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Research Letter

Microfluidic Approach for the Synthesis of Micro- or Nanosized Molecularly Imprinted Polymer Particles

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Molecularly imprinted polymers (MIPs) have specific molecular recognition sites for chemical detection.High affinity receptors can increase the sensitivity of sensors/devices. The synthesis of micro- or nanosized MIP's particles is desirable to improve the sensitivity since MIP's particle sizes are inversely proportional to the affinity between receptors and template molecules. To synthesize nano- or microsized MIPs particles, we demonstrate here a novel microfluidic approach, which presents continuous and uniform MIP's particle generation.

1. INTRODUCTION

Nanotechnology has enabled the fabrication of more compact and smaller devices to meet our diverse demands in miniaturization. For high performance, development of new materials and novel fabrication techniques has been actively studied in this area. Synthesis of new materials for nanoimprinting lithography, soft lithography, microfluidic technique, and plastic electronics is of interest for chemists to expand the scope of current nanotechnology to advanced levels [1–11].

There are many challenges for chemists or material scientists to develop novel materials in this area. Due to limitation on developing materials by conventional synthetic routes, we focused on the development of novel synthetic approaches to functionalize materials and thus to enhance performances of devices. For example, microfluidic synthesis has shown an attractive attention to synthesize novel materials. Microfluidic reactors offer many advantages, which can't be achieved using conventional reactors, for example, high product yields and enhanced catalytic capabilities can be achieved from microfluidic synthesis by controlling complex mixing of multiple reagents with great selectivity at the micron-scale. Excellent chemical homogeneity is also beneficial since any variation in mixing conditions across the microfluidic chamber is liable to influence the nature of products.

Microfluidic reactors have been designed then used for synthesis of both organics and inorganics. Recently several groups have reported microfluidic strategies for the synthesis of organic and inorganic materials[8–11].

For example, Beers et al has demonstrated a high-yield photopolymerization occurred in the micro-fluidic reactor by taking an advantage of its low oxygen permeability [8]. Kobayashi designed several microfluidic reactors for multiphase reactions to achieve effective interactions between the multiple components [9]. Haswell also demonstrated controls of multiple reagents reacted in microfluidic reactors to bring high yields in diverse reactions such as the Suzuki, the Wittig, and Ugi reactions[10].

In this study, we present a microfluidic synthesis of molecularly imprinted polymer (MIP). MIP system is a highly cross-linked thermoset with both high internal surface areas and molecular recognition sites. MIP materials can be provided by a molecular imprinting technique, which is a general protocol for the creation of synthetic receptor sites to detect specific organic molecules in cross-linked network polymers.

2. EXPERIMENTAL

Figure 1 illustrates the molecular imprinting technique. A functional monomer, methacrylic acid, and a template

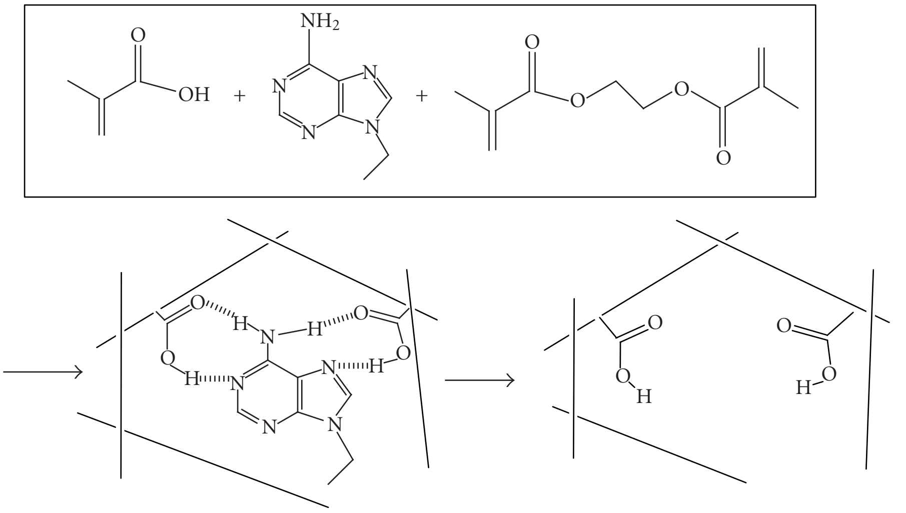


Figure 1: Synthesis of receptor sites in MIP's system.

molecule, 9-ethyl adenine, were combined to form prepolymerization complex [12]. 9-ethyl adenine(9-EA) was synthesized; a mixture of adenine (3.00 g, 22.2 mmol), K_2CO_3 (6.14 g, 44.4 mmol), and ethyl bromide (3.32 mL, 44.4 mmol) was stirred in DMF (60 mL) for 24 hours under nitrogen atmosphere. The yellow solution was filtered then concentrated in vacuo. The resulting yellow solid was purified by silica gel flash chromatography (5:95 MeOH/ $CHCl_3$) to yield 9-EA as a white crystalline solid (1.82 g, 50 % yield): mp = 190–193 °C.

Subsequently, the prepolymerization complex is copolymerized with cross-linking monomer, ethylene glycol dimethacrylate, to produce highly cross-linked imprinted polymers. 2-2-Dimethoxy-2-phenyl-acetophenone was used as a photoinitiator. Porogen was used to mix up the MIPs' monomer mixture and also to extract the template, 9-ethyl adenine, to create binding (or receptor) sites in the imprinted polymeric networks.

Molecular recognition will take place by rebinding of molecules to the imprinted receptor sites. Since MIP's particle sizes are inversely proportional to the affinity and thus are directly related to the affinity functions, we demonstrate a microfluidic approach to synthesize small MIP's particles [12].

The opportunity of employing MIP system as a molecular recognition element in sensors provides incentive challenges. The detection of organic molecules or biological entities has gotten attractive attentions for developing chemical sensors, diagnostic bio-sensors, and drug delivery systems.

Since detection is elicited by change in the physicochemical properties of the interface, the enhancement of affinity is a key contributor to achieve high sensitivities. Therefore, the production of micro- or nanosized MIPs' particles is essential to improve the sensitivity of devices or sensors. To synthesize high affinity binding sites, we demonstrated here a microfluidic approach, which produced micro- or nanosized MIP's particles.

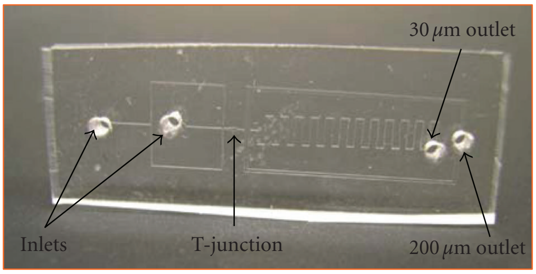
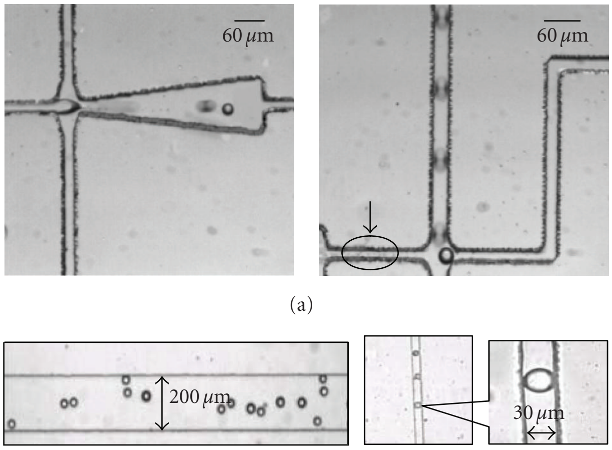


Figure 2: A microfluidic reactor fabricated onto PDMS.

A microfluidic reactor designed for the synthesis of MIPs' particles is shown in Figure 2. The inlet channels are joined at a T-junction that opens to a tapered expansion chamber that is connected in turn to a long series of 30 and 200 μm wide channel switch backs. A PDMS stamp with the microfluidic channel pattern was fabricated from a Sylgard 184 mold which in tern was produced using a master. The surface of the PDMS stamp was subjected to oxygen plasma then directly bonded to a glass slide to fabricate a microfluidic reactor. We then manipulated MIPs' droplet emulsions at controlled rates using syringe pumps used in this experiment were "Harvard apparatus", Pico Plus, a range of flow rate from 1.3 pL/min to 0.44 mL/min.

A mixture of MIPs' monomer in toluene was prepared as a reagent stream and the water phase was used as a carrier fluid to generate MIPs' droplets at the T-junction. The MIP's mixture contained methacrylic acid (0.21 g, 2.40 mmol), ethylene glycol dimethacrylate (3.41 g, 17.2 mmol), 9-ethyl adenenine (0.02 g, 0.12 mmol), and 2-2-dimethoxy-2-phenyl-acetophenone (0.033 g, 0.20 mmol) in toluene (4.5 mL). The device generated MIP's droplets at the opened T-junction, where the two immiscible phases merged by controlling flow rates; the reactor consists of two inlets (30 μm channel-width each) and two outlets with 30 and 200 μm widths.



(a)

(b)

Figure 3: (a) Video motions of droplet generations, (b) a uniformity of MIPs' droplets.

Continuous MIP's droplet generations are presented in this study. The device produced MIP's droplets, enabling precise chemical reactions in picoliters on a single chip. Droplet size is mainly controlled by the pinch junction width where two inlet channels merge; the wider T-junction results in larger droplets regardless of the reagent flow rate. The rate of droplet generation in the microfluidic reactors also depends upon the absolute flow rate between the two immiscible phases injected by using syringe pumps and the channel geometry.

3. RESULTS AND DISCUSSIONS

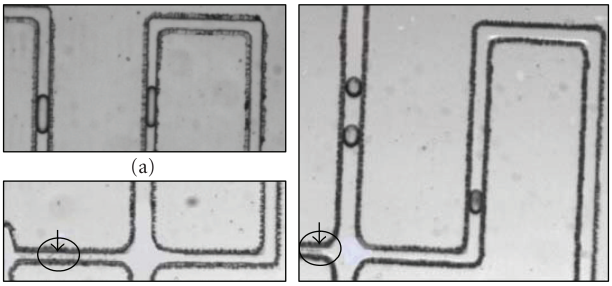
We carried out microfluidic synthesis of MIPs' particles. Figure 3(a) shows dynamic motions of MIPs' droplet generations at the T-junction; flow rates of the MIP mixture and the water phase were 1.0 μL/min and 2.5 μL/min, respectively.

Individual MIPs' droplets were generated and then traveled along the outer switchback channels. The set of images was captured at different magnifications; Figure 3(b) shows uniform MIPs' 30 μm droplets generated in the channels. Subsequently, MIP's droplets in the channels were photocured through the PDMS photomasks using an UV gun (Omnicure, power 20 W/cm^2 at 365 nm).

Figures 4(a) and 4 (b) reveal micro- and nanosized MIPs' droplets in dynamic motions, respectively, before photocuring. Droplets were then photocured. Cured MIP's particles in both of micro- and nanosizes are also shown in Figure 4(c).

Comparison of MIP's droplets before (Figures 4(a) and 4(b)) and after (Figure 4(c)photocuring reveals a significant change in refractive index, which indicates a complete polymerization.

The micro-droplet-reactor permits the controlled synthesis of nano- or micro-sized MIP's particles; those resulting MIP's particles shown in Figure 4(c) are 'Monoclonal' particles, which have 'high affinity binding sites only' to increase the sensitivity of molecular detection devices/sensors



(a)

(b) (c)

Figure 4: MIPs' droplets before (a)–(b) and after (c) photocuring.

Our goal is to carry out all operations normally performed in a chemical laboratory including synthesis, processing, purification and analysis on one microfluidic device efficiently and economically using small amounts of reagents.

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