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Synthesis of Highly Selective Spherical Caffeine Imprinted Polymers via Ultrasound-Assisted Precipitation Polymerization

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ABSTRACT: A facile and efficient method for synthesis of molecularly imprinted polymers via ultrasound-assisted precipitation polymerization was developed. Caffeine was applied as a model template in the imprinting using methacrylic acid and ethylene glycol dimethacrylate as a functional monomer and a crosslinker, respectively. Polymerization under sonochemical conditions proceeded rapidly (within 3 h at 60°C) to afford polymer microspheres with narrow size distributions in excellent yields while maintaining the binding specificity toward the template. It was found that the imprinted polymer prepared at low initial temperature (40°C) exhibited the best caffeine binding performance in terms of specificity and selectivity. © 2012 Wiley Periodicals, Inc. J. Appl. Polym. Sci. 128: 3893–3899, 2013

KEYWORDS: molecularly imprinted polymer; ultrasonic; precipitation polymerization; caffeine; molecular recognition

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INTRODUCTION

Molecularly imprinted polymers (MIPs) are highly selective polymeric sorbents which have been successfully applied in a wide-range of applications such as in chiral separation, solid-phase extraction, biomimetic sensor, and controlled release devices of several drugs.[1,2] These polymers are generally synthesized via non-covalent imprinting whereby polymerization of functional monomers and crosslinker is performed in the presence of target analyte serving as the template (print) molecule for assembly of its own recognition sites. Typically, the method requires long reaction time (24–72 h) to ensure a maximum conversion of feed monomers.[3,4] Such slow process is a bottleneck in the MIPs development where extensive optimization of feed monomers compositions is necessary to achieve successful imprinting.

Among all the polymerization methods available, precipitation polymerization is a unique way to uniformly produce microspherical MIPs free from any supplement surfactant or stabilizer.[5–7] This method relies on phase separation of growing polymer chain from the starting homogeneous polymerization mixture. Unfavorable polymer–solvent interactions cause the polymer to precipitate which in turn produce micro- or nanometer sized particles depending on the synthetic conditions.[7]

Ultrasonication technique has been widely used in polymer synthesis to enhance the reaction rate.[8] Cavitation caused by ultrasonic energy leads to the formation and collapse of small bubbles which gives rise to solubility, diffusivity, penetration, and transportation of species in the media.[9] Compared to the conventional polymerization process, ultrasound-assisted polymerization has several beneficial effects such as rate accelerations, more homogeneous chain growth, greater yields, and milder conditions (e.g., low reaction temperature).[10,11]

In the MIPs production, ultrasound has been applied at various stages of MIPs syntheses such as in facilitating template solubilization,[12] increasing the homogeneity of the prepolymerization mixture,[13,14] and assisting the removal of the template.[15] Only a limited number of literatures have been reported on ultrasound-assisted polymerization reactions and it was found that most MIPs prepared under the action of ultrasound display binding characteristics similar or superior to the thermally synthesized controls.[10,12,16]

Despite all the benefits provided by ultrasound and precipitation polymerization, a combination of both techniques has not yet been applied in the synthesis of imprinted materials. In order to develop fast and efficient method to prepare MIPs free from additive surfactant and/or stabilizer, in this study, caffeine was used as a model template in the MIPs preparation via ultrasound-assisted precipitation polymerization. The physical characteristics and binding performances of the synthesized imprinted polymers were extensively investigated in comparison

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to those of the reference polymers synthesized by the conventional thermal method.

EXPERIMENTAL

Materials

Caffeine, theophylline, theobromine, xanthine, and ethylene glycol dimethacrylate (EGDMA) were purchased from Sigma-Aldrich Co., St. Louis, Missouri, USA. Methacrylic acid (MAA) and benzoyl peroxide (BPO) were obtained from Fluka, Switzerland. BPO was recrystallized in methanol prior to use. All other chemicals were analytical grade and were used without further purification.

Apparatus

Ultrasonic bath equipped with thermostat with operating at 37 kHz (Elmasonic S 30(H), Germany) was used for polymer synthesis. UV–vis spectrophotometer (Perkin–Elmer Lamda 25, Waltham, Massachustts, USA) measurement at maximum absorption wavelength of each analyte was applied in the batch rebinding studies. Fourier transform infrared (FTIR) spectrophotometer (Bruker, TENSOR 27, Ettlingen, Germany) was used to characterize the chemical compositions of polymers. Scanning electron micrographs (SEM) were obtained on a scanning electron microscope (JEOL Co., 5910LV, Tokyo, Japan). Nitrogen adsorption experiments were carried out on Autosorb-1-MP (Quantachrome, Boynton Beach, Florida, USA).

Ultrasound-Assisted Precipitation Polymerization

In a 50-mL round bottom flask, caffeine (58 mg, 0.29 mmol) and MAA (197 μL, 2.32 mmol) were dissolved in 22 mL of acetonitrile (MeCN) and incubated for 10 min. EGDMA, (754 μL, 4.12 mmol) and BPO (118 mg, 0.49 mmol) were then added sequentially. The solution was purged with N_2 gas for 15 min. Polymerization was carried out by placing the round bottom flask at the center of ultrasonic bath filled with water and kept at specified temperature for required hours. After polymerization, the polymer microspheres were collected by centrifugation at 7000 rpm for 3 min. The template was removed by ultrasound-assisted extraction for 5 min with 10 mL methanol containing 20% acetic acid (vol/vol). The washing cycle was repeated with replacing the solvent until no caffeine can be observed by UV. Acetonitrile was then used as a washing solvent in the final wash. After extraction, the imprinted polymers were collected by centrifugation. The microspheres were oven dried at 60°C and the conversion was determined gravimetrically (% conversion is conversion of feed monomers into polymer which was determined from the ratio of dried weight of polymer and the feed amount of monomers). Non-imprinted polymers (NIPs) were prepared in parallel set up with the corresponding MIPs using the above described procedure but in the absence of caffeine.

Thermal Polymerization

The standard thermal initiated polymerization method was used to prepare the reference polymers, MIP**5** and NIP**5**.[17] The identical composition of feed monomers specified in the above described ultrasound-assisted polymerization was adopted except that the polymerization was carried out at 60°C in water bath for 24 h. NIP**5** was prepared using the same procedure as MIP**5** but without the addition of template.

Polymer Characterization

Chemical composition of all polymers was characterized by FTIR. Infrared (IR) spectra (Figure S1) were recorded in the range of 4000–400 cm^{-1} using KBr pellet. Porosity analysis was performed by N_2 adsorption experiments. A 50 mg quantity of dry polymers were used and degassed at 60°C under nitrogen flow for approximately 4 h prior to measurement. The nitrogen adsorption/desorption data were recorded for 10 h at the liquid nitrogen temperature (77 K). Surface area was determined from the Brunauer–Emmett–Teller (BET) plot. Pore volume was the average of Barrett, Joyner, and Halenda (BJH) cumulative adsorption and desorption pore volumes. Average pore diameter was calculated as 4 × BJH adsorption pore volume/surface area. Particle size and morphology of polymers were investigated using a scanning electron microscope. SEM specimens were prepared by placing a drop of diluted particle dispersions in acetone on a stub then sputter coated with gold after allowed to dry at room temperature. SEM were obtained at 15 kV. The number-average particle diameter (d_n) and coefficient of variation (C_v) were determined according to the following equations:

$$d_n\ (\text{nm}) = \sum n_i d_i / \sum n_i \tag{1}$$

$$C_v\ (\%) = (\sigma / d_n) \times 100 \tag{2}$$

$$\sigma = \left\{ \sum n_i (d_i - d_n)^2 / \sum n_i \right\}^{1/2} \tag{3}$$

where d_i and n_i are the particle diameter and the number of particles, respectively.

Equilibrium Batch Binding

The binding of caffeine to the polymers was evaluated using batch binding experiments with UV-detection. The 10 mg of each polymer was incubated in micro-tubes on a rocking table at 25°C for 16 h with 1 mL of caffeine solution (at specific concentrations) in acetonitrile. The tubes were centrifuged for 10 min at 10,000 rpm before removal of the supernatant. The equilibrium-free caffeine concentration in the clear supernatant was then determined using calibration curve determined by UV–vis spectrophotometer at the maximum absorption wavelength. The amount of caffeine bound to the polymers was calculated by subtracting the amount of the free caffeine from the initial concentration. This experiment was performed in triplicate for each MIP. The adsorption capacity (Q, μmol g^{-1}) of tested analyte and the imprinting factor (IF) were calculated according to eqs. (4) and (5), respectively.

$$Q = (C_0 - C) \times V / M \tag{4}$$

where C_0 and C are the initial and equilibrium concentration of analyte (mmol L^{-1}), V is the initial volume of solution (mL), and M is the amount of the polymer (g).

$$\text{IF} = Q_{\text{MIP}} / Q_{\text{NIP}} \tag{5}$$

where Q_{MIP} and Q_{NIP} represent the bound analyte by MIPs and NIP, respectively.

The MIP selectivity was investigated using the above described procedure with caffeine analogs. The selectivity factor (ε) was calculated according to eq. (6),

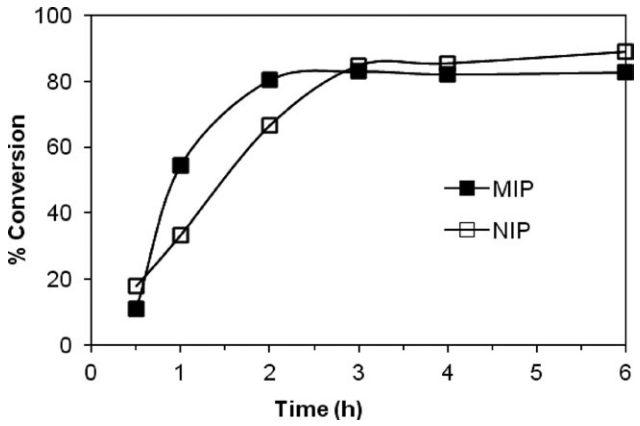


Figure 1. The time–conversion curve of ultrasound polymerization at 60°C.

$$\varepsilon = Q_{analog}/Q_{caffeine} \quad (6)$$

where Q_{analog} represents the micromole number of caffeine analogs binding on 1 g MIP and $Q_{caffeine}$ represents the micromole number of caffeine binding on 1 g MIP.

Binding Isotherms

Binding curves were obtained by incubating increasing concentrations of caffeine (0.26–2.06 m*M* in acetonitrile) with MIP or NIP (10 g L^{-1}) for 16 h. Samples were processed as the above described one-point binding studies. The binding data were fitted to Langmuir isotherms and Freundlich isotherm using GraphPad Prism version 4.0 for Windows (GraphPad Software, San Diego, California, USA). Dissociation constants, K_d, and maximum number of binding sites, *N*, were calculated using linearized form of the Langmuir isotherm which describes *Q* as a function of *C*, according to eq. (7),

$$1/Q = (1/NK_d) + (1/C) \quad (7)$$

Linearized form of the Freundlich isotherm describes the *B* as a function of *C*, according to eq. (8),

$$\log Q = m\log C + \log a \quad (8)$$

where *a* is a Freundlich parameter (related with the sorption capacity and the average affinity) and *m* is the heterogeneity index which can have a value ranging from 0 to 1 (values closer to 0 indicate increasing heterogeneity and 1 being homogeneous).

RESULTS AND DISCUSSION

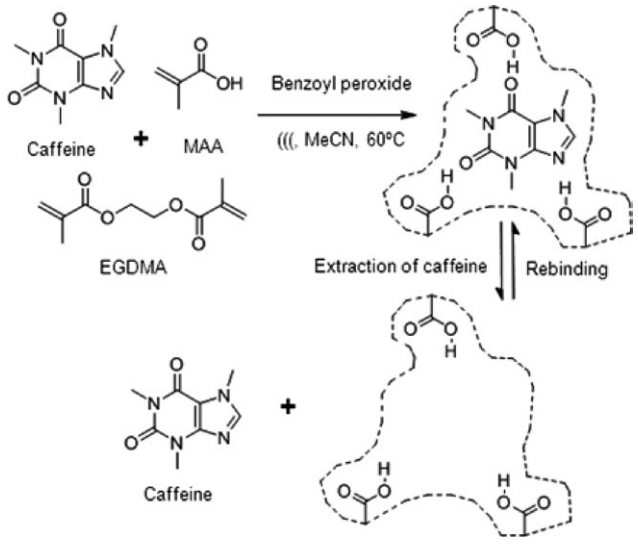
Synthesis and Characterization of Caffeine Imprinted Polymers

Caffeine imprinted polymer microspheres have previously been synthesized in acetonitrile by precipitation polymerization at 60°C for 24 h with the mole ratio of caffeine : MAA : EGDMA of 1 : 8 : 14.[17] In order to accelerate the polymerization rate and improve the efficiency of the MIP production, in this study, the above described monomer feed composition was adopted in the preparation of MIPs toward caffeine under the action of ultrasound. BPO was used as an initiator instead of 2-2′-azoisobutyronitrile due to its availability. The polymerization reactions were carried out in an ultrasonic bath (37 kHz, 320 W) equipped with thermostat.

Initially, progress of the ultrasound-assisted precipitation polymerization was investigated in the synthesis of caffeine-imprinted polymers and their corresponding non-imprinted controls (NIPs) at various reaction times. The chemical feed compositions for all polymers were identical, except that no caffeine was presented in the NIP synthesis. Both MIPs and NIPs were prepared in parallel set up at a constant temperature of 60°C. The time–conversion curve for the polymers production under ultrasonication is illustrated in Figure 1.

It was found that the ultrasonic polymerization proceeded rapidly as the polymerization solutions turned from a transparent to a turbid state within 15 min indicating the occurrence of the particle nucleation process. The rate of MIPs formation was slightly faster than that of NIPs since the conversion reaches the steady values at about 2 h for MIPs and 3 h for NIPs. In control experiments, the ultrasonic-assisted reactions did not take place at lower temperature (40°C) or in the absence of BPO even after 6 h. These results implied that the ultrasonic bath did not generate sufficient energy to initiate the radical formation and the acceleration of the reaction rate is presumably attributed to efficient mixing and degassing effects of ultrasound.

To evaluate the influence of the synthetic conditions on the physical properties and the imprinting efficiency of caffeine imprinted polymers, MIPs**1–4**, were synthesized under sonochemical conditions, whereas MIP**5** was prepared using conventional thermal method according to the reported procedure[17] for comparison. Since low polymerization temperature was commonly known to enhance the imprinting efficiency by facilitating the formation of template–monomer complex,[18] MIP**4** was synthesized with initial polymerization temperature of 40°C before increasing the temperature to 60°C. Schematic representation of the MIPs synthesis is shown in Scheme 1.



Scheme 1. Schematic representation of caffeine imprinted polymer.

Table I. Polymerization Conditions and Physical Characteristics of the Synthesized Polymers

Polymer	Method	Template	Temperature (°C)	Time (h)	d_n (μm)	C_v (%)	Surface area (m^2 g^{-1})
MIP**1**	Ultrasonication	Caffeine	60	3	0.56	13.7	28.08
NIP**1**	Ultrasonication	–	60	3	0.43	11.8	25.20
MIP**2**	Ultrasonication	Caffeine	60	4	0.40	13.8	34.04
NIP**2**	Ultrasonication	–	60	4	0.29	10.8	31.20
MIP**3**	Ultrasonication	Caffeine	60	6	0.59	11.4	22.14
NIP**3**	Ultrasonication	–	60	6	0.24	13.2	20.28
MIP**4**[a]	Ultrasonication	Caffeine	40–60	4	0.35	13.0	40.40
NIP**4**[a]	Ultrasonication	–	40–60	4	0.25	11.8	44.60
MIP**5**	Thermal	Caffeine	60	24	0.28	14.5	42.50
NIP**5**	Thermal	–	60	24	0.26	10.8	48.41

[a]The polymers were subjected to sonication at 40°C for 1 h then at 60°C for 3 h.

The polymerization conditions and the physical properties of the synthesized polymers are summarized in Table I, while their SEM images are illustrated in Figure 2. All the polymers were obtained as spherical beads having average particle diameters (d_n) in the range of 0.28–0.59 μm for MIPs and 0.24–0.43 μm for NIPs. These polymers were highly uniform with narrow size distributions as indicative from the low coefficient of variation (C_v) values (10.8–14.5%).[19] Interestingly, all the NIPs prepared either in the presence or absence of ultrasound similarly showed homogenous spherical particles with relatively smaller sizes than their corresponding MIPs. The data indicated that the polymer coagulation during the nucleation process is facilitated by the presence of caffeine through increasing ionic character of the formed imprinted particles, resulting in the formation of microspheres with higher d_n values.[20] Among all the synthesized MIPs, the thermally produced MIP**5** also appears to have the smallest size (d_n = 0.28 μm). This observation is presumably due to the slower rate of polymer formation and coagulation under the thermal conditions.

It is notable that correlation between the particle sizes of MIPs and sonication times (from 3 to 6 h at 60°C) cannot be made. Since the polymerization reactions seemingly reached completion at 3 h as indicative from the comparable %conversion of MIPs**1–3**, the differences in the polymer sizes was presumably due to the slight variation in the instrumental set up which was highly difficult to control when using ultrasonic bath as the irradiation source.

Binding Characteristics of MIPs

Batch rebinding experiment was used to investigate the imprinting efficiency of the synthesized MIPs by comparing their template rebinding performance to that of the corresponding NIPs.[21] The recognition abilities of MIPs toward caffeine were studied in acetonitrile since it was used as the porogen in the MIPs syntheses. Rebinding efficiency of all polymers was evaluated from the quantity of bound caffeine after reaching equilibrium which was represented in terms of adsorption capacity, Q, while the binding specificity of the imprinted polymers relative to their corresponding non-imprinted controls was assessed from the IF. To examine the polymer selectivity, all the imprinted polymers along with their corresponding NIPs were applied in the batch binding studies with caffeine analogs including theophylline, theobromine, and xanthine. The lower the selectivity factor (ε) for the analogs, the higher the binding preference toward caffeine.

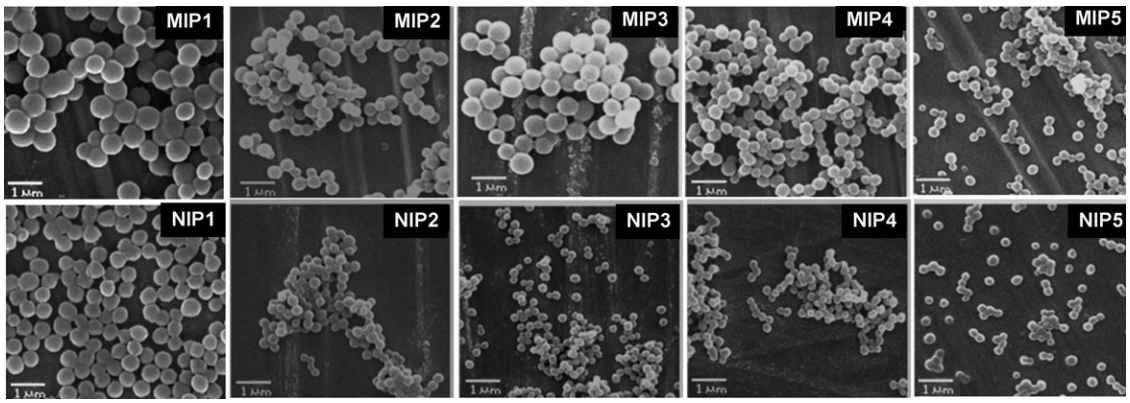
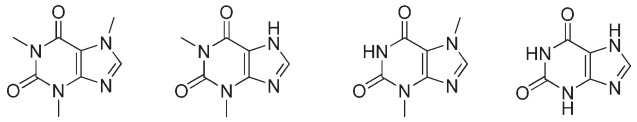


Figure 2. SEM of MIP1–5 and NIP1–5.

Table II. Binding Capacities for Binding of Caffeine and Its Analogs (1.75 m*M* in Acetonitrile) to Polymers 1–5 and the Caffeine Imprinted Factors



	Q (μmol g^{-1})				
Polymer	Caffeine	Theophylline	Theobromine[a]	Xanthine[a]	$IF_{caffeine}$
MIP**1**	14.13 ± 1.68	37.75 ± 0.96	23.61 ± 1.35	26.72 ± 0.85	3.49
NIP**1**	4.05 ± 1.13	10.05 ± 1.76	3.23 ± 0.85	7.00 ± 1.09	-
MIP**2**	27.14 ± 1.81	15.47 ± 0.36	12.95 ± 1.09	16.05 ± 1.14	3.65
NIP**2**	7.45 ± 1.12	4.42 ± 0.61	3.64 ± 0.30	5.31 ± 0.59	-
MIP**3**	17.00 ± 1.10	17.68 ± 0.86	9.17 ± 0.93	10.34 ± 0.92	4.74
NIP**3**	3.58 ± 0.56	3.05 ± 0.47	2.54 ± 0.15	3.53 ± 0.43	-
MIP**4**	21.63 ± 1.13	6.98 ± 1.33	4.03 ± 0.60	9.92 ± 1.97	6.54
NIP**4**	3.31 ± 0.60	1.90 ± 0.15	1.54 ± 0.45	2.66 ± 0.77	-
MIP**5**	17.81 ± 0.51	12.46 ± 1.34	5.32 ± 0.97	8.23 ± 1.00	3.53
NIP**5**	5.04 ± 0.54	5.41 ± 0.66	3.83 ± 0.13	4.11 ± 0.50	-

[a]40% phosphate buffer pH 9/acetonitrile was used as the media due to its insolubility in acetonitrile.

According to Table II, caffeine adsorption capacity of the imprinted polymers were in the order of MIP**2** > MIP**4** > MIP**5**> MIP**3** > MIP**1**, whereas the IF values for the caffeine binding were in the order of MIP**4** > MIP**3** > MIP**2** > MIP**5** > MIP**1**. These results indicate the binding affinity of caffeine on MIP**4** is mainly attributed to specific interactions, whereas that on MIP**2** is less specific. MIP**5** synthesized in the absence of the ultrasound exhibited lower binding efficiency than both MIP**2** and MIP**4** in terms of quantity and specificity of the interactions.

It is also noted that caffeine adsorption capacities of MIPs are irrelevant to their observed surface area since the polymers are all porous. The sorption capacities are thus depended on the polymer porosity which determines substrate accessibility, size, and shape of the binding pocket, while the arrangement of functional group in the recognition sites of the polymeric network will control the degree of specific binding interactions.

For the selectivity study (Figure 3), again MIP**4** showed the best ability to discriminate caffeine from its analogs, whereas MIP**1** and MIP**3** exhibited binding preference toward theophylline. The low initial polymerization temperature presumably facilitates the formation of template–monomer complex leading to the enhancement in the formation of specific binding sites in MIP**4**. For all the NIPs, their adsorption capacities and selectivity for caffeine analogs were relatively lower than those of MIPs indicating the binding was resulted from nonspecific interactions.

From these observations, it is apparent that the synthetic conditions not only have a significant influence on the physiochemical properties of the polymers, but also on the recognition characteristics of the otherwise identical MIPs. The imprinted polymers synthesized under the action of ultrasound exhibited better binding performances than the one prepared in the absence of ultrasound. Although the role of ultrasound is not completely clear, it is plausible that various factors provided under the action of ultrasound including aiding in the

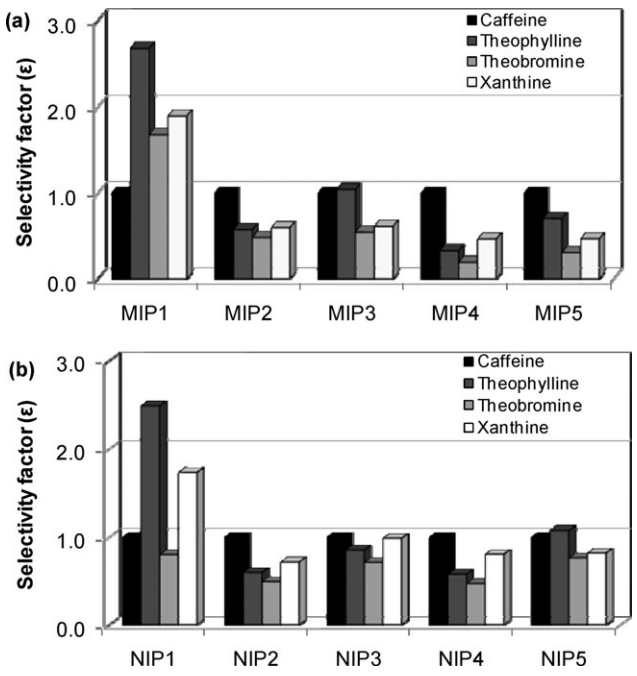


Figure 3. Selectivity factors of MIP1–5 (a) and NIP1–5 (b).

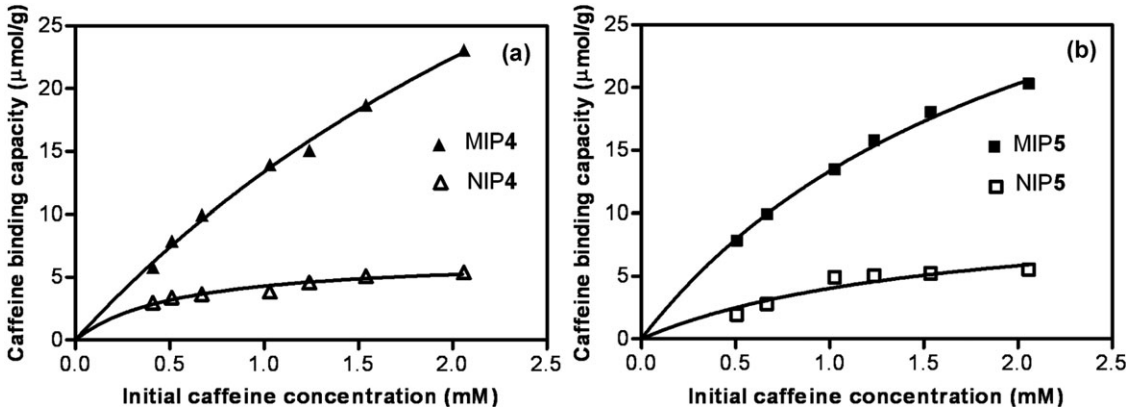


Figure 4. Binding isotherms of caffeine to polymers 4 (a) and polymers 5 (b).

Table III. Binding Parameters for MIP4 and MIP5

Polymer	Isotherm model	Parameters				Regression coefficient
		K_d (mM)	N (μmol g^{-1})	a	m	
MIP**4**	Langmuir	1.91	45.45			0.9270
	Freundlich			0.067	0.672	0.9439
MIP**5**	Langmuir	2.25	50.00			0.9951
	Freundlich			0.068	0.766	0.9893

initiation, increasing solubility of template and monomers, accelerating the reaction rate through efficient mixing, and degassing may enhance the number of specific binding sites and accessibility to the recognition regions of the polymers.

Binding Isotherm

Binding isotherm was used to further verify the imprinting effect in MIP**4** in comparison to MIP**5** (Figure 4). Both MIPs showed higher caffeine binding capacity than their corresponding NIPs over the entire concentration range. The differences in the binding capacity between the MIP and NIP isotherms were found to increase with increasing caffeine concentration.

The adsorption isotherms data for the imprinted polymers were fitted to the Langmuir and Freundlich isotherm equations[21] and the binding parameters were estimated as shown in Table III. Apparently, MIP**4** and MIP**5** showed comparable caffeine binding characteristics in terms of the maximum number of binding sites (N) and the dissociation constant (K_d). Nevertheless, the K_d value for MIP**4** was slightly lower than that of MIP**5** suggesting that MIP**4** contained higher degree of high affinity binding sites than MIP**5**. According to the Freundlich isotherm, the lower m value for MIP**4** indicated that this polymer is more heterogeneous as a result of the presence of high affinity binding sites. The higher value of m for MIP**5** suggested that this polymer is more homogeneous containing higher percentage of low affinity binding sites.[22,23] These observation is in good agreement with the results already observed in the batch rebinding experiments where MIP**4** is more specific and selective than MIP**5**.

Porosity Studies from the BET Analysis

The physical characteristic of the imprinted polymers in terms of the pore size has been used to predict the performance of the MIPs regarding the rebinding ability.[24] To gain insight in the differences in the binding properties of MIP**4** and MIP**5**, these polymers were thus selected for porosity studies by BET analysis. The total pore volumes and the average pore diameters for both imprinted polymers along with their corresponding NIPs were calculated from the N_2 adsorption/desorption experiments and are listed in Table IV.

MIP**5** and its non-imprinted control, NIP**5**, exhibited relatively large pore volumes with an average pore sizes in the upper mesoporous range, while MIP**4** and NIP**4** show smaller pore volumes with pore sizes in the lower mesoporous range. Evidently, ultrasonication seems to have a major impact on the pore volume and pore size of the polymers. Indeed, it was found that all MIPs synthesized via ultrasound-assisted polymerization contained relatively small pore size within the same range (e.g., 13.86 nm for MIP**2** and 13.45 nm for MIP**3**). Homogeneous

Table IV. Total Pore Volume and Average Pore Diameter for Polymers 4–5

Polymer	Total pore volume (mL g^{-1})	Average pore diameter (nm)
MIP**4**	0.159	16.94
NIP**4**	0.197	16.94
MIP**5**	0.447	42.12
NIP**5**	0.471	38.90

mixing and degassing effects from ultrasonication presumably produce more rigid imprinting cavities of a better defined shape that resulted in an apparent increase in specific binding sites in MIP**4**. It should be noted that caffeine imprinted polymer with an average pore diameter of 12.02 nm has also been shown to perform well in the solid-phase extraction studies.[24] For too large pore volume observed in MIP**5**, aggregation of caffeine molecules inside the same pore could lead to nonspecific binding interaction between caffeine and the imprinted polymer.

CONCLUSIONS

Ultrasound was shown to be a facile and effective means for facilitating the MIP preparation by precipitation polymerization. The polymer characteristics and the caffeine binding efficiency were directly dependent on the synthetic conditions. Although comparable caffeine sorption capacity was observed whether the imprinted materials were prepared with or without ultrasound, binding specificity, and selectivity toward caffeine was significantly enhanced in the MIP synthesized at low initial polymerization temperature. With a simple instrument set up and no additive surfactant or stabilizer, highly effective caffeine imprinted microspheres can be produced in a short period of time in excellent yield. The developed method is potentially useful in accelerating optimization process and preparation of polymer microspheres for various applications.

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