Supporting information

Development of hydrophilic magnetic molecularly imprinted polymers by directly coating onto Fe_3O_4 with a water-miscible functional monomer and application in a solid-phase extraction procedure for iridoid glycosides

Wenhua Ji [a, 1], Mingming Zhang [b, 1], Wei Liu [a], Xingmin Wang [a], Wenjuan Duan [a], Hongkai Xie [a], Xiao Wang [a, b, *]

[a] Shandong Key Laboratory of TCM Quality Control Technology, Shandong Analysis and Test Center, Shandong Academy of Sciences, 19 Keyuan Street, Jinan 250014, China

[b] School of Life Sciences, Shandong Normal University, 88 Wenhua East Road, Jinan, 250014, China

[1] These authors have equal contribution to this work. Both persons are the first authors.

Synthesis of alkenyl glycosides glucose (AGG, functional monomer)

Acetyl chloride (11.77 g, 150 mmol) was added to allyl alcohol (102.48 g, 1.76 mol) at -5 °C. After stirring for 1 h at -5 °C, D-(+)-glucose (10.00 g, 55.6 mmol) was added and the reaction mixture was stirred for 2 h at 90 °C. The mixture was quenched with $NaHCO_3$, filtered and co-concentrated with toluene. The residue was purified by column chromatography on silica gel (ethyl acetate/methanol, 8:1) to afford alkenyl glycosides glucose as a colourless solid. Yield: 3.32 g (15.1 mmol, 55 %). Rf-value: 0.34 (ethyl acetate/methanol, 8:1). ^{1}H NMR (D_2O, 400 MHz) δ 5.82-5.90 (m, 1H), 5.26 (d, 1H, J = 17.2 Hz), 5.15 (d, 1H, J = 10.4 Hz), 4.85 (d, 1H, J = 3.6 Hz), 4.09-4.15 (m, 1H), 3.93-3.98 (m, 1H), 3.71-3.81 (m, 1H), 3.61-3.66 (m, 2H), 3.44 (dd, 1H, J = 9.8 and 3.6 Hz), 3.26-3.36 (m, 1H) ppm; ^{13}C NMR (DMSO-*d*6, 100 MHz) δ 135.4, 116.8, 98.3, 73.9, 72.4, 70.8, 69.2, 67.5, 61.5 ppm; ESI-MS *m/z* (%) = 243 (100) [$M+Na^+$].

Measurement of the static water contact angles

Polymers were dispersed ultrasonically in DMF (10 mg mL^{-1}) and the films were carried out by casting the suspension solutions onto the glass surfaces. The resulting films were dried at 25 ^{o}C for 12 h after the solvent was evaporated. The static water contact angles were determined by using an OCA40 video optical contact angle equipment (Dataphysics, Germany).

Dispersion stability of polymers in pure water

The dispersion properties of polymers in pure water were studied. After their ultrasonic dispersion in pure water (1.0 mg mL^{-1}), the dispersed mixture were allowed to settle down for different times at 25 ^{o}C. Fig. 2C and Fig. S1 showed the typical photographs of the resultant solutions, from which it can be seen clearly that there was much faster sedimentation for MMIPs/DVB and R-MMIPs in comparison with MMIPs/MBA, MMIPs/EGDMA, and MMIPs/NOBE.

Selectivity study

The partition coefficient (K) is calculated as:

$$K = Q_e / C_e \quad (1)$$

For comparison of the selectivity of MMIPs, the selectivity coefficient k^{sel} and relative selectivity coefficient k^{rel} values were calculated according to the following formulas:

$$\text{selectivity coefficient: } k^{sel} = K_{GPS} / K_{interfering\ substances} \quad (2)$$

$$\text{relative selectivity coefficient: } k^{rel} = k^{sel}_{MMIPs} / k^{sel}_{NNIPs} \quad (3)$$

Table S1. Effect of the mole ratio of template: functional monomer: cross-linker [a] in imprinted process (n=3, RSD < 5%) and the contact angle of polymers.

Entry		cross-linker	Molar ratio	Q_e (mmol g^{-1})	α	contact angle
1	MMIPs-1 [b]	MBA	1:3:6	0.091	2.12	18.5±1.5
2	MNIPs-1 [b]	MBA	1:3:6	0.043		17.2±2.1
3	MMIPs-2 [b]	MBA	1:3:12	0.11	3.51	16.4±1.3
4	MNIPs-2 [b]	MBA	1:3:12	0.031		18.1±1.7
5	MMIPs-3 [b]	MBA	1:3:15	0.088	2.36	21.5±1.4
6	MNIPs-3 [b]	MBA	1:3:15	0.037		23.4±1.9
7	MMIPs-4 [b]	EGDMA	1:3:6	0.092	2.24	21.5±1.7
8	MNIPs-4 [b]	EGDMA	1:3:6	0.041		23.5±2.2
9	MMIPs-5 [b]	EGDMA	1:3:12	0.13	3.42	19.4±1.5
10	MNIPs-5 [b]	EGDMA	1:3:12	0.038		21.1±1.5
11	MMIPs-6 [b]	EGDMA	1:3:15	0.090	2.31	23.7±2.4
12	MNIPs-6 [b]	EGDMA	1:3:15	0.039		22.4±1.9
13	MMIPs-7 [b]	NOBE	1:3:6	0.085	2.50	21.5±1.7
14	MNIPs-7 [b]	NOBE	1:3:6	0.034		22.3±2.5
15	MMIPs-8 [b]	NOBE	1:3:12	0.089	3.37	22.1±1.5
16	MNIPs-8 [b]	NOBE	1:3:12	0.026		23.4±2.3
17	MMIPs-9 [b]	NOBE	1:3:15	0.082	2.16	23.7±2.4
18	MNIPs-9 [b]	NOBE	1:3:15	0.038		22.5±1.5
19	MMIPs-10 [b]	DVB	1:3:6	0.065	1.98	138.5±5.5
20	MNIPs-10 [b]	DVB	1:3:6	0.033		127.2±4.1
21	MMIPs-11 [b]	DVB	1:3:12	0.074	2.74	136.4±5.3
22	MNIPs-11 [b]	DVB	1:3:12	0.027		148.1±3.7
23	MMIPs-12 [b]	DVB	1:3:15	0.056	1.75	142.5±4.4
24	MNIPs-12 [b]	DVB	1:3:15	0.032		133.4±3.2
25	MMIPs-13 [c]	MBA	1:3:6	0.044	1.22	130.5±3.5

26	MNIPs-13 [c]	MBA	1:3:6	0.036		121.2±4.6
27	MMIPs-14 [c]	MBA	1:3:12	0.057	1.46	146.7±4.7
28	MNIPs-14 [c]	MBA	1:3:12	0.039		138.1±5.1
29	MMIPs-15 [c]	MBA	1:3:15	0.039	1.39	132.5±4.7
30	MNIPs-15 [c]	MBA	1:3:15	0.028		143.4±3.9
31	MMIPs-16 [d]	MBA	1:0:12	0.014	-	124.1±3.1
32	MMIPs-17 [d]	EGDMA	1:0:12	0.017	-	142.7±4.1
33	MMIPs-18 [d]	NOBE	1:0:12	0.021	-	135.6±3.4

[a] GPS was used as the template and the molar ratio of GPS to Fe_3O_4 was 2:1.

[b] AGG was used as the functional monomer.

[c] The reference magnetic molecularly imprinted polymers (R-MMIPs). MAA was used as the functional monomer.

[d] The blank magnetic molecularly imprinted polymers (B-MMIPs). No functional monomers were used.

Table S2. Distribution ratio (*K*), selectivity coefficient (k^{sel}) and relative selectively coefficient (k^{rel}) values of MMIPs-2 and MNIPs-2 for different analytes.

Analytes	K_{NIPs} (L/g)	$k^{sel}{}_{NIPs}$	K_{MIPs} (L/g)	$k^{sel}{}_{MIPs}$	$k^{rel}{}_{MIPs}$
GPS	0.12	-	0.94	-	-
GDS	0.12	1.00	1.20	0.78	0.78
GPA	0.13	0.92	0.75	1.25	1.36
SAM	0.12	1.00	0.75	1.25	1.25
GGB	0.14	0.86	0.59	1.59	1.85
LOG	0.13	0.92	0.70	1.34	1.46
MOS	0.16	0.75	0.84	1.12	1.49
SOL	0.14	0.86	0.54	1.74	2.02
ARB	0.18	0.67	0.24	3.91	5.84
GEP	0.20	0.60	0.28	3.24	5.40

Table S3. Distribution ratio (*K*), selectivity coefficient (k^{sel}) and relative selectively coefficient (k^{rel}) values of MMIPs-14 and MNIPs-14 for different analytes.

Analytes	K_{NIPs} (L/g)	$k^{sel}{}_{NIPs}$	K_{MIPs} (L/g)	$k^{sel}{}_{MIPs}$	$k^{rel}{}_{MIPs}$
GPS	0.16	-	0.27	-	-
GDS	0.15	1.07	0.26	1.03	0.96
GPA	0.17	0.94	0.24	1.12	1.19
SAM	0.18	0.89	0.21	1.28	1.43
GGB	0.13	1.23	0.16	1.68	1.36
LOG	0.16	1.00	0.24	1.12	1.12
MOS	0.14	1.14	0.21	1.28	1.12
SOL	0.16	1.00	0.22	1.23	1.23
ARB	0.13	1.23	0.18	1.50	1.22
GEP	0.16	1.00	0.19	1.42	1.42

Table S4. The lifetime of polymers (Q_e, mmol g^{-1}, RSD < 5.0%, n = 3).

Polymers	2[d]		4[d]		6[d]		8[d]		10[d]	
	Q_e	IF	Q_e	IF	Q_e	IF	Q_e	IF	Q_e	IF
MMIPs-2[a]	0.13		0.12		0.12		0.11		0.092	
		3.42		3.33		3.24		3.14		2.88
MNIPs-2[a]	0.038		0.036		0.037		0.035		0.032	
MMIPs-2[b]	0.12		0.12		0.11		0.11		0.094	
		3.64		3.43		3.06		3.44		3.03
MNIPs-2[b]	0.033		0.035		0.036		0.032		0.031	
MMIPs-2[c]	0.14		0.12		0.12		0.11		0.095	
		3.78		3.16		3.08		3.33		3.17
MNIPs-2[c]	0.037		0.038		0.039		0.033		0.030	

[a] Polymers were damaged at 100 °C for 12 h, then the adsorption capacity of MMIPs to GDS was investigated.

[b] Polymers were soaked with 30% hydrochloric acid for 12 h, then the adsorption capacity of MMIPs to GDS was investigated.

[c] Polymers were soaked with 20% NaOH solution for 12 h, then the adsorption capacity of MMIPs to GDS was investigated.

[d] Adsorption–desorption cycles of polymers.

Table S5. Comparison of the proposed method with reported approaches for the extraction and detection of IGs.

Analytical system	Matrix	Analytes	LOD ($\mu g\ mL^{-1}$)	Adsorbent/Extractant	References
HPLC–ESI/MS	Lonicera flower	LOG, MOS, SOL, et al	0.004–0.019	Direct injection	22
HPLC	Gentiana Fruits	Sweroside, swertiamarin, and gentiopicroside	0.12–0.52	Direct injection	23
HPLC–MS/MS	Longdan Xiegan Decoction	GPS, GGB, swertiamarin, and gentiopicroside	0.007–0.013	Direct injection	24
HPLC	Gardenia Fruits	GPS, GDS, GPA, GGB, SZM	0.17–0.39	-	25
HPTLC–MS	Gardenia Fruits	GPS, GDS, GGB	-	HPTLC silica gel	27
MMSPE–HPLC	Zhizi Jinhua Pills	GPS, GDS, GPA, GGB, SZM, LOG, MOS, SOL	0.007–0.01	MMIP	This work

Table S6. Concentration (mg/g, RSD < 4.5%, n = 3) of IGs in *ZJP* products. *ZJP* were purchased from *Tongrentang* pharmacy co., Ltd., Beijing (TRT, Batch No. 4082322 and 4093411), *Huanrun san-jiu* pharmaceutical co., Ltd., Zaozhuang (999, Batch No. 1408171 and 141108), and *Kong Shengtang* pharmaceutical co., Ltd., Zoucheng (KST, Batch No. 1509402), respectively.

Samples	GDS	GPS	GPA	SAM	GGB	LOG	MOS	SOL
TRT-4082322	2.81(1.21)[a]	7.51(3.21)[a]	0.121(0)[a]	4.21(1.01)[a]	3.87(0.81)[a]	3.35(1.32)[a]	0.102(0)[a]	3.13(1.02)[a]
TRT-4093411	2.94(1.05)[a]	7.64(2.81)[a]	0.134(0)[a]	4.43(1.12)[a]	3.65(0.89)[a]	3.24(1.25)[a]	0.112(0)[a]	3.91(1.04)[a]
999-1408171	2.92(1.13)[a]	7.44(3.01)[a]	0.153(0)[a]	4.65(1.22)[a]	3.12(0.72)[a]	3.14(1.12)[a]	0.114(0)[a]	3.22(1.13)[a]
999-141108	2.88(1.16)[a]	7.32(2.71)[a]	0.157(0)[a]	4.77(1.09)[a]	3.44(0.85)[a]	3.17(1.25)[a]	0.127(0)[a]	3.94(1.41)[a]
KST-1509402	2.84(1.01)[a]	6.91(2.26)[a]	0.187(0)[a]	3.91(1.06)[a]	3.01(0.91)[a]	3.23(1.13)[a]	0.117(0)[a]	3.71(1.21)[a]

[a] Values in parentheses are the concentration of IGs in *ZJP* products when SampliQ

C18 SPE column was used as the pre-treatment.

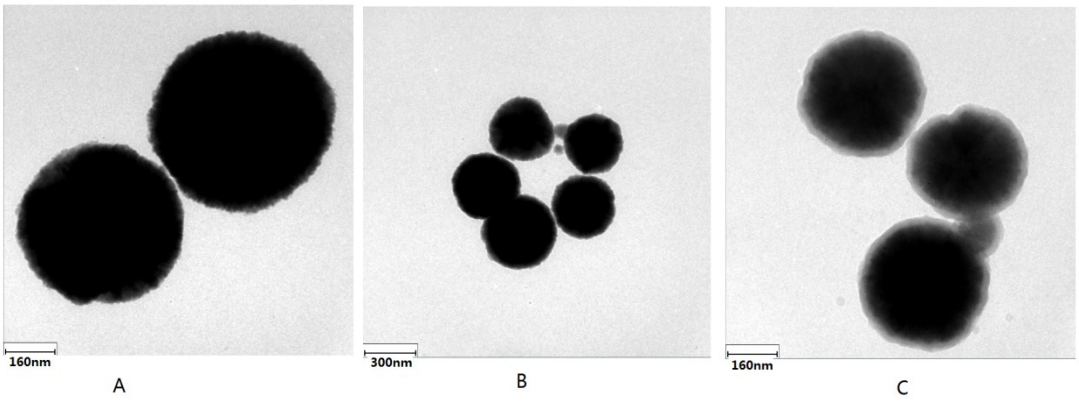

Fig. S1 The effect of the polymerization time on the shell thickness. (A) 3 h, (B) 6 h and (C) 9 h.

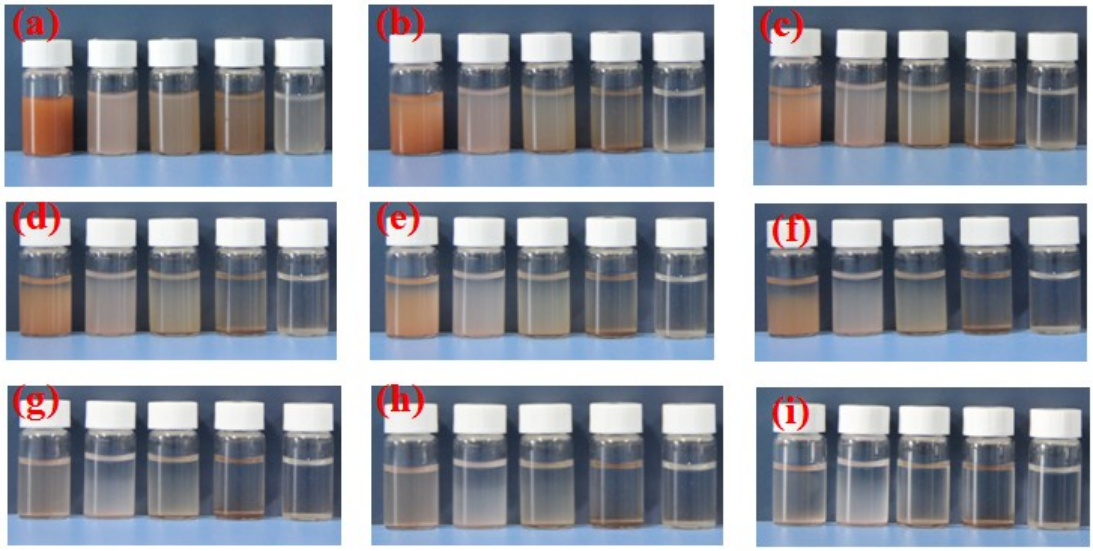

Fig. S2 The detailed photographs for the dispersion stability of polymers in water (1.0 mg mL^{-1}) at 25 ^{o}C after their ultrasonically dispersed solutions being settled down for 0 (a), 0.5 (b), 1.0 (c), 1.5 (d), 2.0 (e), 3.0 (f), 4.0 (g), 5.0 (h), and 6 h (i), respectively. The samples located from left to right in each photograph are MMIPs-2, MMIPs-5, MMIPs-8, MMIPs-11, and MMIPs-14.

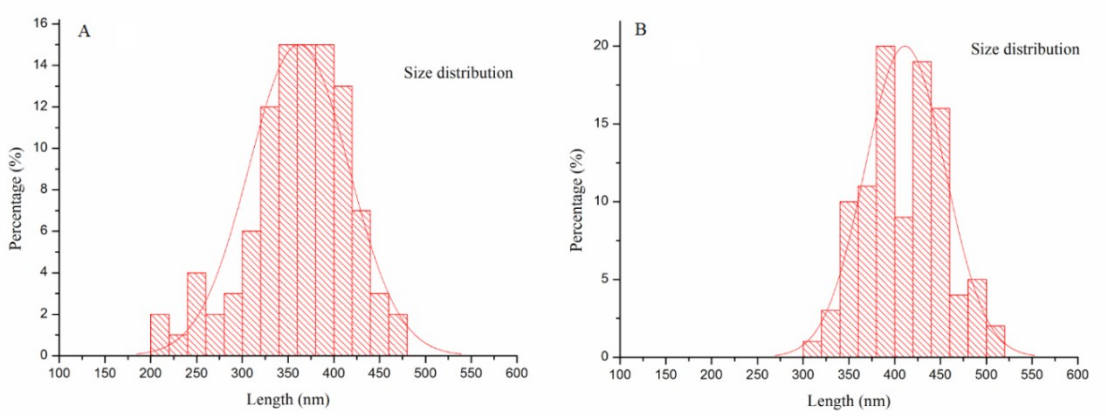

Fig. S3. Size distribution of Fe_3O_4 (A) and MMIPs-2 (B). The particle diameter dispersity of polymers was calculated from the SEM data measuring the size of, at least, 100 particles.

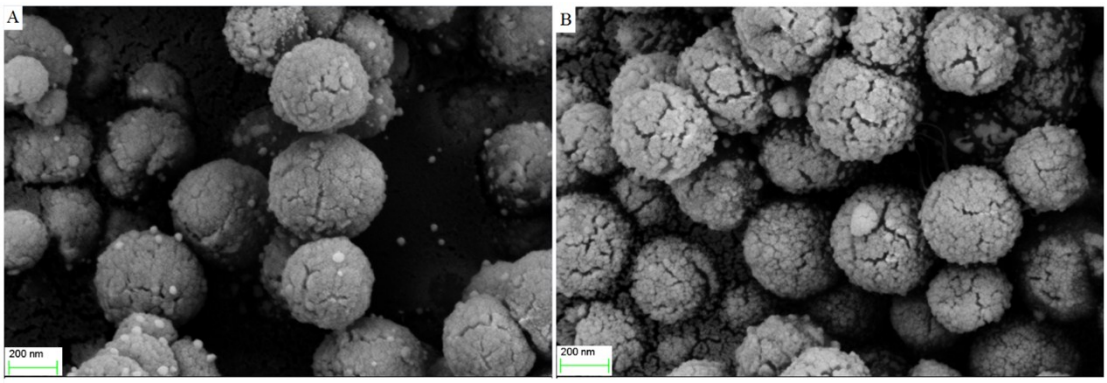

Fig. S4. SEM images of MMIPs-2 (A) and MMIPs-2 damaged at 100 ^{o}C for 12 h (B).

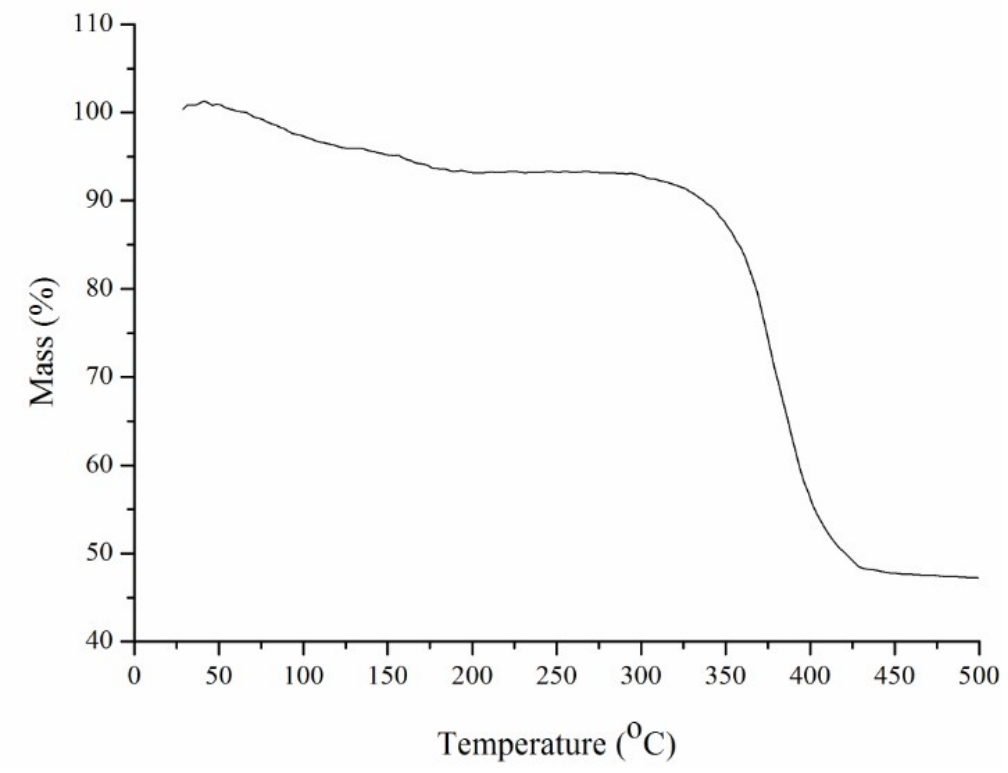

Fig. S5 The thermogravimetric analysis of MMIPs layer.

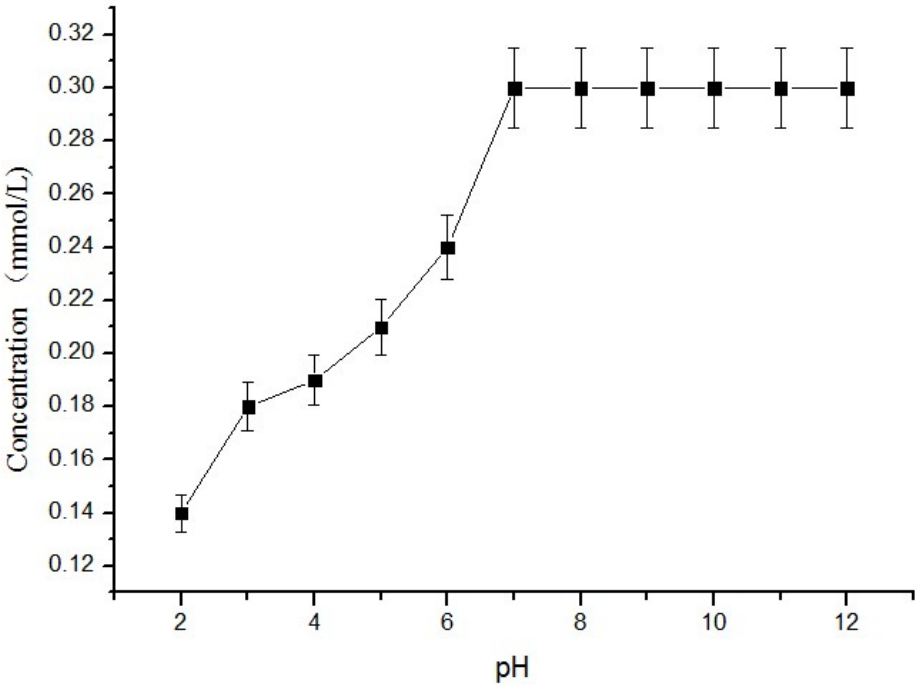

Fig. S6 Effect of pH on the stability of eight IGs without adding MMIPs. Error bars represent one standard deviation for three measurements.

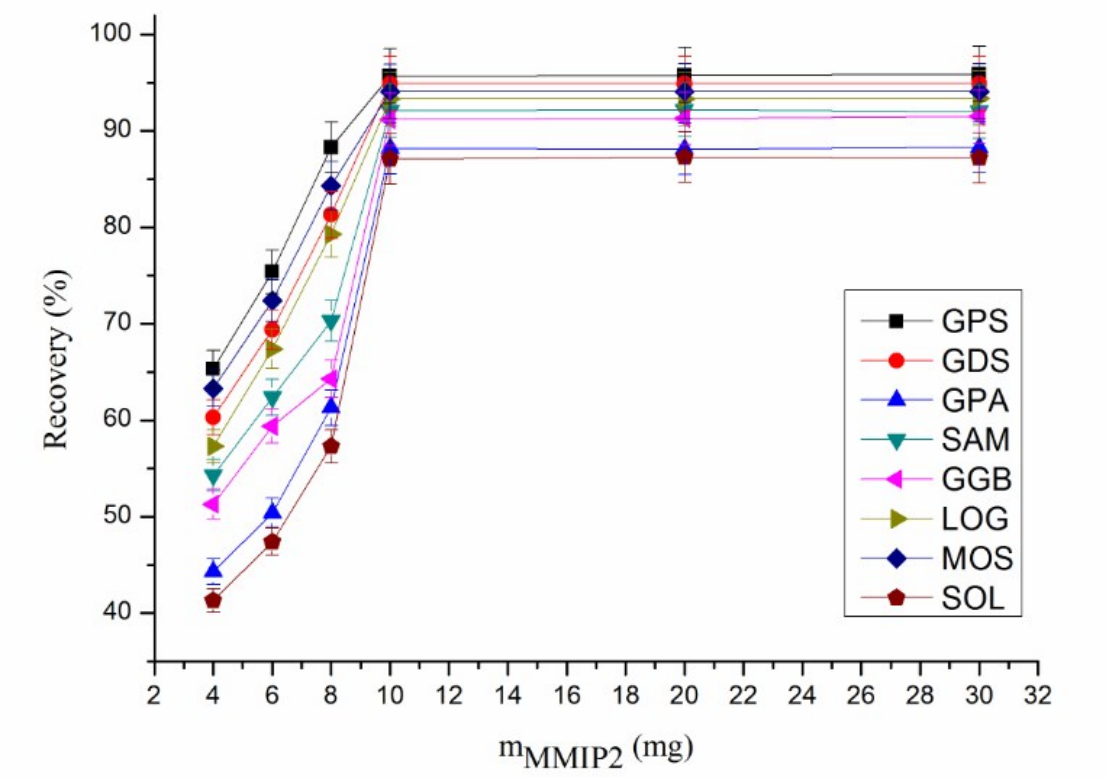

Fig. S7 Effect of MMIPs-2 usage amount on IGs recoveries. Error bars represent one standard deviation for three measurements.

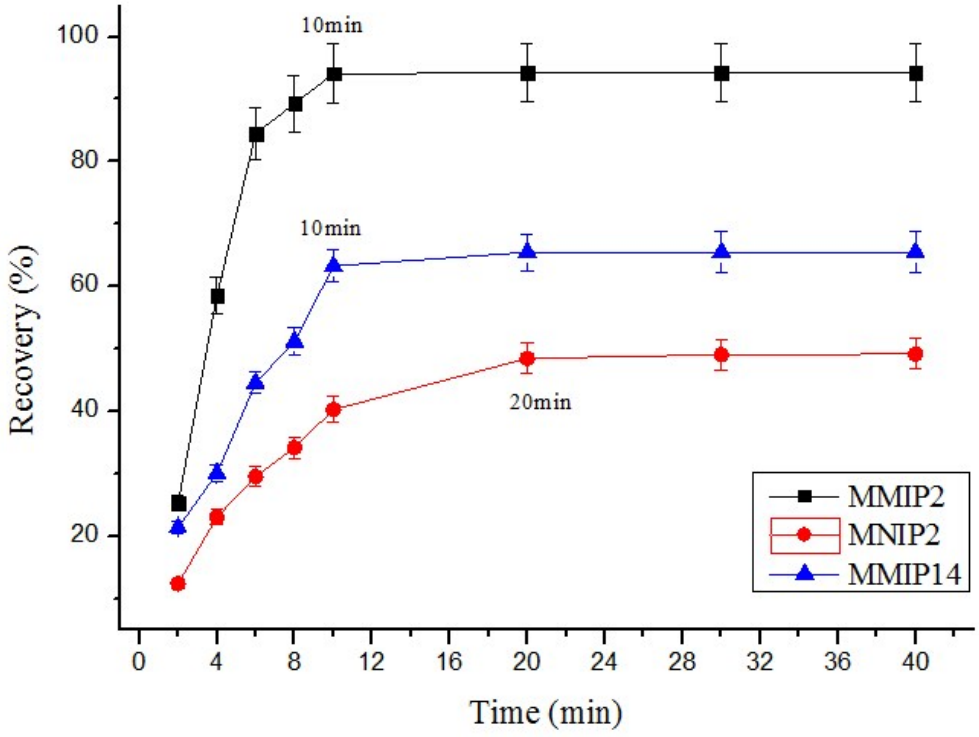

Fig. S8 Extraction time on MMIPs-2, MNIPs-2, and MMIPs-14. Error bars represent one standard deviation for three measurements.

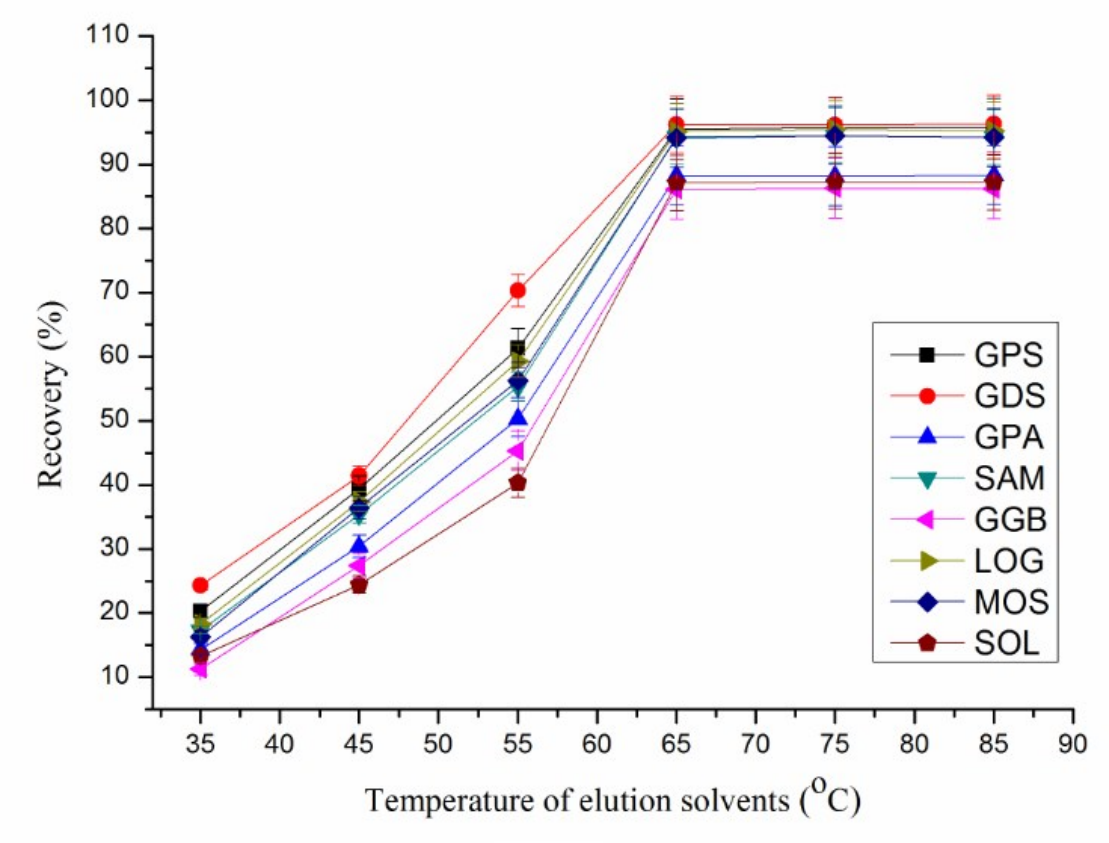

Fig. S9 Effect of different elution solvents on IGs recoveries for MMIPs-2. Error bars represent one standard deviation for three measurements.