomers and cross-linker [1]. Removing the template after the polymerization results in specific binding sites in the cross-linked polymer. Molecular imprinting technology can be used to solve numerous application problems that can only be addressed through the use of highly selective molecular recognition materials [2,3]. MIPs have been used as synthetic antibody mimics in biomimetic sensors [1], immunoassays [4], controlled drug release [5], chromatography separations [6], analytical sample preparation based on solid phase extraction [7,8]. Among the different physical forms of MIPs, imprinted polymer nanoparticles have attracted great interests because of their ease of synthesis, fast molecular recognition kinetics, and possibility of acting as "colloidal molecules" to construct multi-functional materials through high efficiency chemical conjugation [9]. In previous studies, we have demonstrated that MIP nanoparticles can be conjugated to not only

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small molecules [10,11], but also organic and inorganic nanoparticles [12,13] to develop fast analytical separation systems and robust chemical sensors [14]. One common feature of the previous conjugation chemistry used is the high efficiency, *e.g.* the use of Cu (I)-catalyzed click reaction [12] and the perfluorophenyl azide-mediated photo-conjugation [13]. Thanks to the covalent linkage between the nanoparticle building blocks, the multi-functional nanoparticle assemblies displayed high stability and could be used repetitively after regeneration.

Compared to permanently linked particle aggregates, nanoparticle assemblies stabilized by dynamic and reversible bonds can respond to environmental stimuli, *e.g.* to separate into individual nanoparticle components, as well as to reform the original nanoparticle assembly after the initial condition is resumed. This dynamic feature is desirable when considering the versatility of nanoparticle building blocks – it allows valuable nanoparticles to be recovered from one functional system and then used in a different setting by a minimal alteration of chemical/physical stimuli.

In this work, we intended to use reversible boronate ester bond to control the dynamic assembly of molecularly imprinted polymer nanoparticles. The reason to choose boronate ester bond is based on its sensitivity to pH and different types of chemical stimuli, *e.g.* common saccharides and glycosylated biomolecules [15–22]. To demonstrate the principle, we designed propranolol-imprinted polymer core particles grafted with a shell of poly(glycidyl methacrylate). The core-shell nanoparticles were converted into *cis*-diol- and boronic acid-modified nanoparticles, which were used to investigate the dynamic behavior of the particles under different assembly and dissociation conditions. As specific molecular recognition is the most important characteristic of MIPs, an important issue is to modulate the nanoparticle assembly and the molecular binding in a mutually independent fashion. Therefore, the independent controlling of nanoparticle assembly and molecular binding/releasing was also investigated in this work.

2. Experimental section

2.1. Materials

(*R,S*)-Propranolol hydrochloride (99%) was supplied by Fluka (Dorset, UK). Methacrylic acid (MAA, 98.5%) was purchased from ACROS (Geel, Belgium). *N*-Isopropylacrylamide (NIPAm) was purchased from Monomer-Polymer Laboratories (Windham, USA). *N*, *N*′-methylene-bis-acrylamide (MBAAm) was purchased from ICN Biomedicals Inc. (Warrendale, USA). Trimethylolpropane trimethacrylate (TRIM, technical grade), glycidyl methacrylate (GMA), propargylamine, Alizarin Red S (ARS), 3-aminophenylboronic acid (APBA) hemisulfate salt, $CuSO_4$, sodium ascorbate, sodium azide and acetonitrile were purchased from Sigma-Aldrich (Dorset, UK) and used without further purification. Azobisisobutyronitrile (AIBN, 98%) was purchased from Merck (Darmstadt, Germany) and was re-crystallized from methanol before use. Ultrapure water (18.2 MΩ cm) was obtained from an ELGA LabWater System (Vivendi Water Systems Ltd).

2.2. Synthesis of 3-(prop-2-ynyloxycarbonylamino)phenylboronic acid

The experiments were carried out as described previously [23]. $NaHCO_3$ (504 mg, 6 mmol) was added to a 20 mL mixture of methanol/water (MeOH/H_2O, 1/1,) containing 3-APBA hemisulfate (372 mg, 2 mmol). The solution was cooled to 0 °C, followed by drop wise addition of propargyl chloroformate (210 μL, 2 mmol) in 15 min. The reaction mixture was stirred at <10 °C for 3 h. Next, the precipitated solid was filtered off, and the solvent in the permeated solution was removed using a rotary evaporator. The residue was dissolved in ethyl acetate (10 mL), the solution dried over anhydrous $MgSO_4$ and filtered. Finally, the solvent was removed to give the product as white solid.

2.3. Preparation of propranolol in free base form

(*R,S*)-Propranolol hydrochloride (1 g) was dissolved in 100 mL water. Na_2CO_3 (2 g) in 25 mL water was added into the propranolol solution. White precipitate formed immediately. The mixture was extracted with dichloromethane (3 × 100 mL). The organic layer was pooled and dried over anhydrous $MgSO_4$. After filtering off the inorganic salt, the solvent was removed using a rotary evaporator. The product was dried in a vacuum desiccator before use.

2.4. Synthesis of core-shell MIP nanoparticles with epoxide groups (epo-MIP)

Propranolol-imprinted core-shell particles were synthesized following a procedure described by Hajizadeh et al. [24]. Briefly, (*R,S*)-Propranolol (137 mg, 0.53 mmol), which acted as the template molecule, was dissolved in 40 mL acetonitrile in a one-neck round-bottomed flask. After adding MAA (113 mg, 1.31 mmol), TRIM (648 mg, 2.02 mmol) and AIBN (28 mg), the solution was purged with a gentle flow of nitrogen gas for 5 min and then sealed. The flask was then attached to the rotor-arm of a rotary evaporator. The polymerization was carried out at 60 °C for 24 h to give the propranolol-imprinted core particles. After this step, 0.5 mL of the core particles in suspension was collected and stored in a fridge (4 °C) for further characterization. In order to obtain the core-shell imprinted particles, NIPAm (566 mg, 5 mmol), MBAAm (77.2 mg, 0.5 mmol), GMA (355 mg, 2.5 mmol) and AIBN (24 mg) were added into the original reaction flask. The mixture was sonicated for 3 min, then purged with nitrogen gas for 5 min. The reactor was then attached to the same rotor-arm of the rotary evaporator to initiate the second step polymerization for 48 h. After polymerization, the polymer particles were collected by centrifugation at 12000 rpm (13680×*g*) for 15 min. The template was removed by washing with methanol containing 10% acetic acid (v/v), until no template could be detected from the washing solvent by using UV spectrometric measurement at 290 nm. The polymer particles were finally washed with acetone and dried in a vacuum desiccator. For comparison, non-imprinted core-shell nanoparticles (epo-NIP) were synthesized under the same conditions except that no template was added.

2.5. Synthesis of cis-diol-functionalized MIP particles (diol-MIP)

To a mixture of 40 mg of epo-MIP in 6 mL water, 2.5 mL of 0.5 M H_2SO_4 was added. The mixture was stirred at 60 °C for 24 h. After the reaction the particles were washed with water until the pH became neutral. The polymer particles were dried in a vacuum desiccator.

2.6. Synthesis of azide-functionalized MIP particles (azide-MIP)

A mixture of 150 mg of epo-MIP, 78 mg of sodium azide and 64.5 mg of ammonium chloride were prepared in 7.5 mL dimethylformamide and sonicated for a few minutes. The mixture was stirred at 60 °C for 24 h. After washing with water for 5 times, the particles were collected and dried in a vacuum desiccator.

2.7. Synthesis of boronic acid-functionalized MIP particles (BA-MIP)

Azide-MIP (25 mg) suspended in 10 mL methanol/water (MeOH/H_2O, 1/1) was mixed with 2 mL of methanol/water (MeOH/H_2O, 1/1) containing 3-(prop-2-ynyloxycarbonylamino)-p