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Magnetic Solid Phase Extraction of Paeonol and Paeonoflorin from Moutan Bark with Magnetic Graphene Oxide

Jiangui Jiang [1,2], Manman Liu [3], Xiongjie Hu [1], Ruan Chi [1], Junxia Yu [2] and Qingbiao Zhao [1,2,*]

[1] Hubei Three Gorges Laboratory, No. 1 Mazongling Rd, Xiaoting District, Yichang 443007, China; 22309010109@stu.wit.edu.cn (J.J.); hu_xiong_jie@163.com (X.H.); rac@wit.edu.cn (R.C.)

[2] School of Chemistry and Environmental Engineering, Wuhan Institute of Technology, Wuhan 430079, China; yujunxia_1979@163.com (J.Y.)

[3] Public Teaching Department, Zhengzhou Health Vocational College, No. 069 Jingxiang Road, Xingyang, Zhengzhou 450100, China; 1032117017@qq.com (M.L.)

* Corresponding author. E-mail: 23031701@wit.edu.cn (Q.Z.)

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ABSTRACT: Herbal medicine plays an important role in modern medicine and separation of the active ingredients from herbal medicine is vital for convenient and safe usage. Paeonol and paeonoflorin are the active ingredients in the widely used herbal medicine of moutan bark. In this study, the composite of graphene oxide-Fe_3O_4 nanoparticles (GO-Fe_3O_4) was synthesized and used as a magnetic absorbent to extract paeonol and paeonoflorin from the herbal medicine of moutan bark. The adsorption of paeonol and paeoniflorin on GO-Fe_3O_4 rapidly reached equilibrium (within 10 min) due to the high absorption capability of GO. Thermodynamics and kinetics for the absorption process were studied. The optimal condition for the elution of the target compound from GO-Fe_3O_4 was the use of 2 mL of a mixed solvent (methanol and dichloromethane, 1:1 by volume) with 0.2% formic acid for 5 min. The GO-Fe_3O_4 adsorbent possesses the advantages of rapid adsorption and convenient separation. GO-Fe_3O_4 can be used over 6 times without losing absorbing capacity. This method is efficient, convenient and rapid, thus possesses a high potential for the separation of active ingredients from herbal medicine.

Keywords: Graphene oxide; Fe_3O_4; Extraction; Paeonol; Paeoniflorin

1. Introduction

Herbal medicine, with a long history, still plays an important role in modern medicine. The main extraction methods for functional components contained in natural products are reflux extraction (RE), supercritical extraction (SE) and microwave extraction (ME) [1–3]. However, the products extracted using these methods are complex in composition and could be detrimental to health [4–6]. Extraction of active ingredients allows one to use herbal medicine in a more efficient and safe approach. The paeonol and paeonflorin are the primary active ingredient in moutan bark, which is a widely used traditional herbal medicine [7,8]. Paeonol has analgesic, anti-inflammatory, antipyretic and allergy-inhibiting effects [8–10]. Paeoniflorin can be used for treating inflammation and senile chronic respiratory diseases [7,11,12]. The structures of paeonol and paeoniflorin and are shown in Figure 1a,b, respectively.

Paeonol and paeoniflorin can be separated by the method of capillary electrophoresis. The recoveries of the paeonol and paeoniflorin range from 99.5~101.8% and 97.1~99.1%, respectively [8]. Paeonol can also be determined by HPLC method [7]. The extraction methods of paeonol include percolation, steam distillation, reflux, supercritical extraction, *etc.* [13–15]; the extraction methods of paeoniflorin include reflux and decoction [16,17]; if the extraction rates of paeonol and paeoniflorin are to be considered simultaneously, the double extraction method should be used [15]. However, the above methods have problems such as long extraction time and cumbersome operation to varying degrees, and all require heating, which will cause the degradation of the heat-labile component paeoniflorin and the loss of the volatile component paeonol [16]. Therefore, although some extraction methods for paeonol and paeoniflorin have been established, a convenient, rapid, and large-absorption method is urgently needed. Among them, magnetic solid phase

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extraction (MSPE) is a powerful pretreatment technique for the qualitative or quantitative analysis of trace phytochemical compounds in different complex sample matrices. Compared with traditional SPE, it can be more conveniently separated by simple magnetic decantation. In addition, different types of materials such as ionic liquids, MOFs, COFs, GO, DES, BN, aptamers and MWCNTs have been used in MSPE technique to achieve efficient and selective enrichment of various phytochemical compounds [18–20]. For example, Jaber Nasiri et al. used magnetic carbon-based nano-adsorbents to enrich paclitaxel from crude yew extracts [21–23]. The preparation of effective multifunctional magnetic composites for the pretreatment of various phytochemical compounds is currently needed.

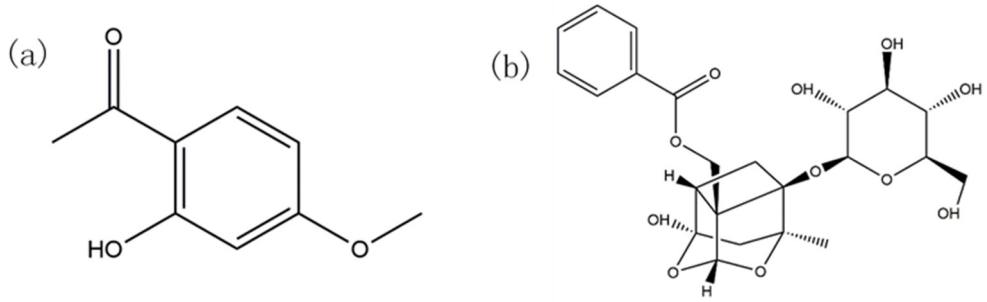

Figure 1. The structure of (**a**) paeonol (2′-Hydroxy-4′-methoxyacetopheone) and (**b**) paeoniflorin (5beta-[(Benzoyloxy)methyl]tetrahydro-5-hydroxy-2-methyl-2,5-methano-1*H*-3,4-dioxacyclobuta[cd]pentalen-1alpha(2*H*)-yl-beta-D-glucopyranoside).

Graphene is a widely used two-dimensional material for its large surface area and interesting physical properties [24,25]. Graphene oxide (GO), the oxide material of graphene, has a high specific surface area and large amounts of oxide-containing functional groups, including epoxy (C–O–C), carboxyl (COOH), –C=O and hydroxyl (OH) [26–30]. Thus, graphene oxide can be easily dispersed in aqueous solution [31–33]. Graphene oxide is an efficient absorbent due to its large surface area [34]. The composite of GO with superparamagnetic Fe_3O_4 (GO-Fe_3O_4) has attracted extensive interest due to the convenient separation by applying an external magnetic field [24,35–38].

In this study, GO-Fe_3O_4 was used as the absorbent for the separation of paeonol and paeonifofrin from the herbal medicine of moutan bark. Thermodynamics and kinetics of the absorption process were studied. The material has high physicochemical stability, long service life, large adsorption capacity, and high separation efficiency of paeonol and paeoniflorin, and the method is convenient and simple, which has a good application prospect in the extraction of effective components of traditional herbal medicine.

2. Materials and Methods

2.1. Synthesis

GO-Fe_3O_4 was prepared according to our previous report [39,40]. Briefly, in the first step, graphite powder, $NaNO_3$ and concentrated sulfuric acid were used to prepare graphene, then hydrogen peroxide solution was used to oxidize nano-graphene, and the product was washed and dried to obtain GO. In the second step, graphene oxide was added to the aqueous suspension of $(NH_4)_2Fe(SO_4)2{\cdot}6H_2O$, $NH_4Fe(SO_4)_2{\cdot}12H_2O$, and then the solution was sonicated to obtain the GO-Fe_3O_4 composite. Detailed synthetic procedures can be found in the previous report.

2.2. Absorption Paeonol and Paeoniflorin by GO-Fe_3O_4 and Elution

The moutan bark extract was obtained by vibrating moutan bark powders (1 g) in 50 mL of deionized water by vibration for 1 h. The mixture was centrifuged for 10 min at ~300× *g*. 1 mL supernatant was used as the extract for separation of paeonol and paeoniflorin. Afterwards, the paeonol and paeoniflorin contents in moutan bark extract were absorbed by GO-Fe_3O_4. 20 mg of GO-Fe_3O_4 were added into 1 mL of moutan bark extract. The mixture oscillated steadily with the optimal adsorption conditions. Then GO-Fe_3O_4 was separated from the mixture by the application of a magnetic field. The solution before and after the extraction was analyzed by LC-MS/MS. Afterwards, GO-Fe_3O_4 was eluted by the solution of methanol and dichloromethane (1:1: in volume) with 0.2% formic acid.

2.3. LC-MS/MS

A UPLC-Xevo TQS micro instrument was used for liquid chromatography. The chromatography was performed with an ACQUITY UPLC BEH C18 column (1.7 μm, 2.1 × 100 mm; Waters Corp., Milford, MA, USA). Eluent A was the aqueous solution of 10 mM ammonium formate and 0.1% formic acid. Eluent B was methanol. A gradient program

was set as the following: 0.00–1.00 min 10% B; 1.1–2.00 min 10–95% B; 2.1–6.0 min 95% B; 6.0–6.1 min 10% B; 6.1–7.0 min 10% B. The overall time was 7 min. Mass spectrometry with an electrospray ionization (ESI) source was used for analysis.

2.4. Kinetic and Thermodynamic Studies of the Absorption Process

The static absorption experiments were conducted in a methanol/water (1:1 in volume) solution. Standard solutions of paeonol and paeoniflorin were used for the kinetic and thermodynamic studies. 20 mg of GO-Fe_3O_4 were added into 5 mL of paeonol and paeoniflorin standard solution of various concentrations. The resulting mixture was oscillated for 4 h and centrifuged at 8000 rpm for 20 min.

The adsorption capacities (Q) of paeonol and paeoniflorin on the absorbent were calculated with Equations (1) and (2).

$$Q_e = \frac{(C_0 - C_e)V}{m} \quad (1)$$

$$Q_t = \frac{(C_o - C_t)V}{m} \quad (2)$$

In Equations (1) and (2), Q_e and Q_t (mol g^{-1}) represent the quantities of paeonol and paeoniflorin absorbed on GO-Fe_3O_4 at equilibrium and time t, respectively; C_0 (mol mL^{-1}), C_e (mol mL^{-1}) and C_t (mol mL^{-1}) represent the concentrations of paeonol and paeoniflorin initially, at equilibrium and at time t, respectively; V (mL) represents the solvent volume; m (g) represents the mass of GO-Fe_3O_4 that is used.

The kinetics of the absorption process was studied at 25 °C in aqueous solution with an initial paeonol concentration of 50 μg/mL and volume of 4 mL.

3. Results and Discussion

3.1. Absorption of Paeonol and Paeoniflorin with GO-Fe_3O_4

20 mg absorbent was added into 1 mL standard solution containing paeonol and paeoniflorin (500 ng/mL each) and the mixture was oscillated steadily for 20 min. After the absorption, the concentration of the paeonol and paeoniflorin remaining in the solution is below the detection limit. This means that the paeonol and paeoniflorin can be efficiently enriched and separated with GO-Fe_3O_4.

3.2. HPLC-MS/MS

The chromatograms for the standards of paeonol and paeoniflorin are shown in Figure 2. The concentrations of paeonol and paeoniflorin in the absorption and desorption process are calculated based on the peak area.

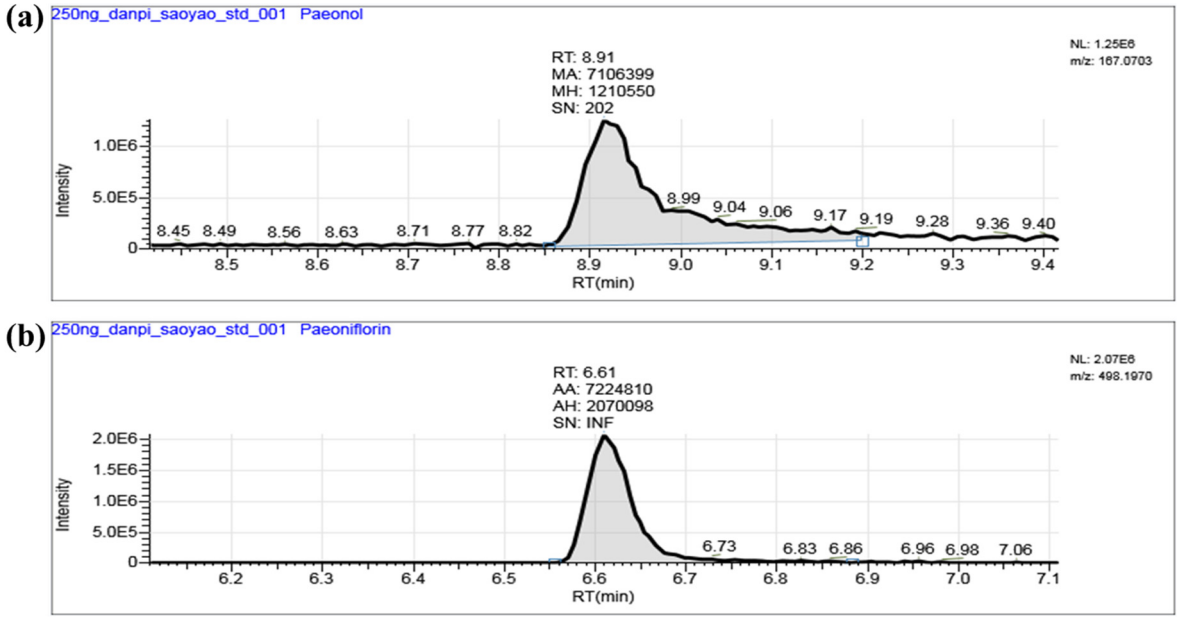

Figure 2. (**a**) chromatogram of paeonol (**b**) chromatogram of paeoniflorin.

3.3. Absorption Kinetics

As shown in Figure 3, the absorption amount increased with a longer time and reached equilibrium at 20 min. The absorption amount of paeonol rapidly increased during the initial 15 min, and the absorption amount exhibited little change after 30 min. This behavior is likely due to the fact that the external active sites are gradually saturated with the absorption of paeonol, and paeonol overcomes the transfer resistance and transfers into the interior of GO-Fe_3O_4.

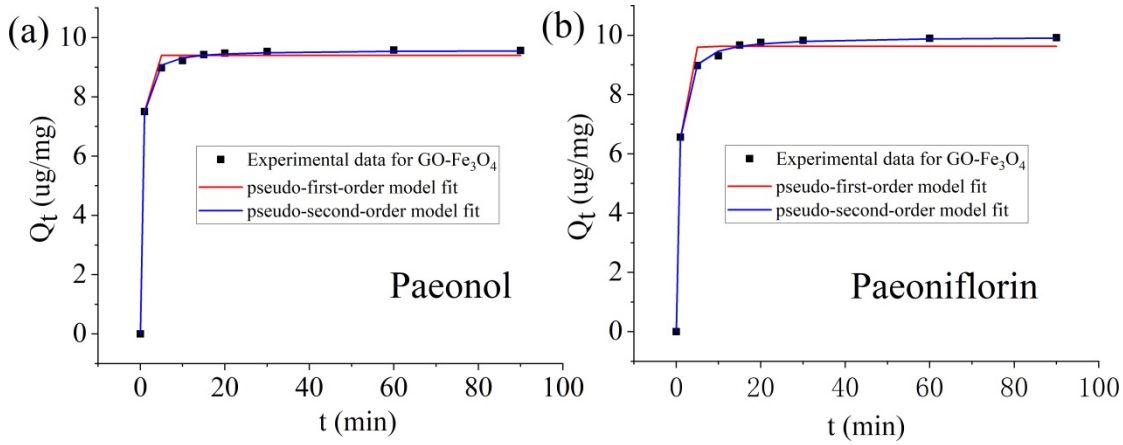

Figure 3. Absorption dynamics curve of (**a**) paeonol and (**b**) paeoniflorin on GO-Fe_3O_4 at 25 °C in water with the fitting of the pseudo-first-order model and the pseudo-second-order model.

To study the kinetic mechanism for the absorption process, pseudo-first-order model and pseudo-second-order model were employed to fit the experimental data. The equation of pseudo-first-order model is as follows:

$$Q_t = Q_e - Q_e e^{-k_1 t} \tag{3}$$

where Q_e and Q_t represent the quantities of paeonol absorbed on GO-Fe_3O_4 at equilibrium and time t, respectively. k_1 represents the pseudo-first-order rate constant.

The equation of the pseudo-second-order model is as follows:

$$Q_t = \frac{K_2 Q_e^2 t}{1 + k_2 Q_e t} \tag{4}$$

where Q_e and Q_t represent the quantities of paeonol absorbed on GO-Fe_3O_4 at equilibrium and time t, respectively. K_2 represents the rate constant for the pseudo-second-order model. As shown in Figure 2, the pseudo-second-order model ($R^2 = 0.9997$) fit the adsorption process of paeonol better than the pseudo-first-order model ($R^2 = 0.9981$). The calculated Q_e values ($Q_{e,cal}$) obtained by using the pseudo-second-order model are closer to the experimental Q_e values ($Q_{e,exp}$) than by using the pseudo-first-order model, suggesting that the absorption follows a diffusion-controlled process.

3.4. Adsorption Isotherms

Figure 4 shows the adsorption isotherm of paeonol on GO–Fe_3O_4 and paeoniflorin at 283, 293 and 303 K. The results show that the Q_e values increase with higher concentrations of the paeonol and paeoniflorin. Moreover, the Q_e values increase as the temperature increases.

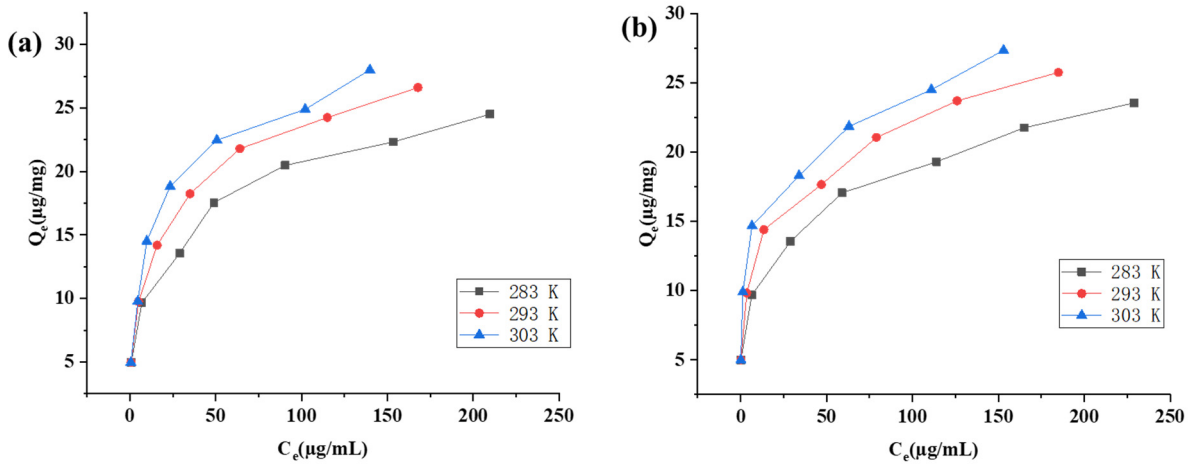

Figure 4. Isotherms for the absorption of (**a**) paeonol and (**b**) paeoniflorin on GO-Fe_3O_4 at 283, 293 and 303 K.

The isotherms of paeonol and paeoniflorin were fitted with Langmuir model and Freundlich model with the following equations, respectively.

$$\frac{C_e}{Q_e} = \frac{1}{Q_0 K_L} + (\frac{1}{Q_0})C_e \tag{5}$$

$$lnQ_e = lnK_F + \frac{1}{n} lnC_e \tag{6}$$

Figure 5 shows the Langmuir fitting and Freundlich fitting for the isotherms of paeonol and paeoniflorin adsorption on GO-Fe_3O_4 at various temperatures. The adsorption equilibrium data was fitted with the Freundlich model with a higher R^2 values than Langmuir model. The adsorption isotherm is consistent with the Freundlich model [41]. The constant K of Freundlich model indicates that the adsorption capacity increases with higher temperatures.

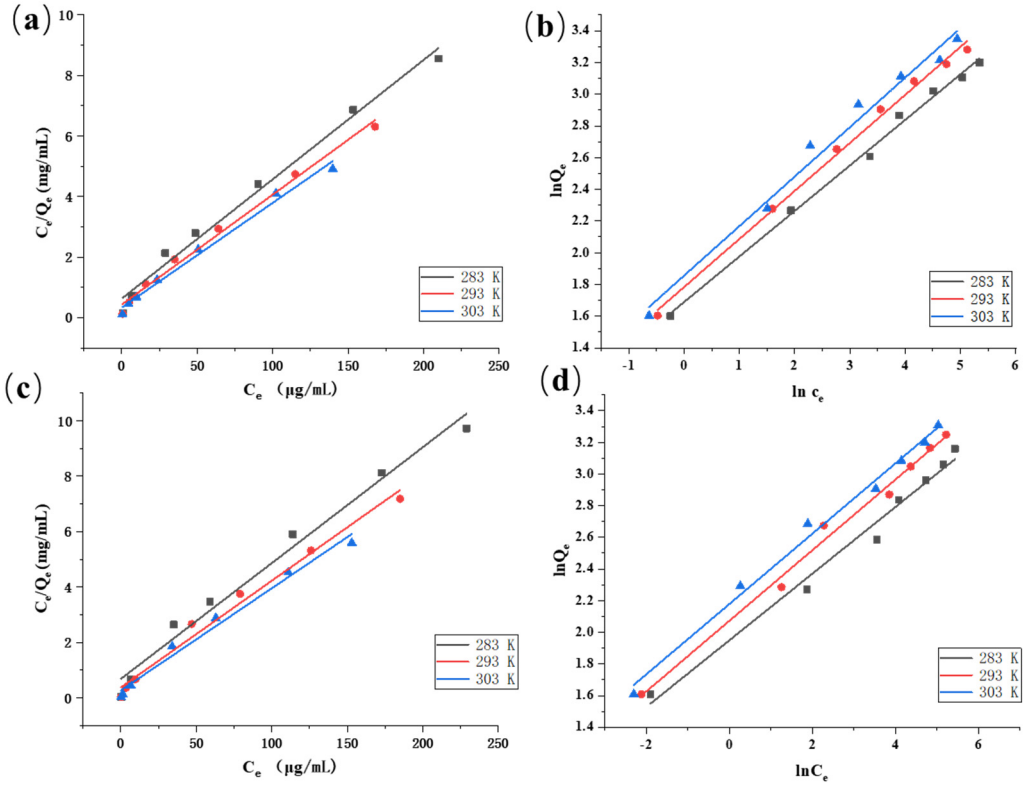

Figure 5. Fitting by (**a**) Langmuir model and (**b**) Freundlich model for the isotherms of paeonol adsorption on GO-Fe_3O_4 at different temperatures. Fitting by (**c**) Langmuir model and (**d**) Freundlich model for the isotherms of paeoniflorin adsorption on GO-Fe_3O_4 at different temperatures.

The van't Hoff equation was used to calculate ΔH and ΔS:

$$ln\,Kc = \frac{\Delta S_0}{R} - \frac{\Delta H_0}{RT} \quad (7)$$

ΔG_0 was calculated according to the following equation:

$$\Delta G_0 = -RTlnK_c \quad (8)$$

Based on the van't Hoff plot for paeonol and paeonifilorin adsorption by GO-Fe_3O_4, ΔG_0 was calculated (Table 1) and confirmed the spontaneous nature and the feasibility of the adsorption [42]. Besides, the decrease in the negative value of ΔG_0 with the increase in temperature indicates that the adsorption is more favorable at higher temperatures [43]. All the thermodynamic parameters mentioned above indicate that GO-Fe_3O_4 is an efficient adsorbent for the separation of paeonol from an aqueous solution [44,45].

Table 1. The thermodynamics parameters for paeonol and paeonifilorin adsorption by GO-Fe_3O_4.

	T **(K)**	**ln** ***Kc***	**Δ*G* (kJ/mol)**	**Δ*H* (kJ/mol)**	**Δ*S* (J/mol K)**
paeonol	283	2.39	−5.62	11.18	59.48
	293	2.59	−6.29		
	303	2.70	−6.81		
paeonifilorin	283	3.82	−8.99	31.18	141.80
	293	4.22	−10.28		
	303	4.70	−11.83		

3.5. Optimization of the Elution Conditions

Besides the absorption of paeonol and paeonifilorin from the solution, the desorption process is also important. Various conditions have effects on the elution of paeonol and paeonifilorin from the GO-Fe_3O_4 absorbents. The parameters, including pH value, choice of elution solvent, volume and time, were optimized.

3.5.1. Effect of pH

The pH values have a significant effect on the elution of paeonol and paeonifilorin from the absorbent. Different amounts of ammonia and formic acid were added to tune the pH value of the elution solution. 1% ammonia (volume fraction), neutral, 0.1% formic acid, 0.2% formic acid, 0.5% formic acid and 1% formic acid were tested. The elution efficiency is higher in the acidic condition than in the neutral and basic conditions (Figure 6a). The volume fraction of formic acid has little effect on the recovery of paeonol, while the amount of formic acid impacts the recovery of paeoniflorin significantly. As the concentration of formic acid is above 0.2%, the recovery of paeoniflorin becomes steady. Therefore, 0.2% formic acid was used for tuning the pH value of the elution solvent.

3.5.2. Effect of the Elution Solvent

To examine the effect of the organic solvent on the elution process, four different organic solvents were tested for the elution of the absorbent after the adsorption of paeonol and paeoniflorin. The results are shown in Figure 6b. The absorbent was eluted using 1 mL of methanol, dichloromethane, acetonitrile and acetic ether, respectively. As shown in Figure 6b, methanol possesses the highest elution capability for paeonol, and dichloromethane has the highest elution capability for paeoniflorin. Thus, the mixed solvent of methanol and dichloromethane (1:1 in volume) was used for elution.

3.5.3. Effect of Volume of Elution Solution

To obtain high desorption recovery, different amount of elution solution ranging from 1 to 3 mL was used to desorb the target analyte from the absorbent. Figure 6c illustrates that higher desorption recovery was obtained with the elution solvent volume of 2 and 3 mL than with 1 mL. Thus, 2 mL was selected as the optimal volume for the elution.

3.5.4. Effect of Elution Time

The elution time has a significant effect on the elution efficiency. The elution was conducted from 5 to 15 min. As shown in Figure 6d, the desorption recovery changes only slightly from 5 to 15 min. This means the desorption process reaches equilibrium within 5 min. Therefore, 5 min was selected as the elution time.

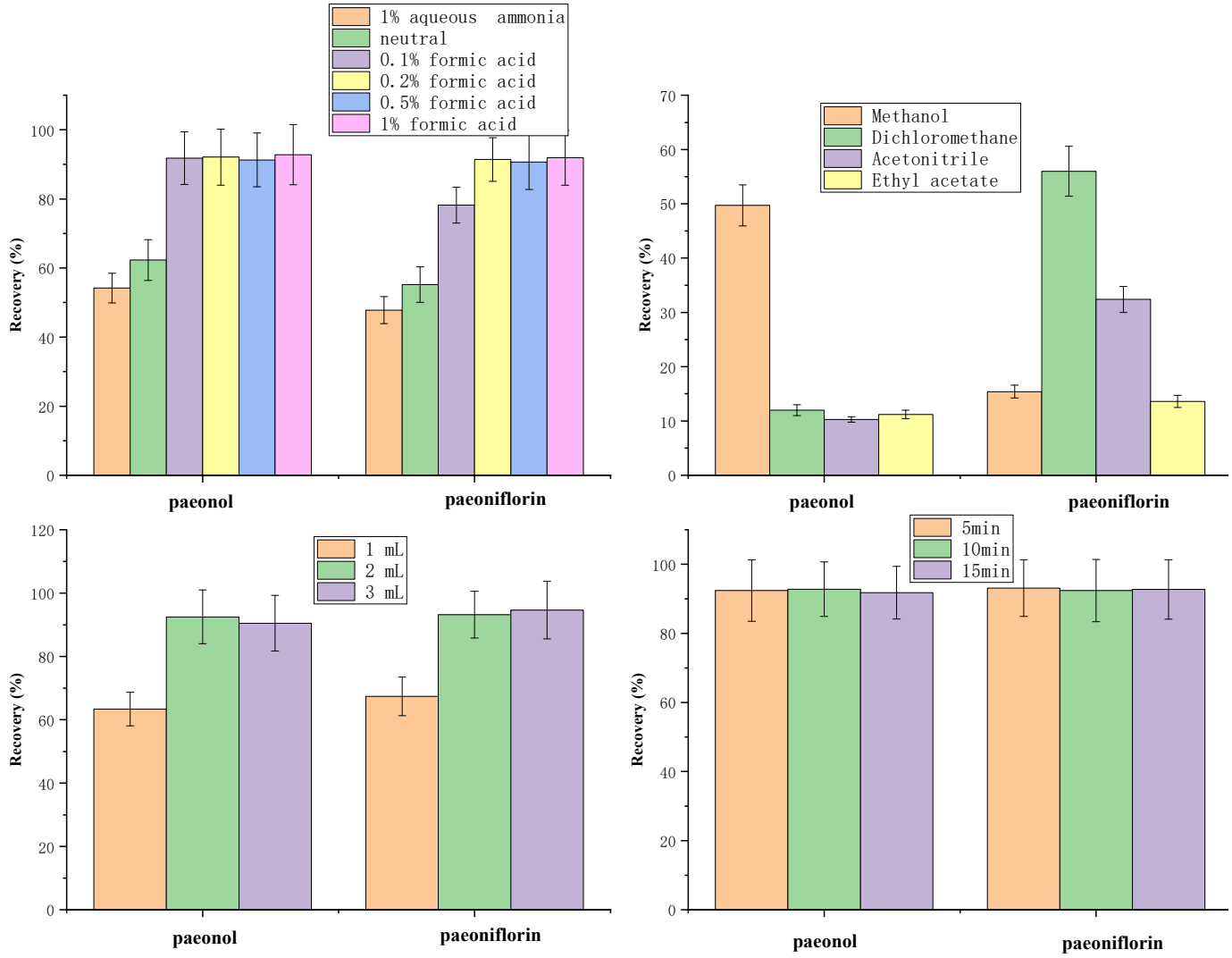

Figure 6. The effect of (**a**) the pH environments (**b**) the organic solvent on recovery (**c**) volume of elution solution (**d**) elution time on the elution of paeonol and paeonifilorin.

3.5.5. Reusability of the Absorbent

The reusability of the absorption material is important for practical application. To examine the reusability of the GO-Fe_3O_4 adsorbent, the adsorbent GO-Fe_3O_4 that has absorbed paeonol and paeoniflorin was eluted with the mixed solvent of methanol, dichloromethane and formic acid (volume fractions: 1:1:0.2) in a vortexer, then the regenerated GO-Fe_3O_4 was reused for the next absorption experiment. The absorption-desorption cycles were repeated for six times under equivalent conditions. After six reuse cycles, the extraction capacity remained essentially constant, demonstrating the good reusability of the GO-Fe_3O_4 absorbent.

4. Conclusions

GO-Fe_3O_4 was used in the enrichment and separation of paeonol and paeoniflorin in the extract of moutan bark. The adsorption kinetic study demonstrated that the adsorption procedure was rapid and can be fitted well with the pseudo-two-order model. 2 mL of the mixed solvent of methanol and dichloromethane (1:1 in volume) with 0.2% formic acid for 5 min was found to be the optimal elution condition. GO-Fe_3O_4 can be reused multiple times without appreciable reduction of extraction capacity. The shortcoming of the absorption of paeonol and paeoniflorin by GO-Fe_3O_4 is the relatively high cost. This method is convenient and efficient, thus having a high potential for the separation of active components from herbal medicine.

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Author Contributions

J.J.: Writing—Original Draft Preparation, Data Curation. M.L. Formal Analysis, X.H. Investigation, J.Y.: Methodology, R.C.: Investigation, Formal analysis. Q.Z.: Writing—Review & Editing, Funding Acquisition, Methodology.

Ethics Statement

Not applicable.

Informed Consent Statement

Not applicable.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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