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Method Validation of Silica Dispersive Solid Phase Extraction Combined with Spectrophotometer UV-Vis for the Determination of Allopurinol in Herbal Medicine

Validasi Metode Ekstraksi Fasa Padat Terdispersi menggunakan Silika Kombinasi Spektrofotometer UV-Vis untuk Analisa Allopurinol dalam Jamu

Eviomitta Rizki Amanda[1]*, Anisa Suci Rosmawati[1], Lilik Nurfadlilah[1], Gama Prakoso Buono[2], Yani Ambari[1]

[1]STIKES Rumah Sakit Anwar Medika,
Jl. Raya By Pass Krian, KM. 33, Sidoarjo, Jawa Timur 61263, Indonesia.
[2]PT. PQ Silicas Indonesia
Jl. Rembang Industri Raya No. 24, Pasuruan, Jawa Timur 67152, Indonesia.

*Corresponding author email: eviomittarizki@gmail.com

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ABSTRACT

A facile sample preparation method based on silica dispersive solid-phase extraction combination with spectrophotometer UV-Vis for the extraction of allopurinol in herbal medicine was successfully developed. Silica was used as a solid sorbent. The extraction process was carried out by inserting and dispersing silicas in a 30 mL sample solution that contained allopurinol, then stirred using a hot plate stirrer. At the end of the extraction process, silicas were collected and desorbed using ethanol by utilizing a vortex. The desorption solution was analyzed by spectrophotometer UV-Vis at a maximum wavelength of 250 nm. Several essential parameters such as silica mass, extraction time, desorption time, and pH of sample solution were optimized. The results showed that the optimum extraction condition was achieved: silica mass. 0.8 grams; extraction time, 45 minutes; desorption time, 2 minutes; and pH of sample solution, pH 7. The optimum extraction condition was then applied for the standard curve and analyzed of allopurinol in herbal medicine samples. The results of the method validation method were obtained the correlation coefficient (R^2), 0.9961; the detection limit, 0.6871 ppm; the quantitation limit, 2.2902 ppm, the percent of recovery (% R) in the range of 96.42-110.25%, percent coefficient of variation (% CV) in the range of 0.0361-0.1322%. The application method in 3 real samples showed that the concentrations of allopurinol were 56.0221 ppm, 54.8706 ppm, and 63.6719 ppm, respectively. The values of % R in the analysis of real samples by using the spiking method were obtained in the range of 49.52-89.74%.

Keywords: Allopurinol, dispersive solid phase extraction, herbal medicine, silica, spectrophotometer UV-Vis.

ABSTRAK

Metode preparasi sampel menggunakan ekstraksi fasa padat terdispersi kombinasi spektrofotometer UV-Vis untuk ekstraksi allopurinol dalam sampel jamu berhasil dikembangkan. Silika digunakan sebagai fasa padat yang berperan sebagai adsorben. Proses ekstraksi dilakukan dengan mendispersikan silika dalam 30 mL larutan sampel yang berisi standard allopurinol, kemudian diaduk dengan hotplate stirrer. Pada akhir proses ekstraksi, silika dikumpulkan dan didesorbsi menggunakan pelarut etanol dengan bantuan vortex. Larutan hasil desorpsi dianalisis menggunakan spektrofotometer UV-Vis pada panjang gelombang maksimum 250 nm. Beberapa parameter penting dioptimasi dengan hasil optimasi menunjukkan bahwa massa optimum silika 0.8 gram, waktu ekstraksi optimum 45 menit, waktu desorpsi optimum 2 menit, dan pH larutan sampel optimum pH 7. Kondisi ekstraksi yang optimum kemudian diaplikasikan untuk pembuatan kurva standar dan analisa allopurinol pada sampel jamu. Hasil validasi metode menunjukkan bahwa koefisien korelasi (R^2) 0.9961; limit deteksi 0.6871 ppm; limit kuantitasi 2.2902 ppm; persen recovery (%R) pada rentang 96.42%-110.25%; dan persen koofisien variasi (%KV) pada rentang 0.0361-0.1332%. Aplikasi metode pada 3 sampel jamu menunjukkan bahwa konsentrasi allopurinol dalam sampel jamu masing-masing 56.0221 ppm, 54.8706 ppm dan 63.6719 ppm. Nilai %R dari analisa sampel yang diperoleh menggunakan metode standar adisi berada dalam rentang 49.52%-89.74%.

***Kata kunci**: Allopurinol, ekstraksi fasa padat terdispersi, jamu, silika, spektrofotometer UV-Vis.*

Introduction

Herbal medicine is one of the famous alternative medicine in Indonesia. There is a lot of traditional herbal medicine in Indonesia containing herbs and plant extract. Herbal medicines are trusted to maintain health performance and treat diseases (Elfahmi et al., 2014). However, the use of herbal medicine without certainty dosage can bring negative effects on human health. In the recent few years, the consumption of herbal medicine has increased in Indonesian society which has triggered an abuse of chemical drugs in herbal medicine. Chemical drugs have been added to some herbal medicine to enhance the therapeutic effect. Meanwhile, according to the regulation of the National Agency of Drug and Food Control, herbal medicine should not contain chemical drugs including synthetic chemicals or isolated compounds from medicinal plants (BPOM, 2021).

Allopurinol is one of the chemical drugs which is usually added into herbal medicine for chronic gout treatment (Sivera et al., 2014). Allopurinol is a xanthine oxidase inhibitor drug that will inhibit xanthine oxidase enzyme to produce uric acid (Singh et al., 2017). Long time consumption of allopurinol with uncontrolled dosage will cause several negative effects such as diarrhea, drug

fever, and hematological abnormalities (Pratiwi et al., 2019). Therefore, monitoring and determination of allopurinol in herbal medicine are important to prevent the toxicity effect of allopurinol.

A different analytical method based on spectrometric, chromatography (Ilango et al., 2003), capillary electrophoresis (Kou et al., 2006), and electrochemical detection method have been developed for allopurinol detection (Ladmakhi et al., 2020; Reinders et al., 2007; Rezaei & Rahmanian, 2011). However, since these methods are selective and sensitive, these methods also have several disadvantages such as time-consuming, tedious, requiring expensive instruments, and toxic solvents (Kou et al., 2006; Pratiwi et al., 2019). Another is that the sample preparation method also becomes an important part of the analytical method besides the instrumentation. Sample preparation methods based on green analytical chemistry (GAC) are needed to clean up and preconcentrate analytes from complex matrices. Solid-phase extraction (SPE) is a popular and common technique for selective and rapid sample preparation methods in the analysis of pharmaceuticals and drugs (Kamaruzaman et al., 2017). SPE has good performance such as high percentage of analyte recovery, analyte concentration, highly purified extract, ability to extract analyte over a wide polarity range, ease of automation, compatibility with instrumental analysis, and reduced use of organic solvents (Jagadeesan et al., 2016).

A quick and simple extraction method of SPE derivatives, namely dispersive solid-phase extraction (DSPE) is carried out with dispersed silica as solid sorbent for preconcentration of the target analytes from the sample solution. The unique and interesting property of this method is that the silica particles are directly dispersed in the sample solution, so they can be in direct contact with the analytes. This condition can improve extraction efficiency and achieve good extraction recovery. Silica is abundant material with low environmental toxicity and good absorbance performance. It serves in a negative surface charge above pH 2, allowing for strong adsorption of cations under neutral conditions, and subsequent release of adsorbates in moderately acidic washes (Piątek et al., 2020). Silica is widely applied as sorbent for solid-phase multi residues extraction (Casado et al., 2016; Li et al., 2017; Speltini et al., 2017). According to the performance, silica has been applied in a lot of fields such as for the adsorption of dyes, drug molecules, protein, and heavy metals (Barczak, 2019; Han et al., 2011; Li et al., 2019). In this work, silica was applied as a solid sorbent for extraction and preconcentration of allopurinol in herbal medicine samples by dispersive solid-phase extraction. Several important parameters including the mass of silica, extraction time, desorption time, dan sample pH have

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been investigated. The best extraction conditions, the performance of the developed method was validated.

Research Method

Materials and Instruments

All chemicals used were analytical grade. All solutions were prepared using aqua demineralization from Brata Chem. Allopurinol was obtained from First Medipharma. Sodium hydroxide, hydrochloric acid, Silica (SiO_2), and ethanol were obtained from Merck. Instruments used were hotplate stirrer (Bione), vortex (Thermo Scientific). Spectrophotometer UV-Vis Genesys 10S (Thermo Scientific).

Preparation of Silica Sorbent

Preparation of silica sorbent as follow Ramadani (2018). Silica sorbents were prepared by dipping SiO_2 in hydrochloric acid 1M. Then, the solution was heated and stirred for 60 minutes then continued to dry overnight until the silica powders were completely suspended. Suspended silicas were separated from the filtrate and washed using demineralized water until to get neutral pH. Silicas were dried in the oven with a temperature of 100 ℃ for 6 hours.

Silica Dispersive Solid Phase Extraction (DSPE)

Stock solutions of allopurinol at a concentration of 1000 µg/mL were prepared in methanol and were stored in the refrigerator. The working solution of allopurinol for studying the extraction performance was prepared by dissolving the standard solution of allopurinol as the model analytes ata concentration of 6 µg/mL in demineralized water. The experimental silica DSPE setup is illustrated in **Figure 1**.

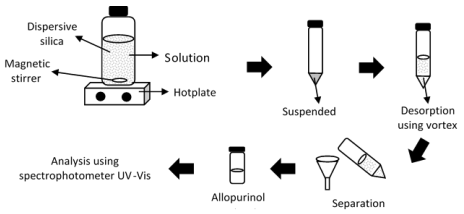

Figure 1. Set-up experimental Silica DSPE

The water sample (30 ml) was transferred into 50 ml Beaker glass. Furtehrmore, a magnetic stirrer and silica powder were placed into the sample. The extraction process was started by stirring the sample solution at 800 rpm. At the end of the extraction process, silicas were collected and desorbed using ethanol by utilizing a vortex. The desorption solution was analyzed by spectrophotometer UV-Vis at a wavelength of 250 nm. Several important parameters such as silica mass, extraction time, desorption time, and pH of sample solution were optimized.

Validation of Analytical Method

The developed method was evaluated for linearity, recovery, coefficient variation, the limit of detection (LOD), and the limit of quantification (LOQ) before being applied to the real sample analysis.

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Sample Analysis

Three kinds of herbal medicines for gout arthritis in various brands was collected from a local retail shop. The sample was determined by qualitative analysis (thin layer chromatography) before applied for quantitative analysis using the silica DSPE method. The samples (positive containing allopurinol) were dissolved in demineralized water. Suspended particles and filtrate were separated by filtration. The filtrate was collected and transferred into Beaker glass. Then, the samples were extracted using silica DSPE.

Results and Discussion

Activation of Silica Sorbent

The addition of hydrochloric acid into SiO_2 aimed to remove metal oxides that blocked the surface and porous of SiO_2. This treatment could increase the capacity of porous and surface area for adsorption. Chemical treatment using acid or basic had a function to open the porous, remove the purityy, and rearrange the exchanged atom (Al Muttaqii et al., 2019). The addition of acidic solution into SiO_2 also could increase the hydrophobicity of SiO_2 that occurs the decreasing of water adsorption (Lu *et al.*, 2009).

Optimization of Silica DSPE.

The optimization procedure was carried out using demineralized water samples spiked with allopurinol to give a concentration of 6 µg/mL (*n*=3).

Mass of silica is one of the important parameters to evaluate the absorption capacity of the silica DSPE. Various mass of silica in the range of 0.6 gram - 1 gram was investigated toward the extraction efficiency. The results showed that the lowest mass of silica (0.6 gram) gave the lowest extraction efficiency. On the other hand, a silica mass of 0.8 grams showed the best extraction efficiency. Therefore, a silica mass of 0.8 grams was chosen for subsequent studies. The silicas played an adsorbent role in this study. The absorbance of allopurinol increased with the increase of the mass of silica and reached an optimum absorbance in 0.8 gram (**Figure 2**).

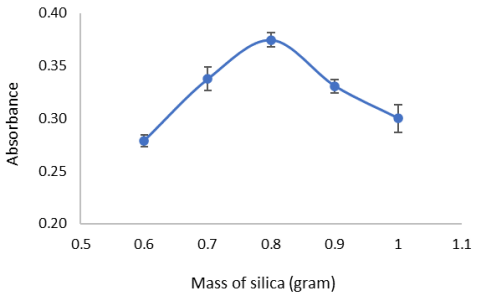

Figure 2. Optimization of the mass of silica

Extraction efficiency improved with the increasing amount of silica. This may be due to the enhancement in the active sites and surface area. The increasing number of active sites on the surface of the adsorbent should be sufficient to trap the total amount of the target compound (Sowa et al., 2018). Activated silica using acidic solution could open the size of porous and surface area. It was also increased the hydrophobicity of silica, which was

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decreasing water sorption and increasing analyte sorption. However, the larger amount of silica could decrease the extraction efficiency because a higher mass of silica triggered collision between particles, thus it could release the adsorbed analyte (Lu *et al.*, 2019). Therefore, the mass of silica of 0.8 gram was adopted in the subsequent experiments.

The bond strength of allopurinol in silica sorbents is time-dependent. The partition of the analyte between the solution and the sorbent is a dynamic process and precise timing is required to obtain equilibrium (Pashaei et al., 2017). Extraction times in the range of 15 to 75 minutes were investigated to achieve the optimum equilibrium time. The optimum equilibrium time was reached in 45 minutes (**Figure 3**).

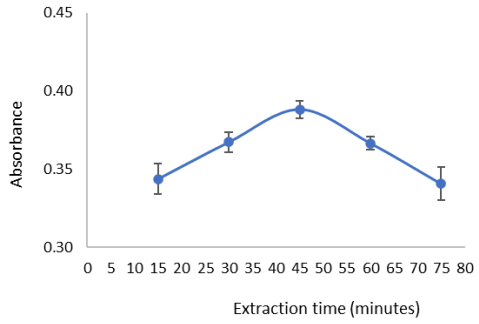

Figure 3. Optimization of extraction time

The longer extraction time cause allopurinol tended to be entrapped in closed interstitial spaces between aggregates and caused incomplete desorption (Loh et al., 2013). Therefore, an extraction time of 45 minutes was chosen for subsequent experiments.

Desorption time is one of the important parameters to achieve good efficiency by determining the time required for mass transfer of analytes from sorbent to the organic phase (desorption solvent). Hence, it was optimized by increasing the shaking time from 1 to 5 minutes. The Vortex method was used to desorb allopurinol from the silica sorbent. It showed that the maximum desorption time of the analyte was achieved within 2 minutes of a vortex (**Figure 4**).

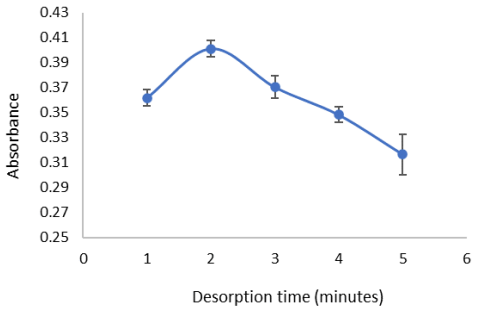

Figure 4. Optimization of desorption time

This indicated that 2 minutes is sufficient to elute allopurinol from the surface of the silica sorbent. Desorption time has closely related to the partition of analytes between desorption solvent and sorbent to obtain equilibrium conditions. Longer desorption time decreased the efficiency might be due to the saturation of desorption solvent. The decrease in absorbance may also be caused by re-adsorption of the target analyte from the sorbent to the sample (Rozaini et al., 2019). Therefore, a desorption time of 2 minutes was chosen for subsequent experiments.

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The pH of the sample solution plays an important role to get the best extraction efficiency because it can influence the determination of the molecular or ionic form of the target analyte and the charge of the silica sorbent. Thus, in this experiment, the pH of the sample solution was carried out in the pH range of 3 to 11. As the results, it can be shown that the maximum extraction efficiency of the silica for allopurinol was obtained at pH 7, whereas the lowest efficiency was at pH 3 (**Figure 5**).

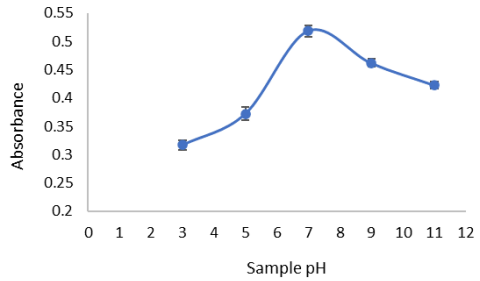

Figure 5. Optimization of sample pH

Method Validation

Method validation was carried out based on the calibration curve of allopurinol in demineralized water under optimum extraction conditions. The analytical evaluation was carried out based on the coefficient of correlation (R^2), the limit of detection (LOD), the limit of quantification (LOQ), % recovery (%R), and % coefficient variation (%KV). The results were shown in **Table 1**.

The results of the method validation method were obtained the correlation coefficient, 0.9961; the detection limit, 0.6871 µg/mL; the quantitation limit, 2.2902 µg/mL, the percent of recovery (% R) in the range of 96.42-110.25%, percent coefficient of variation (% CV) in the range of 0.0361-0.1322%.

Tabel 1. Method validation data of silica DSPE

Parameter	Value
Calibration range (µg/mL)	2 - 10
R^2	0.9961
LOD (µg/mL)	0.6871
LOQ (µg/mL)	2.2902
Recovery (%)	96.42 – 110.25
RSD* (%)	0.0026 – 0.0043
KV* (%)	0.0331 – 0.1323

*RSD = Relative standard deviation, KV = coefficient variation

Analysis of Real Sample using Silica DSPE

The Silica DSPE was applied for the determination of allopurinol in herbal medicine samples. Before quantitative identification, herbal medicine samples were evaluated by the qualitative identification thin layer chromatography (TLC) method. The results were shown in **Table 2**. The positive samples were determined the concentration of allopurinol using silica DSPE method combination with spectrophotometer UV-Vis.

Table 2. Qualitative analysis of allopurinol using TLC method

Sample	Retardation factor (Rf)		Result
	Control	Sample	
A	0.5125	0.4925	+
B	0.5125	0.5025	+
C	0.5125	0.4925	+
D	0.5125	0.2625	-
E	0.5125	0.8125	-

Table 3. Quantitative analysis of allopurinol using silica DSPE-Spectrophotometer UV-Vis

Sample	Concentration of allopurinol (µg/mL)*, %RSD	%R and % RSD Spike		
		2 µg/mL	6 µg/mL	10 µg/mL
A	56.0221; 0.0102	49.52; 0.0094	68.55; 0.0081	80.50; 0.0574
B	54.8706; 0.0306	88.17; 0.0161	73.82; 0.0182	78.04; 0.0191
C	63.6719; 0.0227	89.74; 0.0377	75.39; 0.0791	84.82; 0.0369

*) Dilution factor ten times

The quantitative results were shown in **Table 3.** The results showed that between five samples of herbal medicine, there are three samples positive containing allopurinol as chemical drugs in herbal medicine, namely sample A, sample B, and sample C. Silica DSPE method was selective, efficient, and suitable for quantitative analysis of allopurinol in herbal medicine samples, with the %R in spiking method in the range of 49.52 – 89.74. The results of the decrease in %R indicated that other components in the herbal medicine inhibited the silica porous silica. This makes the ability of silica to absorb analytes also decreases

Conclusion

The present study revealed that silica DSPE is suitable for the determination of chemical drugs in herbal medicine. This method has eliminated classical separation techniques such as liquid-liquid extraction and solid-phase extraction. This method is capable to stand as an alternative green analytical method for the miniaturization of solid-phase extraction.

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by Eviomitta Rizki Amanda

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Method Validation of Silica Dispersive Solid Phase Extraction Combined with Spectrophotometer UV-Vis for the Determination of Allopurinol in Herbal Medicine

Validasi Metode Ekstraksi Fasa Padat Terdispersi menggunakan Silika Kombinasi Spektrofotometer UV-Vis untuk Analisa Allopurinol dalam Jamu

Eviomitta Rizki Amanda[1]*, Anisa Suci Rosmawati[1], Lilik Nurfadlilah[1], Gama Prakoso Buono[2], Yani Ambari[1]

[1]STIKES Rumah Sakit Anwar Medika,
Jl. Raya By Pass Krian, KM. 33 Sidoarjo, Jawa Timur 61263, Indonesia.
[2]PT. PQ Silicas Indonesia
Jl. Rembang Industri Raya No. 24, Pasuruan, Jawa Timur 67152, Indonesia.

*Corresponding author email: eviomittarizki@gmail.com

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ABSTRACT

A facile sample preparation method based on silica dispersive solid-phase extraction combination with spectrophotometer UV-Vis for the extraction of allopurinol in herbal medicine was successfully developed. Silica was used as a solid sorbent. The extraction process was carried out by inserting and dispersing silicas in a 30 mL sample solution that contained allopurinol, then stirred using a hot plate stirrer. At the end of the extraction process, silicas were collected and desorbed using ethanol by utilizing a vortex. The desorption solution was analyzed by spectrophotometer UV-Vis at a maximum wavelength of 250 nm. Several essential parameters such as silica mass, extraction time, desorption time, and pH of sample solution were optimized. The results showed that the optimum extraction condition was achieved: silica mass. 0.8 grams; extraction time, 45 minutes; desorption time, 2 minutes; and pH of sample solution, pH 7. The optimum extraction condition was then applied for the standard curve and analyzed of allopurinol in herbal medicine samples. The results of the method validation method were obtained the correlation coefficient (R^2), 0.9961; the detection limit, 0.6871 ppm; the quantitation limit, 2.2902 ppm, the percent of recovery (% R) in the range of 96.42-110.25%, percent coefficient of variation (% CV) in the range of 0.0361-0.1322%. The application method in 3 real samples showed that the concentrations of allopurinol were 56.0221 ppm, 54.8706 ppm, and 63.6719 ppm, respectively. The values of % R in the analysis of real samples by using the spiking method were obtained in the range of 49.52-89.74%.

Keywords: Allopurinol, dispersive solid phase extraction, herbal medicine, silica, spectrophotometer UV-Vis.

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ABSTRAK

Metode preparasi sampel menggunakan ekstraksi fasa padat terdispersi kombinasi spektrofotometer UV-Vis untuk ekstraksi allopurinol dalam sampel jamu berhasil dikembangkan. Silika digunakan sebagai fasa padat yang berperan sebagai adsorben. Proses ekstraksi dilakukan dengan mendispersikan silika dalam 30 mL larutan sampel yang berisi standard allopurinol, kemudian diaduk dengan hotplate stirrer. Pada akhir proses ekstraksi, silika dikumpulkan dan didesorbsi menggunakan pelarut etanol dengan bantuan vortex. Larutan hasil desorpsi dianalisis menggunakan spektrofotometer UV-Vis pada panjang gelombang maksimum 250 nm. Beberapa parameter penting dioptimasi dengan hasil optimasi menunjukkan bahwa massa optimum silika 0.8 gram, waktu ekstraksi optimum 45 menit, waktu desorpsi optimum 2 menit, dan pH larutan sampel optimum pH 7. Kondisi ekstraksi yang optimum kemudian diaplikasikan untuk pembuatan kurva standar dan analisa allopurinol pada sampel jamu. Hasil validasi metode menunjukkan bahwa koefisien korelasi (R^2) 0.9961; limit deteksi 0.6871 ppm; limit kuantitasi 2.2902 ppm; persen recovery (%R) pada rentang 96.42%-110.25%; dan persen koofisien variasi (%KV) pada rentang 0.0361-0.1332%. Aplikasi metode pada 3 sampel jamu menunjukkan bahwa konsentrasi allopurinol dalam sampel jamu masing-masing 56.0221 ppm, 54.8706 ppm dan 63.6719 ppm. Nilai %R dari analisa sampel yang diperoleh menggunakan metode standar adisi berada dalam rentang 49.52%-89.74%.

***Kata kunci**: Allopurinol, ekstraksi fasa padat terdispersi, jamu, silika, spektrofotometer UV-Vis.*

Introduction

Herbal medicine is one of the famous alternative medicine in Indonesia. There is a lot of traditional herbal medicine in Indonesia containing herbs and plant extract. Herbal medicines are trusted to maintain health performance and treat diseases (Elfahmi et al., 2014). However, the use of herbal medicine without certainty dosage can bring negative effects on human health. In the recent few years, the consumption of herbal medicine has increased in Indonesian society which has triggered an abuse of chemical drugs in herbal medicine. Chemical drugs have been added to some herbal medicine to enhance the therapeutic effect. Meanwhile, according to the regulation of the National Agency of Drug and Food Control, herbal medicine should not contain chemical drugs including synthetic chemicals or isolated compounds from medicinal plants (BPOM, 2021).

Allopurinol is one of the chemical drugs which is usually added into herbal medicine for chronic gout treatment (Sivera et al., 2014). Allopurinol is a xanthine oxidase inhibitor drug that will inhibit xanthine oxidase enzyme to produce uric acid (Singh et al., 2017). Long time consumption of allopurinol with uncontrolled dosage will cause several negative effects such as diarrhea, drug

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fever, and hematological abnormalities (Pratiwi et al., 2019). Therefore, monitoring and determination of allopurinol in herbal medicine are important to prevent the toxicity effect of allopurinol.

A different analytical method based on spectrometric, chromatography (Ilango et al., 2003), capillary electrophoresis (Kou et al., 2006), and electrochemical detection method have been developed for allopurinol detection (Ladmakhi et al., 2020; Reinders et al., 2007; Rezaei & Rahmanian, 2011). However, since these methods are selective and sensitive, these methods also have several disadvantages such as time-consuming, tedious, requiring expensive instruments, and toxic solvents (Kou et al., 2006; Pratiwi et al., 2019). Another is that the sample preparation method also becomes an important part of the analytical method besides the instrumentation. Sample preparation methods based on green analytical chemistry (GAC) are needed to clean up and preconcentrate analytes from complex matrices. Solid-phase extraction (SPE) is a popular and common technique for selective and rapid sample preparation methods in the analysis of pharmaceuticals and drugs (Kamaruzaman et al., 2017). SPE has good performance such as high percentage of analyte recovery, analyte concentration, highly purified extract, ability to extract analyte over a wide polarity range, ease of automation, compatibility with instrumental analysis, and reduced use of organic solvents (Jagadeesan et al., 2016).

A quick and simple extraction method of SPE derivatives, namely dispersive solid-phase extraction (DSPE) is carried out with dispersed silica as solid sorbent for preconcentration of the target analytes from the sample solution. The unique and interesting property of this method is that the silica particles are directly dispersed in the sample solution, so they can be in direct contact with the analytes. This condition can improve extraction efficiency and achieve good extraction recovery. Silica is abundant material with low environmental toxicity and good absorbance performance. It serves in a negative surface charge above pH 2, allowing for strong adsorption of cations under neutral conditions, and subsequent release of adsorbates in moderately acidic washes (Piątek et al., 2020). Silica is widely applied as sorbent for solid-phase multi residues extraction (Casado et al., 2016; Li et al., 2017; Speltini et al., 2017). According to the performance, silica has been applied in a lot of fields such as for the adsorption of dyes, drug molecules, protein and heavy metals (Barczak, 2019; Han et al., 2011; Li et al., 2019). In this work, silica was applied as a solid sorbent for extraction and preconcentration of allopurinol in herbal medicine samples by dispersive solid-phase extraction. Several important parameters including the mass of silica, extraction time, desorption time, dan sample pH have

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been investigated. The best extraction conditions, the performance of the developed method was validated.

Research Method

Materials and Instruments

All chemicals used were analytical grade. All solutions were prepared using aqua demineralization from Brata Chem. Allopurinol was obtained from First Medipharma. Sodium hydroxide, hydrochloric acid, Silica (SiO_2), and ethanol were obtained from Merck. Instruments used were hotplate stirrer (Bione), vortex (Thermo Scientific). Spectrophotometer UV-Vis Genesys 10S (Thermo Scientific).

Preparation of Silica Sorbent

Preparation of silica sorbent as follow Ramadani (2018). Silica sorbents were prepared by dipping SiO_2 in hydrochloric acid 1M. Then, the solution was heated and stirred for 60 minutes then continued to dry overnight until the silica powders were completely suspended. Suspended silicas were separated from the filtrate and washed using demineralized water until to get neutral pH. Silicas were dried in the oven with a temperature of 100 ℃ for 6 hours.

Silica Dispersive Solid Phase Extraction (DSPE)

Stock solutions of allopurinol at a concentration of 1000 µg/mL were prepared in methanol and were stored in the refrigerator. The working solution of allopurinol for studying the extraction performance was prepared by dissolving the standard solution of allopurinol as the model analytes ata concentration of 6 µg/mL in demineralized water. The experimental silica DSPE setup is illustrated in **Figure 1**.

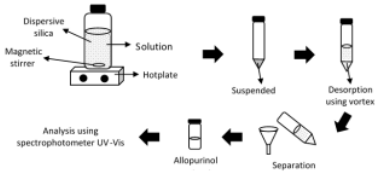

Figure 1. Set-up experimental Silica DSPE

The water sample (30 ml) was transferred into 50 ml Beaker glass. Furtehrmore, a magnetic stirrer and silica powder were placed into the sample. The extraction process was started by stirring the sample solution at 800 rpm. At the end of the extraction process, silicas were collected and desorbed using ethanol by utilizing a vortex. The desorption solution was analyzed by spectrophotometer UV-Vis at a wavelength of 250 nm. Several important parameters such as silica mass, extraction time, desorption time, and pH of sample solution were optimized.

Validation of Analytical Method

The developed method was evaluated for linearity, recovery, coefficient variation, the limit of detection (LOD), and the limit of quantification (LOQ) before being applied to the real sample analysis.

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Sample Analysis

Three kinds of herbal medicines for gout arthritis in various brands was collected from a local retail shop. The sample was determined by qualitative analysis (thin layer chromatography) before applied for quantitative analysis using the silica DSPE method. The samples (positive containing allopurinol) were dissolved in demineralized water. Suspended particles and filtrate were separated by filtration. The filtrate was collected and transferred into Beaker glass. Then, the samples were extracted using silica DSPE.

Results and Discussion

Activation of Silica Sorbent

The addition of hydrochloric acid into SiO_2 aimed to remove metal oxides that blocked the surface and porous of SiO_2. This treatment could increase the capacity of porous and surface area for adsorption. Chemical treatment using acid or basic had a function to open the porous, remove the purityy, and rearrange the exchanged atom (Al Muttaqii et al., 2019). The addition of acidic solution into SiO_2 also could increase the hydrophobicity of SiO_2 that occurs the decreasing of water adsorption (Lu *et al.*, 2009).

Optimization of Silica DSPE.

The optimization procedure was carried out using demineralized water samples spiked with allopurinol to give a concentration of 6 µg/mL (*n*=3).

Mass of silica is one of the important parameters to evaluate the absorption capacity of the silica DSPE. Various mass of silica in the range of 0.6 gram - 1 gram was investigated toward the extraction efficiency. The results showed that the lowest mass of silica (0.6 gram) gave the lowest extraction efficiency. On the other hand, a silica mass of 0.8 grams showed the best extraction efficiency. Therefore, a silica mass of 0.8 grams was chosen for subsequent studies. The silicas played an adsorbent role in this study. The absorbance of allopurinol increased with the increase of the mass of silica and reached an optimum absorbance in 0.8 gram (**Figure 2**).

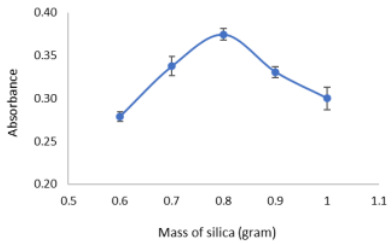

Figure 2. Optimization of the mass of silica

Extraction efficiency improved with the increasing amount of silica. This may be due to the enhancement in the active sites and surface area. The increasing number of active sites on the surface of the adsorbent should be sufficient to trap the total amount of the target compound (Sowa et al., 2018). Activated silica using acidic solution could open the size of porous and surface area. It was also increased the hydrophobicity of silica, which was

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decreasing water sorption and increasing analyte sorption. However, the larger amount of silica could decrease the extraction efficiency because a higher mass of silica triggered collision between particles, thus it could release the adsorbed analyte (Lu *et al.*, 2019). Therefore, the mass of silica of 0.8 gram was adopted in the subsequent experiments.

The bond strength of allopurinol in silica sorbents is time-dependent. The partition of the analyte between the solution and the sorbent is a dynamic process and precise timing is required to obtain equilibrium (Pashaei et al., 2017). Extraction times in the range of 15 to 75 minutes were investigated to achieve the optimum equilibrium time. The optimum equilibrium time was reached in 45 minutes (**Figure 3**).

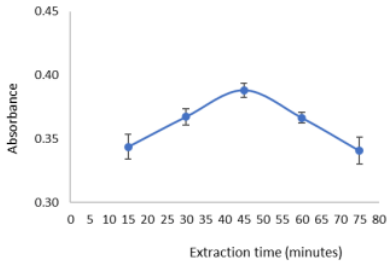

Figure 3. Optimization of extraction time

The longer extraction time cause allopurinol tended to be entrapped in closed interstitial spaces between aggregates and caused incomplete desorption (Loh et al., 2013). Therefore, an extraction time of 45 minutes was chosen for subsequent experiments.

Desorption time is one of the important parameters to achieve good efficiency by determining the time required for mass transfer of analytes from sorbent to the organic phase (desorption solvent). Hence, it was optimized by increasing the shaking time from 1 to 5 minutes. The Vortex method was used to desorb allopurinol from the silica sorbent. It showed that the maximum desorption time of the analyte was achieved within 2 minutes of a vortex (**Figure 4**).

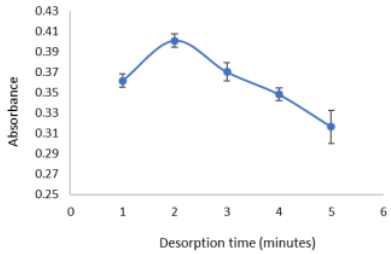

Figure 4. Optimization of desorption time

This indicated that 2 minutes is sufficient to elute allopurinol from the surface of the silica sorbent. Desorption time has closely related to the partition of analytes between desorption solvent and sorbent to obtain equilibrium conditions. Longer desorption time decreased the efficiency might be due to the saturation of desorption solvent. The decrease in absorbance may also be caused by re-adsorption of the target analyte from the sorbent to the sample (Rozaini et al., 2019). Therefore, a desorption time of 2 minutes was chosen for subsequent experiments.

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The pH of the sample solution plays an important role to get the best extraction efficiency because it can influence the determination of the molecular or ionic form of the target analyte and the charge of the silica sorbent. Thus, in this experiment, the pH of the sample solution was carried out in the pH range of 3 to 11. As the results, it can be shown that the maximum extraction efficiency of the silica for allopurinol was obtained at pH 7, whereas the lowest efficiency was at pH 3 (**Figure 5**).

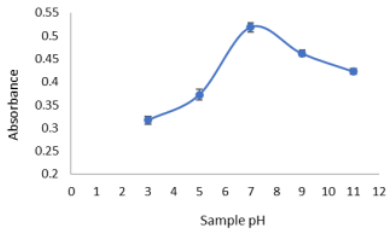

Figure 5. Optimization of sample pH

Method Validation

Method validation was carried out based on the calibration curve of allopurinol in demineralized water under optimum extraction conditions. The analytical evaluation was carried out based on the coefficient of correlation (R^2), the limit of detection (LOD), the limit of quantification (LOQ), % recovery (%R), and % coefficient variation (%KV). The results were shown in **Table 1**.

The results of the method validation method were obtained the correlation coefficient, 0.9961; the detection limit, 0.6871 µg/mL; the quantitation limit, 2.2902 µg/mL, the percent of recovery (% R) in the range of 96.42-110.25%, percent coefficient of variation (% CV) in the range of 0.0361-0.1322%.

Tabel 1. Method validation data of silica DSPE

Parameter	Value
Calibration range (µg/mL)	2 - 10
R^2	0.9961
LOD (µg/mL)	0.6871
LOQ (µg/mL)	2.2902
Recovery (%)	96.42 – 110.25
RSD* (%)	0.0026 – 0.0043
KV* (%)	0.0331 – 0.1323

*RSD = Relative standard deviation, KV = coefficient variation

Analysis of Real Sample using Silica DSPE

The Silica DSPE was applied for the determination of allopurinol in herbal medicine samples. Before quantitative identification, herbal medicine samples were evaluated by the qualitative identification thin layer chromatography (TLC) method. The results were shown in **Table 2**. The positive samples were determined the concentration of allopurinol using silica DSPE method combination with spectrophotometer UV-Vis.

Table 2. Qualitative analysis of allopurinol using TLC method

Sample	Retardation factor (Rf)		Result
	Control	Sample	
A	0.5125	0.4925	+
B	0.5125	0.5025	+
C	0.5125	0.4925	+
D	0.5125	0.2625	-
E	0.5125	0.8125	-

Table 3. Quantitative analysis of allopurinol using silica DSPE-Spectrophotometer UV-Vis

Sample	Concentration of allopurinol (µg/mL)*, %RSD	%R and % RSD Spike		
		2 µg/mL	6 µg/mL	10 µg/mL
A	56.0221; 0.0102	49.52; 0.0094	68.55; 0.0081	80.50; 0.0574
B	54.8706; 0.0306	88.17; 0.0161	73.82; 0.0182	78.04; 0.0191
C	63.6719; 0.0227	89.74; 0.0377	75.39; 0.0791	84.82; 0.0369

*) Dilution factor ten times

The quantitative results were shown in **Table 3.** The results showed that between five samples of herbal medicine, there are three samples positive containing allopurinol as chemical drugs in herbal medicine, namely sample A, sample B, and sample C. Silica DSPE method was selective, efficient, and suitable for quantitative analysis of allopurinol in herbal medicine samples, with the %R in spiking method in the range of 49.52 – 89.74. The results of the decrease in %R indicated that other components in the herbal medicine inhibited the silica porous silica. This makes the ability of silica to absorb analytes also decreases

Conclusion

The present study revealed that silica DSPE is suitable for the determination of chemical drugs in herbal medicine. This method has eliminated classical separation techniques such as liquid-liquid extraction and solid-phase extraction. This method is capable to stand as an alternative green analytical method for the miniaturization of solid-phase extraction.

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