Korean J. Chem. Eng., 35(4), 956-963 (2018)
DOI: 10.1007/s11814-018-0001-4

pISSN: 0256-1115
eISSN: 1975-7220

Combination of supercritical fluid elution and resin adsorption for removal of procymidone from ginseng extracts

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(*Received 11 August 2017 • accepted 3 January 2018*)

Abstract−We propose a new method of resin adsorption (RA) coupled with supercritical fluid elution (SFE) for removal of pesticide residue and recovery of ginsenosides from ginseng extracts. D-101-1 resin was selected as the proper adsorption resin, acetone-*n*-hexane (4 : 6, v : v) served as the modifier with the flow rate of 1.5 mL/min during supercritical CO_2 elution of procymidone at 25 MPa, 55 °C for 2 h, and absolute ethanol as the modifier at a flow rate of 1 mL/min for supercritical CO_2 elution of ginsenosides at 20 MPa, 60 °C and 1 h. The results showed that the content of procymidone in the final products was only 0.0089 mg/kg. Meanwhile, the recovery rate of ginsenosides reached up to 92.5%. RA-SFE procedure provides an efficient approach to remove pesticide residue traces with little loss of active ingredients. The used resin can be recycled without any additional regeneration.

Keywords: Procymidone, Pesticide Residues, Ginsenosides, Supercritical CO_2 Extraction, Resin Adsorption

INTRODUCTION

Procymidone, N-(3,5-dichlorophenyl)-1,2-dimethyl-1,2-cyclopropane dicarboximide, is one of the broadest applied organochlorine fungicides. Virulence determination in vitro has confirmed that the fungicide can have a desirable effect on preventing disease spot development and has good control over the fungal pathogens, which can infect many economic crops and herbs [1,2]. So it has been generally used to fight against sclerotinia and botrytis of ginseng during the planting process. However, procymidone can accumulate through soil and other environmental factors due to the long cultivation period of ginseng and will still exist in ginseng extract even after the extraction process from ginseng, which can negatively affect human health because of the high toxic of fungicide [3-5]. High procymidone content has become a major bottleneck in ginseng products export to other countries. The European Community and Japan have set the standard that the maximum residue limits of procymidone in products are 0.1 and 0.5 mg/kg respectively [5]. It is particularly urgent to find an efficient method to determine and remove the traces of pesticide residues in ginsengs and ginseng products.

Different separation methods such as matrix solid-phase extraction [6], dispersive liquid-liquid microextraction [7], Soxhlet extraction [8] and ultrahigh pressure extraction [9], ultrasound-assisted extraction [10] have been used for pesticide residue removal or ginsenoside extraction from ginseng and ginseng products, followed by resin adsorption for further purification and recovery of ginseng products [11,12]. However, these techniques have some disadvantages, including long production period, large amounts of solvent consumption and low recovery of active ingredients.

As a green and effective extraction technology, supercritical CO_2 extraction has been used for the removal of pesticide residue including benzenehexachloride (BHC) [13,14], pentachloronitrobenzene (PCNB), heptachlor epoxide (HEP) [14] from ginsengs with the advantages of high removal rate, short time and no or low consumption of organic solvent [15]. And it is easy to remove supercritical CO_2 (SC-CO_2) by pressure reduction at the end of the process. However, low selectivity and high ginsenoside loss rate remain no improvements.

Adsorption resin has good characteristics such as excellent acid and alkali resistance, high mechanical strength and porous availability which can absorb many kinds of chemical substances from plant or vegetables [16,17]. A majority of resins are insoluble, but chemical substances can dissolve in SC-CO_2 and organic solvents. And low polarity of supercritical CO_2 solvent can be adjusted with operating conditions. Some chemical substances can be selectively desorbed from resins under supercritical state. A few references [18,19] reported the processes to remove pesticides with supercritical fluid extraction followed by resin adsorption. Chikushi et al. [20] reported the reverse operation order that water samples containing the pesticides were mixed with particulate adsorbents in batch-wise adsorption, after which the pesticides were extracted from the adsorbents using supercritical carbon dioxide.

To meet the export demand on procymidone content (<0.1 mg/kg), the RA-SFE method was for the first time developed to remove procymidone from actual ginseng extracts in our study. Resins are screened and used for adsorption of procymidone and ginsenosides, followed by supercritical CO_2 elution for complete removal of procymidone from resins and high recovery of ginsenosides in final products. The effects of modifier type, modifier composition,

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modifier flow rate as well as supercritical elution temperature, pressure and time on the procymidone removal and ginsenosides recovery were studied.

EXPERIMENTAL

1. Materials

Procymidone standard was purchased from Aladdin Biological Technology Co., Ltd. (Shanghai, China). Ginsenoside Re was from Shilan Science and Technology Co., Ltd. (Tianjin, China). HPLC grade acetonitrile was obtained from Concord Technology Co., Ltd. (Tianjin, China). Acetone, ethyl ether, absolute ethanol, *n*-butanol, trichloromethane and hydrochloric acid, petroleum ether (boiling range of 60-90 °C), *n*-hexane, absolute methanol, perchloric acid (<70%), glacial acetic acid and vanillin (4-hydroxy-3-methoxybenzaldehyde) were from Guangfu Fine Chemical Industry Research Institute (Tianjin, China). High-purity CO_2 (>99.9%) was purchased from Tianjin Liufang Industrial Gases Co., Ltd. (Tianjin, China). All the chemicals were used as received without further purification. Ginseng extracts were provided by Jilin Hongjiu Bio-technology Co., Ltd. (Jilin, China).

H-103, AB-8, D-301, NKA-2 resins were obtained from Xingnan Yunneng High Polymer Co., Ltd. (Tianjin, China). D-101-1 resin was offered from Haiguang Chemical Industry Co., Ltd. (Tianjin, China). The physical properties of these resins are summarized in Table 1.

2. Analysis and Characterization

The content of procymidone was determined by L-3000 HPLC system (RIGOL Technology Co., Ltd., Beijing, China) combined with a UV detector at 220 nm and an ZORBAX SB - C18 column (4.6×250 mm, 5 μm). HPLC analysis was conducted with 20 μL of injection and acetonitrile and water (4/6, v/v) as the mobile phase composition at a flow rate of 1.0 mL/min. The ginsenosides content was analyzed at 552 nm wavelength by UV-9600 ultraviolet spectrophotometer (Rayleigh Analytical Instrument Co., Ltd., Beijing, China), following Vanillin-Acetic acid colorimetric method described in the Standard of PRC DB22/T 1668-2012. The morphology of adsorption resin was recorded on a Nanosem 430 scanning electron microscope (FEI, USA). The nitrogen adsorption and desorption isotherm was measured on a Tristar 3000 ASAP analyzer (Micromeritics, USA).

3. Pretreatment of Adsorption Resins

Prior to use, the adsorption resins were pretreated in according with previous studies [24-26] with some modifications. First, the resins were loaded in the column and then soaked with absolute ethanol for 24 h, followed by washing with absolute ethanol and deionized water, respectively, to remove impurities trapped inside the pores during the synthesis process. After that, the resins were placed into NaOH (4%) and liquid level was about 5 cm higher than resin for 3 h and washed with deionized water until the effluent was at a near-neutral pH. Finally, the resins were soaked into HCl (5%) and washed with deionized water to implement chemical neutrality.

4. The Process of Resin Adsorption

In a typical procedure [24], pretreated resin (25 g) was packed in the column with wet method. Then 100 mL ginseng extract solution (25 g/L) was pumped through the adsorption column at 2 BV/h flow rate to adsorb procymidone and ginsenosides. Finally, the adsorbed resin was dried in an oven at 60 °C for 1 h and used for the sequent supercritical fluid elution process.

5. The Process of Supercritical Fluid Elution

In our experiments, supercritical fluid elution process was conducted in a supercritical extraction equipment (The Spe-ed SFE) from Applied Separations Inc., USA. The dried resins were packed in a stainless extraction column of 32 mL. In a typical process, the initial extraction conditions were 20 MPa, 45 °C, 3 h and 0.2 L·min^{-1} CO_2 flow rate with acetone-*n*-hexane as the modifier at a flow rate of 2 mL/min to elute procymidone. Then the modifier was changed to 70 vol% ethanol aqueous solution to elute ginsenosides from the resin at a flow rate of 1 mL/min with 15 MPa, 50 °C, 2 h and 0.2 L·min^{-1} CO_2 flow rate. After removing the solvent from the eluent in a rotary vacuum evaporator at 60 °C, the final ginsenoside products were obtained.

6. Determination of Procymidone

1.0 g ginseng extract was dissolved in the deionized water at 50 °C for 10 min. Then procymidone was extracted with petroleum ether at room temperature, and the extract liquor was concentrated in a rotary vacuum evaporator at 50 °C. The dried samples were dissolved in acetonitrile and analyzed by HPLC system. Procymidone standard samples were also dissolved in acetonitrile with different concentrations of 0.05, 0.1, 0.5, 1.0 and 2.0 mg/L and analyzed to get standard curve of procymidone.

The procymidone content of the ginseng extract can be calculated with the following formula (1):

$$\text{Procymidone content (mg/kg)} = \frac{C \times V}{M} \quad (1)$$

where C (mg/L) is procymidone concentration in sample solution, V (L) is the volume of sample solution and M (kg) is the mass of ginseng saponin extracts under test.

The removal rate of procymidone can be calculated with the following formula (2):

Table 1. Properties of adsorption resins

Resins	Polarity	Surface area (m^2/g)	Pore size (nm)	References
H-103	Nonpolar	1000-1100	8.5-9.5	21
AB-8	Weakly polar	480-520	13.0-14.0	12, 16, 22, 23
NKA-2	Polar	250-290	14.5-15.5	21
DM-301	Moderately polar	≥330	14.0-17.0	23
D-101-1	Nonpolar	≥650	9.0-10.0	This work

$$\text{Removal rate of procymidone (\%)} = \frac{C_1 - C_2}{C_1} \times 100 \quad (2)$$

where C_1 and C_2 (mg/kg) mean the procymidone content in ginseng extract before and after the removal process, respectively. And C_1 is 44.51 mg/kg in our experiments.

7. Determination of Ginsenosides

0.1 g ginseng extract or final product was extracted with 10 mL diethyl ether and 10 mL of water saturated *n*-butanol solution three times, respectively. The upper extraction liquid was collected and the solvent was removed with a rotary vacuum evaporator at 60 °C. The final sample was obtained and analyzed by UV spectrophotometer. The standard curve as the benchmark for the content determination was obtained according to the reported method [9]. Ginsenoside standard methanol solutions with different volumes were, respectively, analyzed to get the standard curve of ginsenosides.

Ginsenosides recovery rate was calculated according to the following formula:

$$\text{Recovery rate (\%)} = \frac{m_2}{m_1} \times 100 \quad (3)$$

Here m_1 and m_2 are the ginsenosides mass (mg) in ginseng extract before and after the supercritical fluid elution process, respectively.

RESULTS AND DISCUSSION

1. Optimization of Resin Adsorption Process

1-1. Screening of Adsorption Resins

Five adsorption resins (H-103, AB-8, D-301, NKA-2, D-101-1) were employed for the removal of procymidone and recovery of

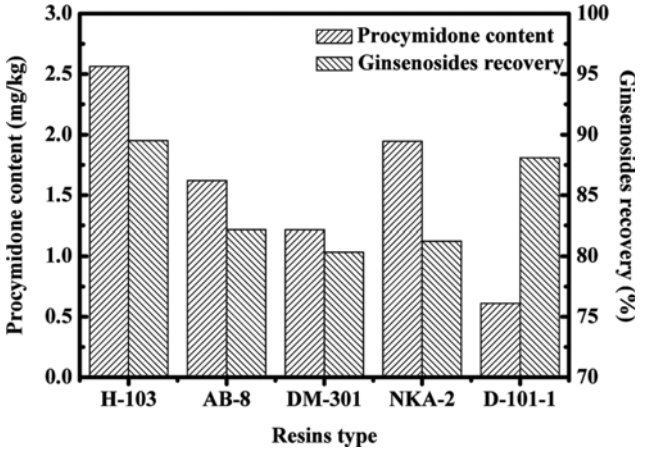

Fig. 1. Effect of the different resins on procymidone content and ginsenosides recovery in final products.

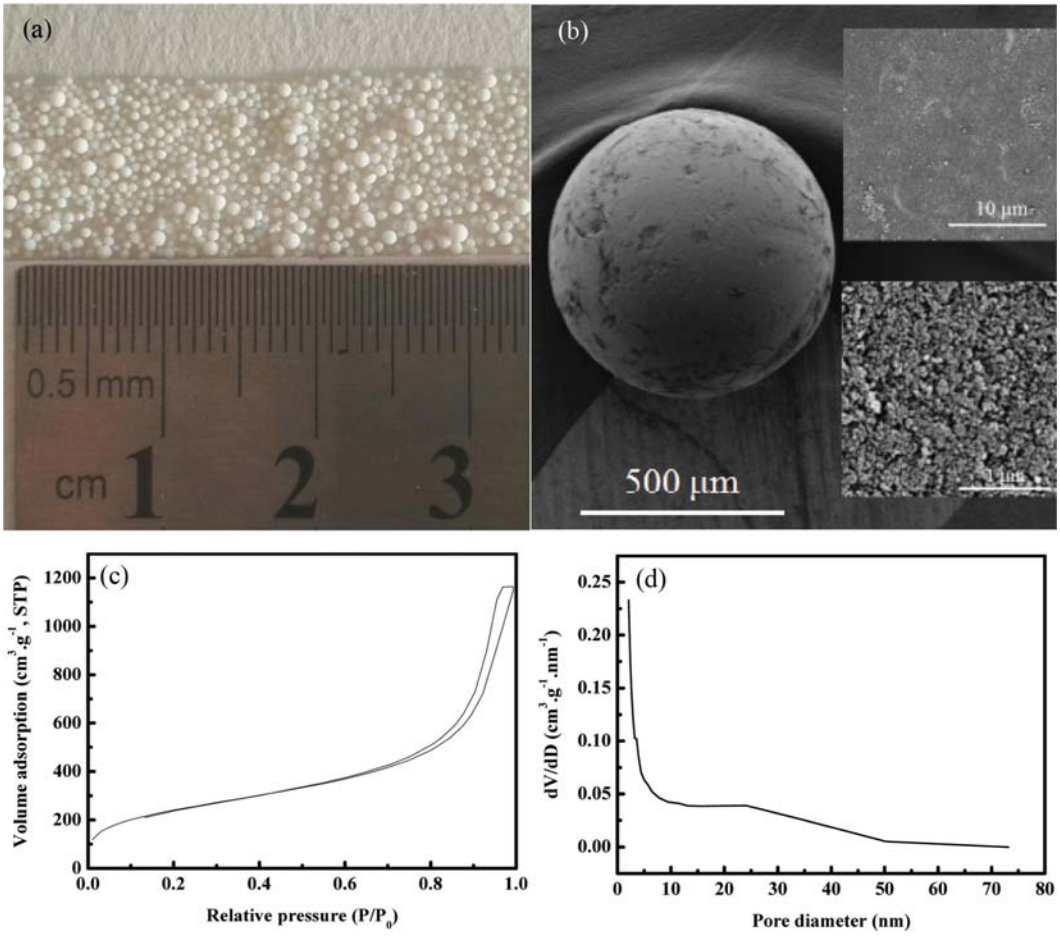

Fig. 2. Photo (a), SEM images (b), N_2 adsorption-desorption isotherm (c) and pore size distribution (d) of D-101-1 resin.

ginsenosides. Procymidone content and ginsenosides recovery rate after treatment with the different resins are shown in Fig. 1.

The adsorption capacity of resins is related to the physical and chemical properties, including pore size, surface area and polarity. As seen in Fig. 1, D-101-1 resin had the best adsorption ability among the five resins with the lowest procymidone content of 0.61 mg/kg and pretty high ginsenosides recovery rate of 88.1%. On one hand, the high surface area and large pore size are beneficial for the adsorption behavior of resins [26]. Therefore, D-101-1 resin shows fairly high procymidone and ginsenosides adsorption capacities during the resin adsorption process. On the other hand, low-polarity resin possesses relatively weak binding force with polar substances so that procymidone can easily desorb from the resin with the elution of polar solvents, which is the reason that D-101-1 resin achieves the lowest procymidone content after supercritical elution. Considering the combination of high ginsenosides recovery and low procymidone content of the final product, D-101-1 resin was selected for further study on procymidone removal and ginsenosides recovery.

The morphology and pore diameters of D-101-1 resin are shown in Fig. 2. As seen from Fig. 2(a), D-101-1 resin is a spherical particle and the particle size mainly ranges from 0.3 to 1.2 mm. The SEM images are shown in Fig. 2(b), which indicated that D-101-1 resin has rough surface with random distribution of various different sizes. Seen from Fig. 2(c) and 2(d), D-101-1 resin has a IV type curve with H4 type hysteresis loop, suggesting that the resin is mesoporous material with a large specific surface area of 884 $m^2 \cdot g^{-1}$, wide pore size distribution and the average pore size of around 9.16 nm. The results are in accordance with its commercial specifications and the data in other researches (Table 1).

1-2. Dynamic Leakage Curve of Procymidone

Fig. 3 gives the curve of procymidone content of the effluent *vs.* the volume of the sample solution. It can be found that no target compound could be detected while the sample loading amount is no more than 2 BV. However, procymidone leakage was observed with the sample loading further increasing. So the sample loading in all the subsequent experiments remained at 2 BV.

2. Procymidone Removal Using Supercritical Fluid Elution

Following the resin adsorption of procymidone and ginsenosides, supercritical CO_2 with modifiers is used to remove procymidone and recover ginsenosides from the resins.

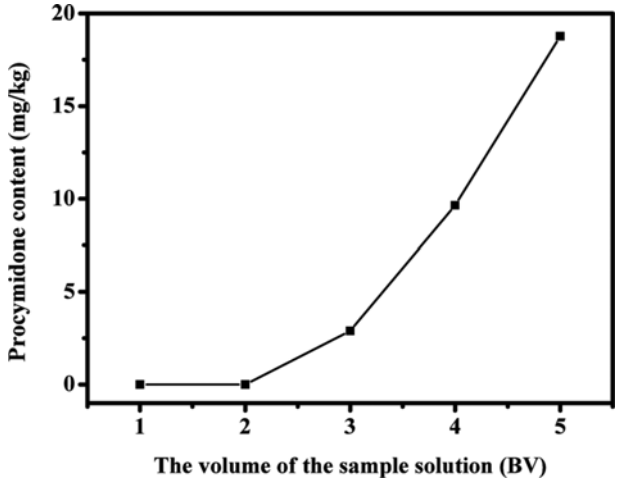

Fig. 3. Leakage curve of procymidone with D-101-1 resin.

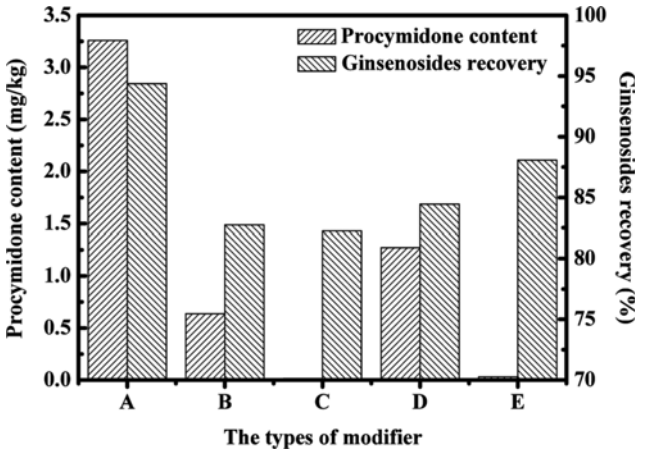

Fig. 4. Effect of the modifier type on procymidone removal and ginsenoside recovery in final products. A. *n*-Hexane B. Trichloromethane C. Acetone D. Trichloromethane-*n*-hexane (3 : 7, v : v) E. Acetone-*n*-hexane (3 : 7, v : v).

2-1. Selection of the Modifier

Since procymidone and ginsenosides are both polar compounds, modifiers are needed for non-polar supercritical CO_2 elution to adjust the polarity of supercritical fluids and boost the procymidone removal and ginsenosides recovery. *N*-hexane, trichloromethane, acetone, trichloromethane-*n*-hexane and acetone-*n*-hexane were, respectively, considered as the modifiers in our experiments. Fig. 4 shows the effect of modifier type on procymidone content and ginsenosides recovery rate.

As shown in Fig. 4, acetone as the modifier could obtain the lowest procymidone content but the lowest recovery rate of ginsenosides; meanwhile, the modifier *n*-hexane corresponds to the highest ginsenoside recovery rate, but the procymidone content is also the highest. Undoubtedly, it is preferable for acetone-*n*-hexane mixture as the modifier to achieve a quite low procymidone content and relatively high recovery rate of ginsenosides, just as shown in Fig. 4. Acetone-*n*-hexane was used as the modifier in the following experiments.

2-2. Effect of Modifier Composition

The concentration of acetone in acetone-*n*-hexane modifier has opposite effects upon the removal of procymidone and recovery of ginsenosides from actual ginseng extracts. On one hand, procymidone easily dissolves in acetone. The more the acetone is, the less the procymidone content is. On the other hand, ginsenosides can also dissolve in acetone. The increased acetone concentration can greatly increase the solubility of ginsenosides, which leads to a large amount of loss in ginsenosides recovery.

The effects of modifier composition on procymidone content and ginsenoside recovery rate were studied at five different acetone concentrations of 10, 20, 30, 40 and 50% (v/v). In Fig. 5, both procymidone content and ginsenosides recovery rate decrease with the increase of acetone concentration. When the volume fraction of acetone is more than 40 vol%, the pesticide residue decreases no longer, but the recovery rate of ginsenosides still keeps falling.

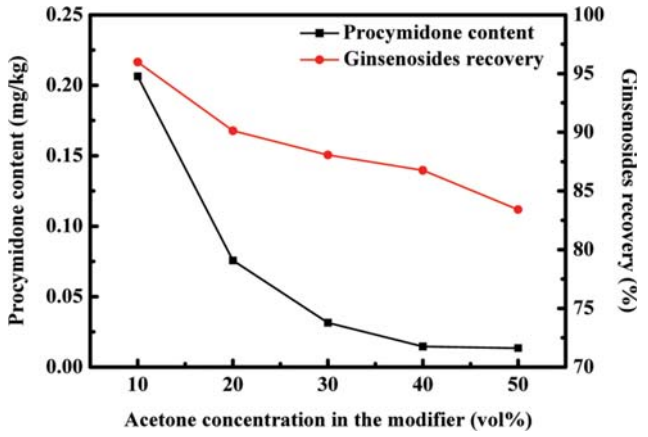

Fig. 5. Effect of the modifier composition on procymidone content and ginsenosides recovery in final products.

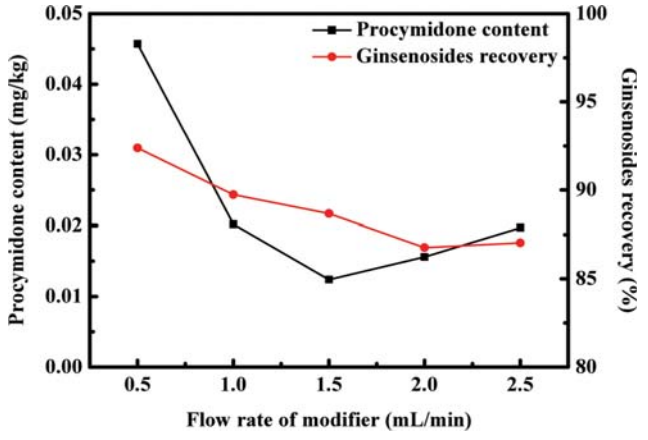

Fig. 6. Effect of the modifier flow rate on procymidone content and ginsenosides recovery in final products.

Therefore, acetone-*n*-hexane with 40 vol% acetone is regarded as the optimal modifier composition.

2-3. Effect of Modifier Flow Rate

Fig. 6 reveals the influence of the modifier flow rate on the removal of procymidone. The procymidone content sharply decreases with the increase of the modifier flow rate rises from 0.5 mL/min and reaches a minimum of 0.0124 mg/kg at the modifier flow rate of 1.5 mL/min. It suggests that the strengthened mass transfer with the increase of the modifier flow rate can improve the dissolution of procymidone in the supercritical eluent [27,28]. However, the procymidone content begins to increase with the further increase of the modifier flow rate from 1.5 mL/min, which should be attributed to shorter residence time of the modifier in the resin bed. Since the ginsenosides recovery rate only has a few changes, the optimal modifier flow rate is 1.5 mL/min.

2-4. Effect of Supercritical Elution Temperature

In supercritical state, temperature has two opposite effects on solubility of the solute. One is the positive impact because of the enhancement of the vapor pressure of the solute (in this part means procymidone) and desorption kinetics with higher temperature [29,30]; the other is a negative influence due to the decreasing sol-

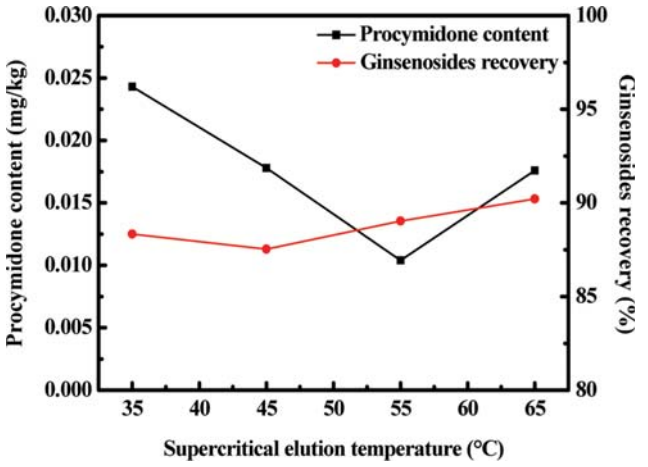

Fig. 7. Effect of supercritical elution temperature on procymidone content and ginsenosides recovery in final products.

ubility of the solute with temperature increasing [27].

In Fig. 7, the procymidone content gradually reduces to the minimum of 0.011 mg/kg, while the temperature increases from 35 to 55 °C and then begins to increase with the further increase of the elution temperature from 55 to 65 °C at the constant pressure of 20 MPa. Meanwhile, the ginsenoside recovery rate slowly rises with the temperature from 35 to 65 °C in overall and reaches the lowest at 45 °C, which should be due to the rather high solubility of ginsenosides in supercritical fluid. Considering both high procymidone removal and ginsenosides recovery, 55 °C was selected as the optimal supercritical elution temperature.

2-5. Effect of Supercritical Elution Pressure

The effect of supercritical elution pressure on procymidone removal and ginsenosides recovery was studied at constant temperature of 55 °C, where the pressure varied between 10 and 30 MPa. Shown in Fig. 8, the procymidone content in final products falls to the lowest of 0.0089 mg/kg at 25 MPa with the pressure increasing from 10 MPa to 25 MPa because of the enhancement of the procymidone solubility in supercritical eluent. However, the procymidone content becomes increasing, while the supercritical pressure further increases from 25 to 30 MPa, which should be due to lower diffusion rate of procymidone from the resin column to the supercritical fluid at higher pressure [31]. And this can also explain the tendency of ginsenosides recovery with the pressure as shown in Fig. 8. Finally, 25 MPa was considered as the optimal supercritical elution pressure to achieve the lowest procymidone content and acceptable ginsenosides recovery rate.

2-6. Effect of Supercritical Elution Time

In this part, supercritical elution time is optimized in the range of 0.5-3.0 h while keeping other parameters at the above optimal conditions. Undoubtedly, the procymidone content and ginsenosides recovery rate will decrease with the elution time as shown in Fig. 9. The procymidone content sharply falls at the beginning and gradually goes to a plateau when the elution time is over 1.5 h, suggesting the maximal removal of procymidone. Meanwhile, the curve of ginsenosides recovery with time has a similar tendency.

Considering that further increase in the elution time will lead to

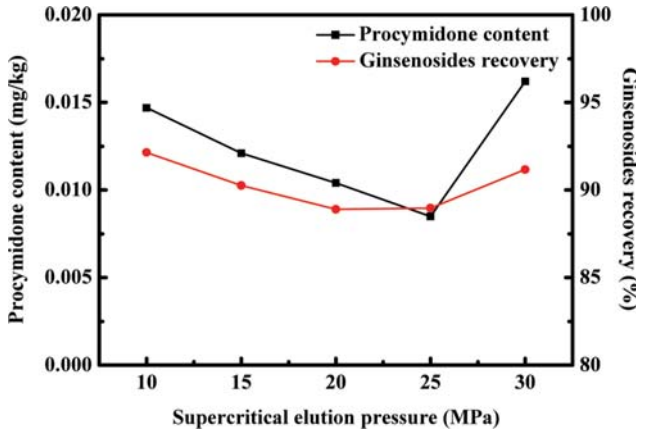

Fig. 8. Effect of supercritical elution pressure on procymidone content and ginsenosides recovery in final products.

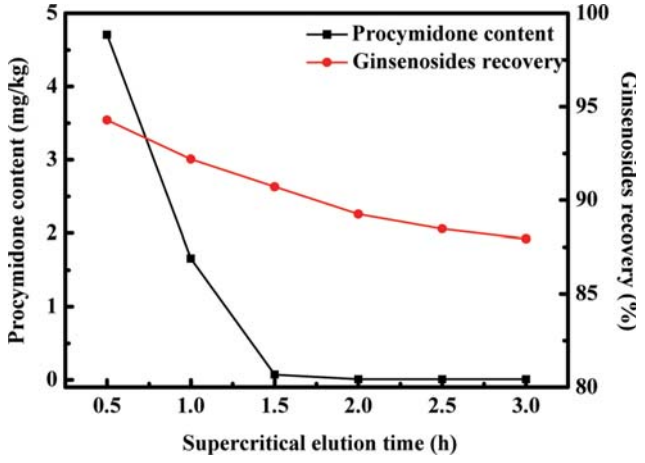

Fig. 9. Effect of supercritical elution time on procymidone content and ginsenosides recovery in final products.

the decrease of ginsenosides recovery, the increasing consumption of organic solvent and even the destruction of the structure and properties of the resin, the supercritical elution time is optimized at 2 h since the procymidone content in final products is below 0.01 mg/kg.

In brief, the optimal conditions for procymidone elution with supercritical fluid are as follows: acetone-*n*-hexane (40 : 60, v : v) as the modifier at a flow rate of 1.5 mL/min, 25 MPa, 55 °C and 2 h. Consequently, the supercritical elution of ginsenosides will be optimized with a similar method.

3. Ginsenosides Recovery Using Supercritical Fluid Elution

Ginsenosides as a series of polar compounds are freely soluble in methanol or ethanol, and some kinds of large polarity ginsenosides can dissolve in water [32]. In our experiment, ethanol water solution was chosen as the modifier for supercritical CO_2 to elute ginsenosides. The effect of ethanol concentration on ginsenosides recovery was mainly studied with four different ethanol concentration of 40%, 60%, 80% and 100% (v/v) at the initial extraction conditions of 15 MPa, 50 °C, 2 h, 0.2 L·min^{-1} CO_2 flow rate and 1.0 mL/min modifier flow rate.

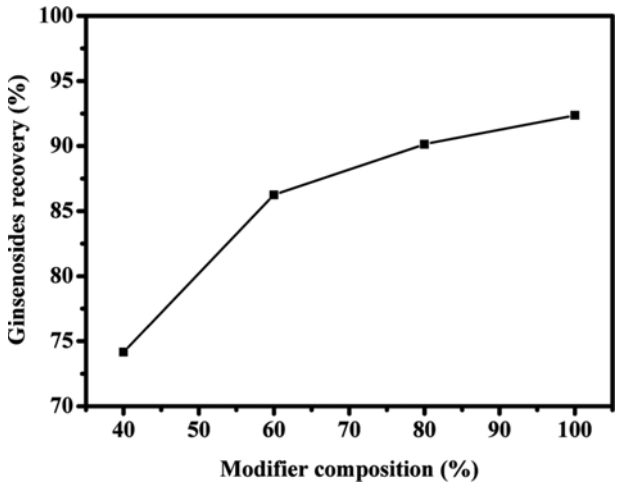

Fig. 10. Effect of the modifier composition on procymidone content and ginsenosides recovery in final products.

Fig. 10 shows that the ginsenosides recovery rate increases from 74.2% to 92.4% with the ethanol concentration increasing from 40% to 100%. The results suggest high solubility of ginsenosides in ethanol. Therefore, absolute ethanol was selected as the optimal modifier composition.

Similarly, the effects of elution pressure, temperature, the flow rate of modifier, elution time on ginsenosides recovery rate were, respectively, investigated to obtain the final optimal elution conditions of ginsenosides as follows: the absolute ethanol as the modifier at a flow rate of 1 mL/min, 20 MPa, 60 °C, 1.5 h and 0.2 L·min^{-1} CO_2 flow rate. After this process, the mean ginsenosides recovery rate can reach 92.5%.

4. Repeated Experiments at the Optimal Conditions

The elution procedures of procymidone removal and ginsenosides recovery were repeated three times under the above determined optimal conditions. The experimental results are shown in Table 2. The average procymidone content is 0.0089 mg/kg in final products, which meets the export standard for ginseng products, and the procymidone removal rate is up to 99.98%. Meanwhile, the average ginsenosides recovery rate reaches 92.5% with a relative standard deviation of 0.80%, which indicates that high procymidone removal rate as well as high ginsenosides recovery rate with good data reproducibility can be achieved using the supercritical fluid elution with resin adsorption processes.

5. Reuse of D-101-1 Resin

In the conventional resin adsorption process, the used resins

Table 2. The experimental results under the optimal conditions

No.	Procymidone content (mg/kg)	Ginsenosides recovery rate (%)
1	0.0087	91.8
2	0.0092	93.2
3	0.0089	92.4
Average	0.0089	92.5
RSD (%)	2.86	0.80

Table 3. The procymidone content and ginsenosides recovery with recycle times under the optimal conditions

Recycle times	Procymidone content (mg/kg)	Ginsenosides recovery (%)
1	0.0085	93.1
2	0.0092	92.2
3	0.0095	92.1
4	0.013	91.8
5	0.038	91.4
6	0.0689	91.0
7	0.1076	89.7

usually need to be regenerated with solvents, which causes a longer production period and higher costs. In comparison, for our RA-SFE method, the used resin will be easily regenerated while procymidone is removed and ginsenosides are recovered from the resin by supercritical CO_2 with the modifier and can be directly reused for the next run without any additional regeneration.

To evaluate the regeneration effect and adsorption performance of the reused resin, the RA-SFE process was run for seven cycle times at the optimal conditions, and the results are listed in Table 3. It demonstrates that the resin always shows excellent adsorption performance during recycling. Procymidone content in final products is still below 0.01 mg/kg and ginsenoside recovery rate remains above 90% even after six recycles of the resin.

CONCLUSION

A method of resin adsorption combined with supercritical fluid elution, or simply called RA-SFE method, has been developed for the removal of procymidone and the recovery of ginsenosides from actual ginseng extracts. D-101-1 resin was chosen and used for the adsorption of procymidone and ginsenosides. Supercritical fluid elution process was followed to remove the adsorbed procymidone from the resin and obtain ginsenoside products, and meanwhile, D-101-1 resin was directly regenerated for reuse. Significantly, the RA-SFE method achieved high procymidone removal rate of 99.98% (or the procymidone content of 0.0089 mg/kg) and high ginsenosides recovery rate of 92.5% in final products at the optimal conditions. Particularly, the resin can be directly reused without additional regeneration and shows prominent performance during recycling. Procymidone content in final products keeps below 0.1 mg/kg and ginsenosides recovery rate keeps above 90% even after six recycles of the resin. This is the first exploration to combine resin adsorption technology with supercritical fluid technology for removal of pesticide residue traces. Compared with conventional resin adsorption-desorption technology, RA-SFE method has advantages of more complete removal of pesticide residues, higher recovery of effective ingredients, less solvent consumption and less time-consuming.

ACKNOWLEDGEMENT

This work was supported by the National Natural Science Foundation of China (21328601).

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