

# Magnetic restricted-access microspheres for extraction of adrenaline, dopamine and noradrenaline from biological samples

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**Abstract** Epoxy propyl bonded magnetic microspheres were prepared by atomic layer deposition using  $\text{Fe}_3\text{O}_4@\text{SiO}_2$  microspheres as a core support material. Then, a restricted-access magnetic sorbent was prepared that contains diol groups on the external surface and m-aminophenylboronic acid groups on the internal surface. This kind of microspheres achieved excellent specific adsorption of the ortho-dihydroxy compounds (dopamine, adrenaline and noradrenaline). Following desorption with sorbitol, the ortho-dihydroxy compounds were quantified by HPLC. The limits of detection for dopamine, adrenaline and noradrenaline were 0.074, 0.053 and 0.095  $\mu\text{g mL}^{-1}$ , respectively. Recoveries from spiked mice serum samples range from 80.2 to 89.1 %.

**Keywords** Restricted-access materials · Magnetic microspheres · Boronic acid · Solid-phase extraction · Core-shell microspheres ·  $\text{Fe}_3\text{O}_4@\text{SiO}_2$  · Scanning electron microscopy

## Introduction

Analysts encounter an ongoing challenge to pursue high efficient and rapid separation techniques with the rapid development of biotechnology, biomedicine and environmental monitoring technology. Due to low concentration of analytes and unavoidable interference of complex matrices to instrumental analysis, an appropriate sample pre-treatment becomes the pivotal issue to achieving high efficiency and rapid detection in analysis [1]. Currently, solid-phase extraction (SPE) is the dominant strategy for the enrichment of small analytes from complex biological samples. However, a main problem is that biological macromolecules, such as proteins and nucleic acids, are denatured when they are adsorbed to the hydrophobic reversed stationary phase, and because of their size, they are bonded to the outer surface preferentially, blocking the access of smaller analytes, which causes serious interference with the detection [2]. Moreover, biological macromolecules and humic acids bring similar problems when using SPE to deal with environmental water.

Restricted-access materials (RAMs) have been developed to overcome the above problems [3–7]. Since first proposed by Hagestam and Pinkerton in 1985, RAMs have attracted attention because of their size exclusion effect against macromolecules and selective enrichment for small molecular analytes. Generally, they possess an interior hydrophobic or ion exchange surface for retaining small molecular compounds and an external hydrophilic and biocompatible layer serving as a physical barrier to exclude macromolecules. Due to these distinctive properties, RAMs have enormous potential for isolating and enriching trace analytes from biological samples. At present, RAMs launched on the market are divided into the following five categories: mixed-functional phase [8–10], internal surface reversed-phase (ISRP) [11, 12], shielded hydrophobic phase (SHP) [13, 14], semi-permeable surface (SPS) [15–17], protein-coated ODS

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[18]. Magnetic adsorbents have been successfully introduced into SPE in order to simplify the operation procedure, enhance the extraction efficiency and lower the cost. Via a magnetic solid-phase extraction (MSPE), trace components can be maximally enriched, and the simplification automation of operation procedure can be easily accomplished.

In this work, a restricted-access magnetic sorbent, using  $\text{Fe}_3\text{O}_4@\text{SiO}_2$  magnetic microspheres as support materials, with diol groups on the external surface and *m*-aminophenylboronic acid (*m*-APBA) groups on the internal surface was successfully synthesized. The suitable pore size keeps the proteins outside the nanopores, and the hydrophilic diol groups on the outer surface inhibit the irreversible denaturation and adsorption of proteins. Meanwhile, the *m*-APBA groups on the internal surface can specifically adsorb ortho-dihydroxy compounds. Then, bovine serum albumin (BSA) was used as the model of proteins and three kinds of catecholamine drugs as the model of ortho-dihydroxy compounds [19, 20]. The results demonstrated the high adsorption ability for ortho-dihydroxy compounds with a low protein adsorption, which showed the excellent prospects of this kind of MSPE absorbent.

## Experimental

### Reagents and apparatus

*m*-aminophenylboronic acid was purchased from Beijing Xinyuan Technology (Beijing, China).  $\gamma$ -Glycidoxypropyltrimethoxysilane was obtained from Diamond Advanced Materials (Yingcheng, Hubei, China). Urea (AR), formaldehyde (AR), ferric chloride (AR), sodium bicarbonate (AR) and concentrated nitric acid (AR) were acquired from Tianjin University COWI Company (Tianjin, China). Noradrenaline, adrenaline and dopamine were obtained from Aladdin (Shanghai, China). Silica sol (30 %  $\text{SiO}_2$ , 10–15 nm) was obtained from Guolian Chemical Co. (Jiangyin, China). Autoclave was from Xintai Chemical Equipment Factory (Weihai, China). The particle size distribution of magnetic microspheres was obtained from Coulter granulometer (Beckman Company, USA). The morphology of the materials was studied using a S-3000 scanning electron microscopy (SEM, Hitachi Corporation, Japan).

### Preparation and surface modification of $\text{Fe}_3\text{O}_4@\text{SiO}_2$ magnetic microspheres

$\text{Fe}_3\text{O}_4@\text{SiO}_2$  microspheres were prepared according to the literature [21]. In a typical preparation, hematite suspension was obtained by adding 5.1 g of  $\text{NaHCO}_3$  to 7.2 g of  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  dissolved in 50 mL of distilled water and stirring

the mixture vigorously for 10 min, yielding a reddish solution with pH  $\sim$ 2. The silica suspension was prepared separately by adding dropwise concentrated  $\text{HNO}_3$  to 100 mL of silica sol until a pH 2 was reached. The hematite and silica suspensions thus obtained were then mixed under vigorous stirring. To the suspension was added 3.0 g of urea and 4.0 mL of formaldehyde (37 %) under stirring, and the mixture was allowed to stand at ambient temperature overnight. The resulting composites were washed, dried and reduced, then the obtained  $\text{Fe}_3\text{O}_4@\text{SiO}_2$  microspheres (5.0 g) were placed into a crucible, after which the crucible was placed into the autoclave. 3.0 mL of  $\gamma$ -glycidoxypropyltrimethoxysilane and 1.0 mL of triethylamine were added into the autoclave. The autoclave was sealed and vacuumed. The reaction was performed at 120 °C for 4 h. Then the epoxy propyl bonded magnetic microspheres (epoxy propyl MM) were successfully prepared via atomic layer deposition (ALD) [22, 23].

Epoxy propyl MM (1.0 g) reacted with sulfonated polymer microspheres (1.0 g, 50  $\mu\text{m}$ ) in deionized water (50 mL) at 65 °C for 48 h under the shaking table. The resulting products were rinsed with deionized water and then centrifuged with chloroform (50 mL), after which sulfonated polymer microspheres floated on the chloroform, whereas the magnetic microspheres with diol groups on the external surface and epoxy propyl on the internal surface (epoxy propyl/diol MM) were deposited to the bottom of the centrifuge tube due to the difference of density.

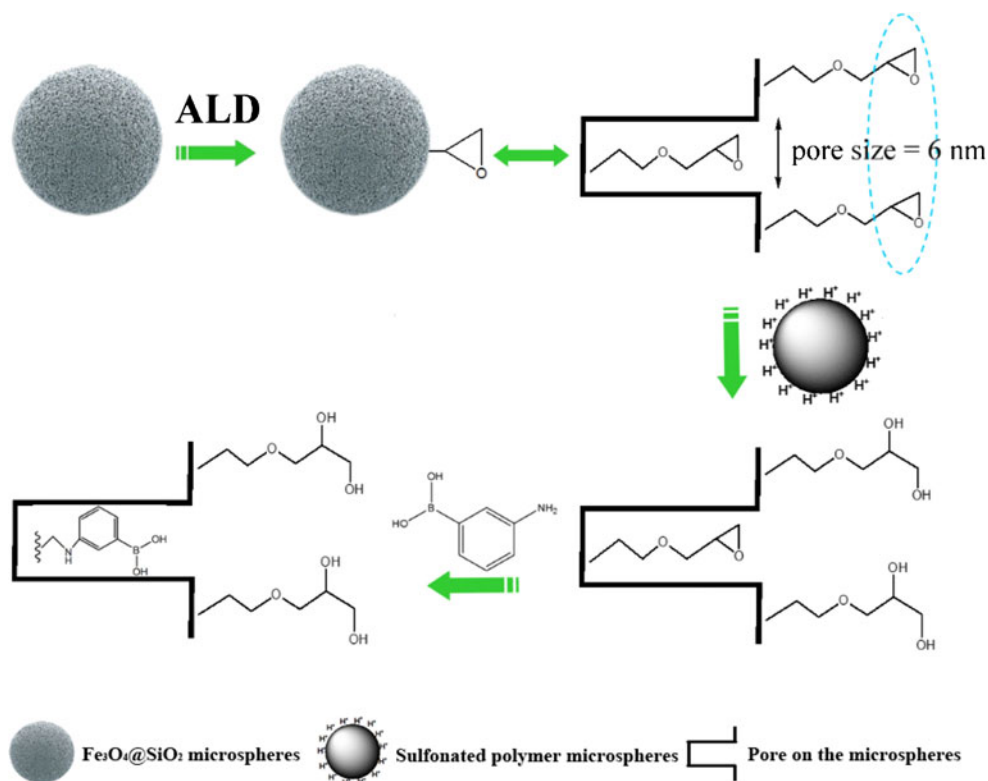
Epoxy propyl/diol MM (1.0 g) was mixed with *m*-APBA (0.4 g) in deionized water. The mixture was subjected to ultrasonic vibration and then adjusted to pH 8.5 using NaOH solution. The reaction was performed for 24 h under the ambient temperature. As shown in Fig. 1, the magnetic microspheres with diol groups on the external surface and *m*-APBA groups on the internal surface (*m*-APBA/diol MM) were obtained after washing and drying. The preparation of magnetic microspheres bonded *m*-APBA groups on both surface (*m*-APBA MM) were similar to the above procedures, except that the epoxy propyl/diol MM was changed to epoxy propyl MM.

Epoxy propyl MM (1.0 g) was weighed into the three-necked bottle, followed by addition of hydrochloric acid solution (50 mL, pH = 3). The mixture was reacted at 90 °C for 2 h and then rinsed with deionized water and methanol sequentially. After drying at 60 °C in vacuum for 12 h, the magnetic microspheres bonded diol groups on both surfaces (diol MM) were prepared successfully.

### Characterization and applications

In order to systematically study the properties of this restricted-access magnetic sorbent, two kinds of magnetic microspheres (diol MM and *m*-APBA MM) were used as control. Then the restricted-access properties for the proteins of

**Fig. 1** Preparation process of the magnetic restricted-access microspheres



these three kinds of magnetic microspheres and the specific adsorption properties for the compounds containing ortho-dihydroxy structure were compared, respectively.

Each kind of magnetic microspheres (5 mg) was weighed and placed into five Eppendorf tubes, respectively. Then the bovine serum albumin (BSA) solution (1 mL) with five different concentrations was added into each tube. The mixture was vibrated and magnetically separated. Then the supernatant was stained by Coomassie brilliant blue, after which the absorbance value was detected at 595 nm via UV spectrophotometer.

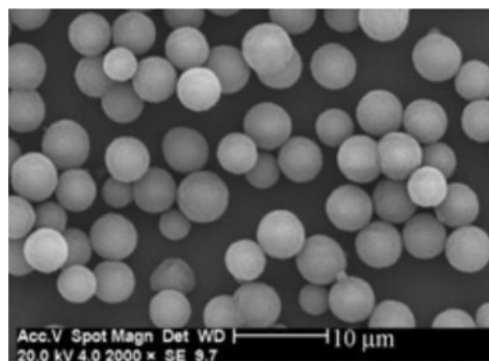
Each kind of magnetic microspheres (5 mg) was weighed and placed into Eppendorf tubes, respectively. Then the dopamine solution (1 mL) with eight different concentrations was added into each tube. The mixture was vibrated and magnetically separated. The supernatant was detected at 280 nm via UV spectrophotometer.

Three kinds of catecholamine drugs (dopamine, adrenaline, noradrenaline) were used as the model of ortho-dihydroxy compounds. Four kinds of magnetic microspheres (epoxy propyl MM, diol MM, m-APBA MM, and m-APBA/diol MM, 5 mg) were weighed separately and placed into Eppendorf tubes, followed by addition of catecholamine drug solution (0.70 mL,  $10 \mu\text{g}\cdot\text{mL}^{-1}$ , respectively), mice serum (0.2 mL) and acetonitrile (0.10 mL) sequentially. The mixture was rinsed with methanol and then eluted with sorbitol solution ( $0.20 \text{ mol}\cdot\text{L}^{-1}$ ). Then, the recovery of ortho-dihydroxy compounds to magnetic microspheres was determined by HPLC.

## Results and discussion

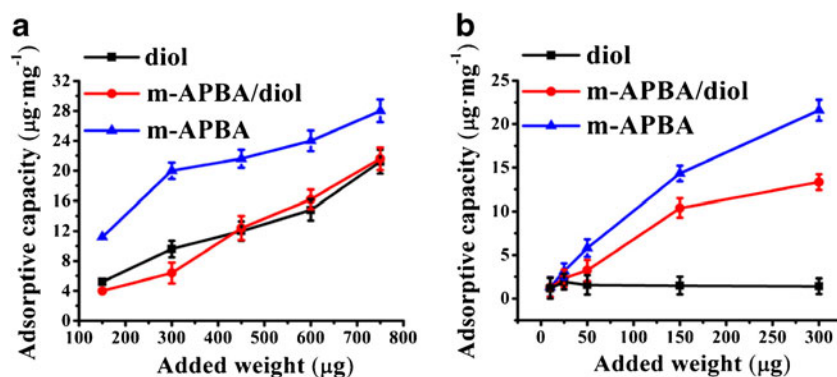
### The morphology of magnetic microspheres

The resulting materials were employed to study the morphology feature by SEM. As shown in Fig. 2, the magnetic microspheres were regular spheres. The particle size distribution of magnetic microspheres was obtained from Coulter granulometer and the diameters of equivalent spherical microspheres corresponding to cumulative volumes of 10 ( $d_{10}$ ), 50 ( $d_{50}$ ) and 90% ( $d_{90}$ ) of the total solid volume are, respectively, 3.8, 4.5 and 5.9  $\mu\text{m}$ . This method had been reported previously, and other typical data were as follows: specific surface area  $250 \text{ m}^2\cdot\text{g}^{-1}$ , saturation magnetization  $10 \text{ emu}\cdot\text{g}^{-1}$  [21].



**Fig. 2** SEM of magnetic microspheres

**Fig. 3** Adsorption of BSA (a) and dopamine (b)



### Evaluation of the adsorption capacity of proteins

Using BSA as the model of proteins, the adsorption properties to proteins of these three kinds of magnetic microspheres (m-APBA MM, m-APBA/diol MM, and diol MM) were investigated, respectively. As shown in Fig. 3a, the adsorption behavior of m-APBA/diol MM to proteins was similar to diol MM, which showed that this restricted-access magnetic sorbent had a certain restricted-access property. Nevertheless, there was a certain amount adsorption of BSA, which might be because the ring-opening reaction of epoxy propyl on the external surface was difficult to complete.

### Evaluation of adsorption properties of Ortho-dihydroxy compounds

As shown in Fig. 4, the boronic acid was specifically binding with the compounds containing ortho-dihydroxy or 1,3-dihydroxy structure under alkaline conditions, whereas also easily eluted under acidic conditions.

Using dopamine as the model of ortho-dihydroxy compounds, the adsorption properties of these three kinds of magnetic microspheres (m-APBA MM, m-APBA/diol MM, and diol MM) to ortho-dihydroxy compounds were investigated, respectively. As shown in Fig. 3b, diol MM almost had no absorption of dopamine, whereas the specific adsorption properties of m-APBA/diol MM to dopamine were similar to m-APBA MM, which demonstrated that m-APBA had been successfully bonded on the inner surface. We measured that the amount of propyl epoxy groups on the surface of epoxy propyl MM was  $1.508 \mu\text{mol}\cdot\text{m}^{-2}$ , while the amount of m-APBA

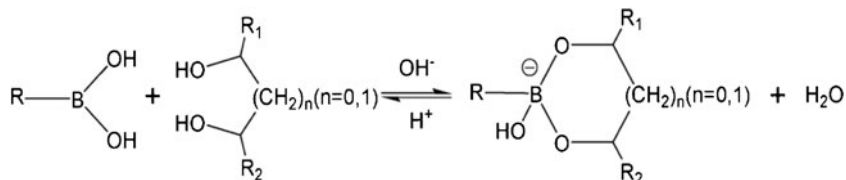
bonded on the surface of m-APBA/diol MM was  $0.858 \mu\text{mol}\cdot\text{m}^{-2}$  by titration.

### Recovery of Ortho-dihydroxy compounds in spiked biological samples

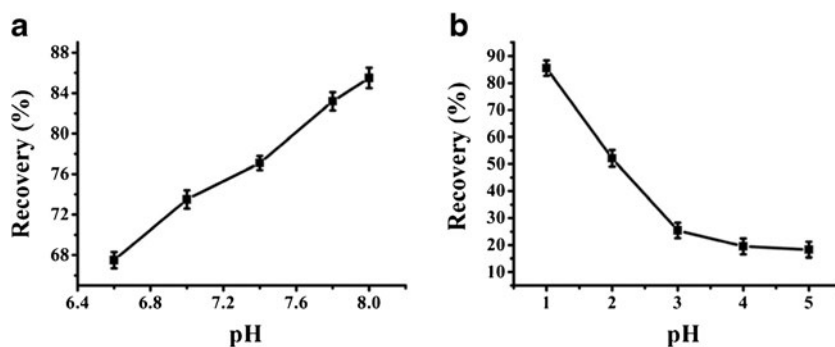
For biological samples, a certain amount of mice serum was added into the ortho-dihydroxy compounds solution. Then the effect of pH of loading solution and eluent on the recovery was investigated, respectively. As shown in Fig. 5a, with the increasing pH of the loading solution, the recovery of the dopamine also increased, which demonstrated that the drug was better adsorbed to the support materials under weak alkaline conditions. However, considering the stability of the drug, dopamine was stable under acidic conditions but easily degraded under alkaline conditions. Hence, the best pH of the loading solution was 8.0. On the other hand, with the increasing pH of the eluent (Fig. 5b), the recovery of dopamine decreased. That was because the boron atom of m-APBA was sp<sup>2</sup> hybridization and had planar structure under acidic and neutral conditions, whereas the boron atom was sp<sup>3</sup> hybridization and had tetrahedral structure under alkaline condition, which formed a stable ring structure with the ortho-dihydroxy compounds. Additionally, this structure was easily hydrolyzed under acidic conditions and the hydrolysis rate became faster with the increasing of the acidity [24]. Therefore, the pH of the eluent should be as low as possible provided that the magnetic microspheres do not be destroyed.

The chromatographic conditions were optimized (Fig. 6) and the recovery to three catecholamine drugs of four support

**Fig. 4** Adsorption principle of ortho-dihydroxy or 1, 3-dihydroxy compounds



**Fig. 5** Effect of pH of loading solution (a) and eluent (b) on recovery of dopamine



materials (epoxy propyl MM, diol MM, m-APBA MM and m-APBA/diol MM) in spiked biological samples was measured in this condition (Fig. 7). The recovery of m-APBA MM and m-APBA/diol MM to three kinds of catecholamine drugs was significantly higher than epoxy propyl MM and diol MM, which demonstrated that the m-APBA/diol MM was able to adsorb ortho-dihydroxy compounds selectively even in the spiked biological samples. This restricted-access magnetic sorbent had not only the advantage of RAMs, but also achieved separation by magnet instead of centrifugation, which was more efficient and selective than the traditional SPE.

### Method validation

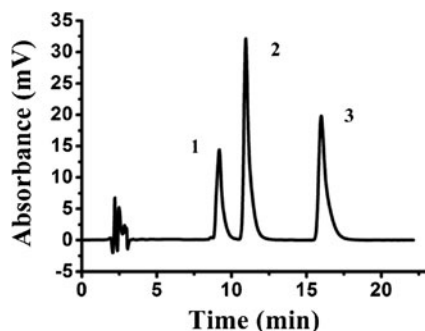
To evaluate the accuracy and feasibility of the method developed, mice serum samples spiked with the three ortho-dihydroxy compounds were analyzed. The samples were dealt with the proposed SPE method before injection. Blank extractions from mice serum were performed to ensure that no interference from the biological matrix extracted by the magnetic restricted-access microspheres, and the result demonstrated that no matrix effects such as the proteins and endogenous components in mice serum samples were observed, which implied the excellent specificity for the

determination of ortho-dihydroxy compounds with this MSPE method.

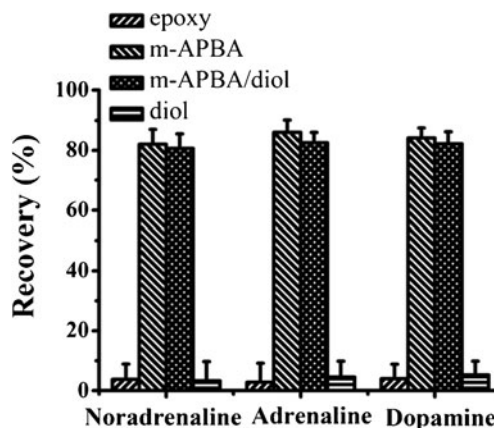
Under the optimized conditions, the quantitative parameters of the proposed method, including linear range, correlation coefficients, precision, limits of detection (LOD), limits of quantification (LOQ), recovery and relative standard deviation (RSD), were evaluated.

As shown in Table 1, the linear ranges of analysis were 0.5–10  $\mu\text{g mL}^{-1}$  for dopamine, adrenaline and noradrenaline. The correlation coefficient ( $R^2$ ) ranged from 0.9965 to 0.9982. The limit of detection (LOD) and limit of quantification (LOQ) were considered as the analyte minimum concentrations that can be confidently identified and quantified by the method, respectively. The LOD calculated on the basis of signal-to-noise ratio of 3 ( $S/N = 3$ ) for dopamine, adrenaline and noradrenaline were 0.074, 0.053 and 0.095  $\mu\text{g mL}^{-1}$ , respectively. The LOQ values taken by signal-to-noise ratio of 10 ( $S/N = 10$ ) were 0.254, 0.210 and 0.285  $\mu\text{g mL}^{-1}$  for dopamine, adrenaline and noradrenaline, respectively.

The reproducibility of the magnetic restricted-access SPE procedure was assessed by preparing and measuring three different levels of sample concentration six times. As shown in Table 2, the repeatability calculated as the RSD for each analyte at a given concentration varies from 3.9 % to 7.0 %. Thus the method was suitable for analyzing the urine samples.



**Fig. 6** Chromatogram of noradrenaline, adrenaline and dopamine (HPLC conditions: C18, Ion-pair reagent buffer: acetonitrile =90:10, 1 mL·min<sup>-1</sup>, 150 × 4.6 mm, 280 nm). 1. noradrenaline 2. adrenaline 3. dopamine



**Fig. 7** Recovery of noradrenaline, adrenaline and dopamine in serum

**Table 1** Analytical parameters of the proposed method

Compound ( <i>n</i> = 6)	Linear range ( $\mu\text{g mL}^{-1}$ )	Linearity ( $R^2$ )	LOD ( $\mu\text{g mL}^{-1}$ )	LOQ ( $\mu\text{g mL}^{-1}$ )
Dopamine	0.5–10	0.9965	0.074	0.254
Adrenaline	0.5–10	0.9978	0.053	0.210
Noradrenaline	0.5–10	0.9982	0.095	0.285

### Comparison with traditional sample preparation procedures

One of the ultimate goals in bio-matrix samples preparation is to eliminate the interference from sample matrix as complete as possible. The proposed method shows no interference from the bio-matrix extracted by the magnetic restricted-access microspheres, implying it is superior to most of the previous methods due to time-saving, reduced expenditures for labor and organic solvents. Moreover, to test the regeneration of magnetic restricted-access microspheres, five adsorption/desorption (regeneration) cycles were conducted with ortho-dihydroxy compounds. The adsorbents can be used for five cycles with the loss less than 8.5 % of their recovery on average. No obvious decrease in adsorption capacity was observed, suggesting that the adsorbents was stable and can be reused in bio-matrix samples.

### Conclusions

In this study, a restricted-access magnetic sorbent was successfully prepared using  $\text{Fe}_3\text{O}_4@\text{SiO}_2$  composites as support materials. Three analytes in biological samples, noradrenaline, adrenaline and dopamine, were used to test the adsorption property of the sorbent. This unique MSPE sorbent showed high selectivity and rapidity as well as convenience of the procedure. The hydrophilic external surface of the material prevents irreversible adsorption and denaturation of the proteins

**Table 2** Reproducibility of recoveries of ortho-dihydroxy compounds extracted from mice serum spiked with different drug concentrations

Compound ( <i>n</i> = 6)	Conc. ( $\mu\text{g mL}^{-1}$ )	Mean accuracy (%)	RSD (%)
Dopamine	0.5	88.2	5.1
	2	89.1	4.2
	10	89.5	3.9
Adrenaline	0.5	81.3	6.9
	2	83.4	4.5
	10	82.6	4.1
Noradrenaline	0.5	80.2	7.0
	2	85.3	4.3
	10	86.7	4.9

in the biological samples and the hydrophobic internal surface provides binding sites for three kinds of catecholamine drugs which can freely diffuse through the nanopores. Therefore, this material is promising as a selective sorbent for applications in biological samples.

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