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Original Research Article

Solid-phase Extraction of Valproic Acid Using a Surfaced Imprinted Silica Gel Adsorbent

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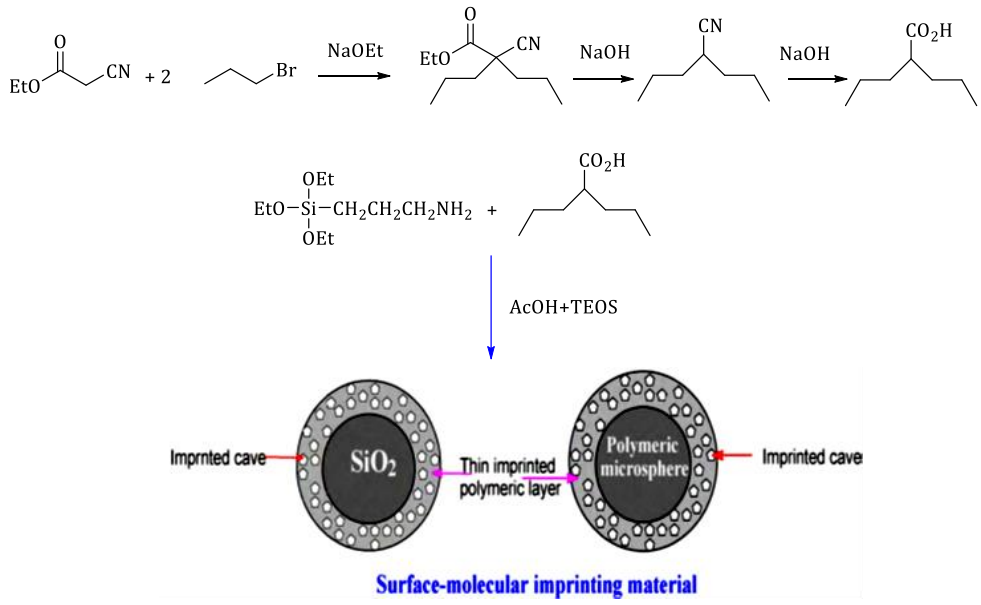
ABSTRACT

Using a solid-phase extraction for the determination of VPA, this study aimed to prepare a valproic acid (VPA) imprinted silica gel adsorbent by surface molecular imprinting technique. VPA-imprinted silica adsorbent was characterized by FTIR spectroscopy. The VPA adsorption from solutions was studied in SPE mode. All influenced parameters on adsorption efficiency, including the elution concentration, MIP amount, VPA concentration, pH and salting effect, sample flow rate, column performance repeatability (relative standard deviation) were optimized independently. The prepared adsorbent showed significant adsorption capacity and selectivity for VPA. In the condition of sodium hydroxide solution (0.1 M), MIP polymer (250 mg), VPA (10^{-4}M), sample flow rate (1 ml min^{-1}), pH around 2-6 in the presence of 4 % NaCl, total VPA retention showed better reproducibility than 5%. Recovery of VPA was about 94.6 to 98.1% and the relative standard deviation was less than 5.69%. These results demonstrated that the prepared adsorbent can be used to measure VPA in biological samples.

GRAPHICAL ABSTRACT



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Introduction

Epilepsy is one of the most common diseases affecting people around the world. It is characterized by tardive dyskinesia, tremor, muscle rigidity, and also has numerous neurological, cognitive, and psychosocial consequences [1].

Valproic acid (2-propyl-pentanoic acid, VPA) is one of the most common drugs for epilepsy and seizures treatment [2]. However, it has a narrow therapeutic window in the range of 50–100, and toxicity starts at 150 mg/l [3]. Therefore, the measurement of VPA seems important.

Sample preparation methods before measuring organic chemicals, such as drugs are the most important step in analytical methods [4]. The free fraction of VPA in plasma has been determined by various methods, including immunoassay [5], high-performance liquid chromatography (HPLC) [6, 7], high-performance liquid chromatography-mass spectrometry (UHPLC-MS) [8, 9], and potentiometric methods [10, 11]. Current trace analyses are sensitive, rapid, selective, and cost-effective [12].

Because of economic considerations and the high efficiency, the molecularly imprinted polymers (MIPs) method has received much attention today [13]. MIP is a synthetic polymer that has the property of selective molecular recognition due to having known locations in the polymer matrix that complement the analyte molecule, commonly called the template [14]. MIPs have been used to develop electrochemical sensors as a highly selective diagnostic element [15].

Combining SPE with MIPs has led to a new method called molecularly-imprinted polymers solid-phase extraction (MISPE) [16]. Even though MIPs showed many advantages, they still have problems including imperfect deletion of the template and low use of binding sites and slow mass transfer [17]. So, surface molecular imprinting technology has attracted much attention [18] for the following characteristics: High surface-to-volume ratio, more accessible sites, and faster binding kinetics [19, 20]. Usually, to investigate the physicochemical properties of MIPs, Fourier transforms infrared (FTIR) is used [21].

The MIPs-based potentiometric has been applied in the organic, environment, food and beverage examination, and drug. However, so far no report is available on the MIPs-based potentiometric sensor which is applied to the assurance of VPA [22].

The aim of this study was accordingly a simple molecularly imprinted silica gel adsorbent preparation using a surface imprinting technique to determine the VPA in samples for use in the SPE procedure.

Material and methods

All reagents including silica gel (2-25 μm in particle size (Merck, Germany)), valproic acid (VPA) (Merck, Germany), 3-aminopropyl triethoxysilane (APS(Merck, Germany)), tetra ethoxy silane (TEOS(Merck, Germany)), acetic acid (HAc(Merck, Germany)), methanol, hydrochloric acid (Merck, Germany), and sodium hydroxide (Merck, Germany) were analytically equivalent. A commercial pharmaceutical sample containing 250 mg of VPA was purchased from a local pharmacy in Ilam, Iran (Abidi. Co).

Instruments

FTIR spectra were recorded by the FTIR spectrometer (Shimadzu, F8400, Japan). The VPA determination was done by a potentiometer (Lab Junction Potentiometer with Stirrer (Digital), Model: LJ-118/S).

VPA- imprinted silica gel adsorbent preparation & characterization

The silica gel surfaces activation was done by reflux of silica gel (10 g, 80–120 mesh) with 100 ml of HCL (6 M) for 6-8 h under stirring. Then to neutralize, it was filtered and washed by doubly distilled water several times and dried at 70 °C for 8 h [23].

VPA-imprinted silica gel adsorbent was prepared by VPA dissolving (0.5 ml, 10^{-2} M) in methanol (40 ml) under stirring and heating, then APS (2.5 ml) was added. After 30 min, the silica gel was

added. Then TEOS (5 ml, 10 min stirring) and then acetic acid (1.5 ml, 1 M) was added, followed by the stirring of the mixture for 20 h. After filtration and being rinsed with water, the dried powder was then stirred with 25 ml of methanol and 25 ml of HCL (1 M) solution for 3 h. Next, the precipitate was filtered and washed 5-6 times with methanol (25 ml) and of HCL (25 ml, 6 M) solution and then washed 5-6 times with sodium hydroxide (5%) to completely neutralize the precipitate. The precipitate was finally washed with pure methanol to remove the drug residue [24].

The final product was characterized by FTIR. FT-IR spectrometer recorded the IR spectra (4000–400 cm^{-1}) on an FTIR spectrometer (Shimadzu, F8400, Japan) as a KBr pellet [22].

Solid-phase extraction procedure

VPA Adsorption in solutions was evaluated in SPE mode. Glass columns (I.D. 1 cm) were manually filled with the final product (250) mg and washed with HCL (0.01 M, 3-4 times). After preconditioning, pure methanol (1 ml) and then the solvent (1 ml, water) were inserted into the column. Then, 20 ml of the 10^{-5} M sample solution was passed through it and collected at the end of the column for analysis. The sodium hydroxide detergent solution (0.1 M) was then transferred and collected for analysis. The samples were analyzed by the potentiometric method [25].

Evaluation of analytical performance

Based on the external standard method, quantification was carried out. For this purpose, before and after passing through the column, the potential of VPA solution (10^{-5} mM as the standard solution) was measured [26].

Extraction conditions Optimization

To obtain the optimal preconcentration conditions, the effect of the eluent concentration, amount of MIP, sample volume, sample pH, ambient ionic strength (salting effect), rate of passage of the sample solution, and column performance reproducibility (relative standard deviation) were examined. All parameters were optimized independently and the concentrations of the analytes were determined potentiometrically.

Interference study

The influence of some interference species (different compounds often present in the pharmaceutical sample) on the determination of VPA was evaluated. For this purpose, at specific intervals (20 seconds) the potentials of 10^{-2}, 10^{-3}, 10^{-4}, 10^{-5}, 10^{-6} M VPA solutions (containing 0.1 M sodium, potassium, magnesium, calcium, glucose, and uric acid solutions), using control Ag/AgCl electrodes were measured by a potentiometer and selectivity coefficients were calculated. Also, to investigate the potentiometric behavior of the intrusive ions, at specific time intervals (20 s), the potentials of 10^{-2}, 10^{-3}, 10^{-4}, 10^{-5}, 10^{-6} mM sodium, potassium, magnesium, and calcium solutions were determined [27].

Analytical performance and application

For this purpose, 10 tablets of VPA (containing 145 mg of VPA, 333 mg of sodium valproate, calcium chloride, and silica) were weighed and powdered. An exact weight ratio of powder (equivalent to five mg of the active ingredient) was dissolved in sodium hydroxide solution (5 ml). The solution was completely uniformed and filtered. Then, before measurement, the prepared solutions were diluted appropriately for linear measurement. Next, at specified intervals (20 s), the potentials of 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4}, 10^{-3}, and 10^{-2} mM solutions of the drug were measured by a potentiometer.

Result and Dissection

Preparation and Characterization of VPA-imprinted silica gel adsorbent

FT-IR spectra were taken from the initial silica gel and activated silica gel for confirming its activation. The reduction of the absorption spectrum of hydroxyl in the region of 3200-3700

cm^{-1}, indicated that silica gel was activated by HCL (Figure 1a and b).

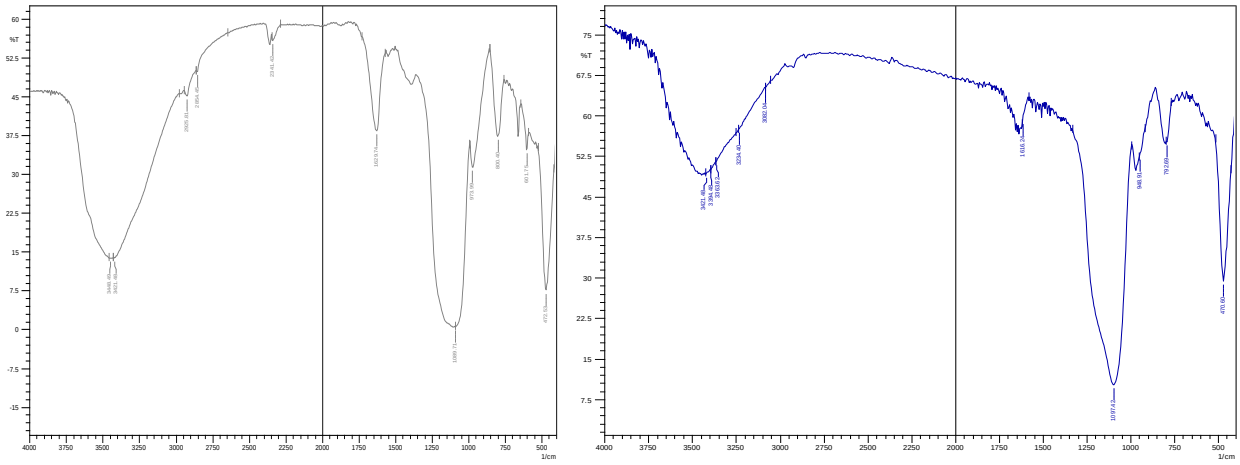

Figure 1: FTIR spectrum of silica gel **a.** before and **b.** after activation by HCl

FT-IR spectra were obtained from pure VPA, and VPA-imprinted silica gel adsorbents (Figure 2a, b) to confirm the synthesis of MIP. As illustrated in Figure 2a, VPA is an aliphatic carboxylic acid having a strong absorption peak in the carbonyl group in the 1700-1710 cm^{-1} and a broad hydroxide absorption peak in the 2400-3400 cm^{-1}. A comparison of Figures 1b and 2b shows that the synthesized polymer is a VPA surface imprinted polymer.

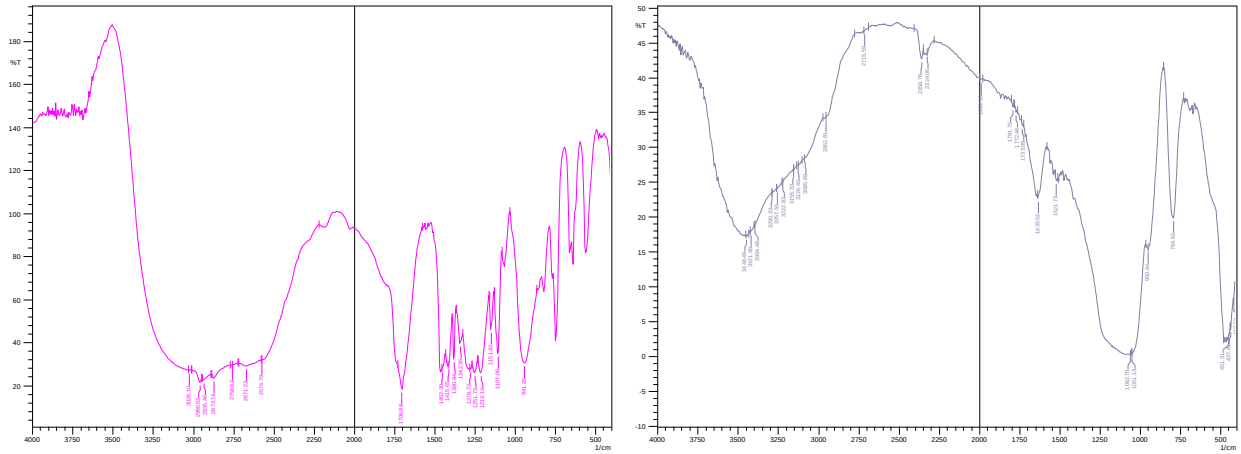

Figure 2: FTIR spectrum of **a.** pure valproic acid **b.** activated silica gel after imprinting

Evaluation of sodium hydroxide efficiency in clearance VPA on Column

The IR spectra of the imprinted polymer after passing the VPA solution (10^{-4} mM) and the detergent solution through the column were examined. As shown in Figures 3 a and b, due to the spectral region of carbonyl adsorption of 1680-1820 cm^{-1} and the decrease in carbonyl absorption in the imprinted polymer after passing washing solution, sodium hydroxide solution showed high performance for VPA wash.

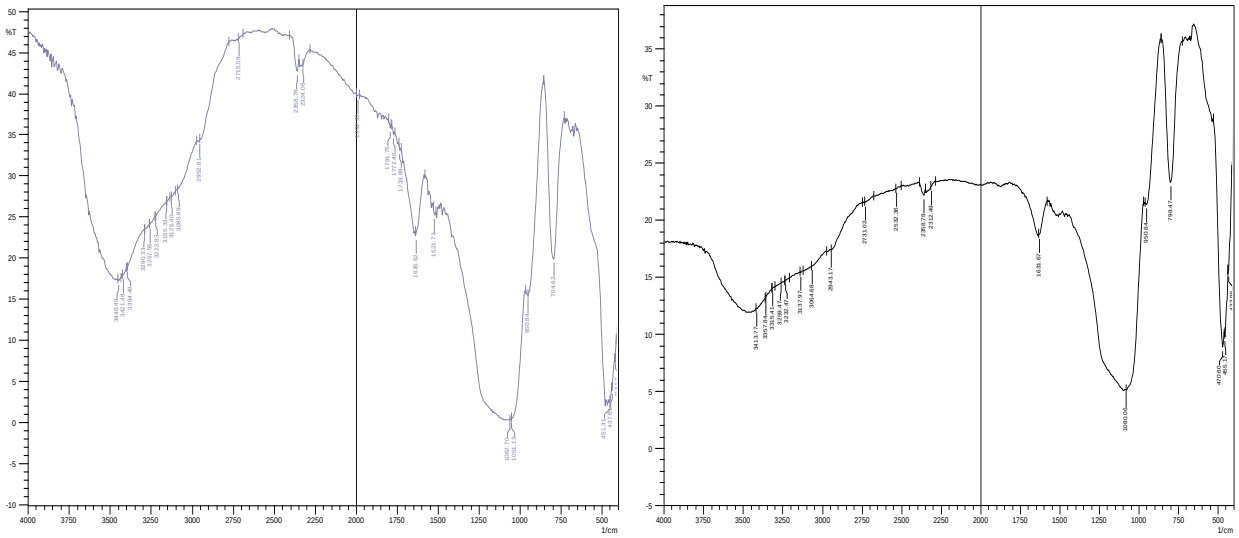

Figure 3: FTIR spectrum of imprinting silica gel **a.** after passing the solution of VPA b. after passing the washing solution

Optimization of the extraction conditions

Effect of the eluent concentration

A solid-phase extraction column filled with 250 mg of VPA- imprinted polymer was designed. After passing the VPA solution (10^{-5} Mm), the columns were washed with sodium hydroxide 1, 0.1, and 0.01 mM, separately. The detergents were then adjusted to neutral pH by diluting HCL. At specified time intervals (20 s), the potential of VPA (10^{-5}Mm) and detergent solution was measured by a potentiometer before and after passing the column against the Ag/AgCl control electrode. VPA solution (10^{-5} mM) was considered as the standard solution (Figure 4 and Table 1).

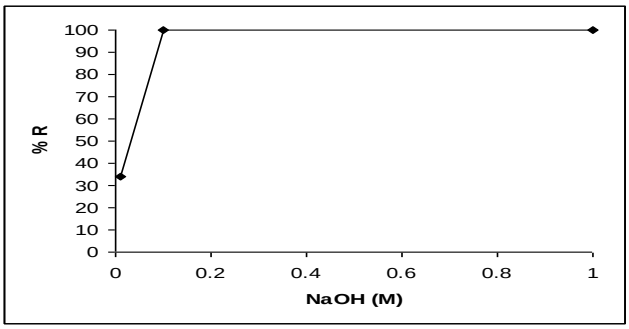

Figure 4: Effect of eluent concentration on the extraction efficiency of VPA

Table 1: Effect of eluent concentration on VPA extraction

E_{VPA} (10^{-5} M) before passing through the column	0.603	0.603	0.603
E_{VPA} (10^{-5} M) after passing through the column	0.570	0.570	0.570
E_{NaOH} (0.01M) after passing through the column	0.592	-	-
E_{NaOH} (0. 1M) after passing through the column	-	0.603	-
E_{NaOH} (1M) after passing through the column	-	-	0.603

As shown in Table 1 and Figure. 4, sodium hydroxide solution was suitable for column washing, and by increasing concentration from 0.01 to 0.1 mM, its efficiency was improved but further increase in concentration did not affect its performance. As can be seen in Table 1, the potential of valproic acid decreases after passing through the column, which indicates the adsorption of valproic acid molecules by the polymers inside the column. In the next step, the column was washed with sodium hydroxide as an eluent, which increased the potential of sodium hydroxide after passing through the column, indicating that it was able to separate the adsorbed valproic acids.

Effect of MIP amount

Three types of SPE columns with 200, 250, and 300 mg polymer were designed. After passing the VPA solution (10^{-5} mM), all columns were washed with sodium hydroxide solution (0.1 M). Then, the solutions were adjusted to neutral pH by diluting HCL and at specified intervals (20 s), the potential of the solution and detergent before and after passing the column against the Ag/AgCl control electrode was measured by a potentiometer (Figure 5 and Table 2).

Table 2: Effect of MIP amount on VPA extraction efficiency

Amount of polymer (mg)	The rate of sample solution passage (mL/min)	E_{VPA} (10^{-5} M) before passing through the column	E_{VPA} (10^{-5} M) after passing through the column	E_{NaOH} (0. 1M) after passing through the column
200	2	0.603	0.595	0.603
250	0.5	0.603	0.570	0.603
300	0.033	0.603	0.560	0.603

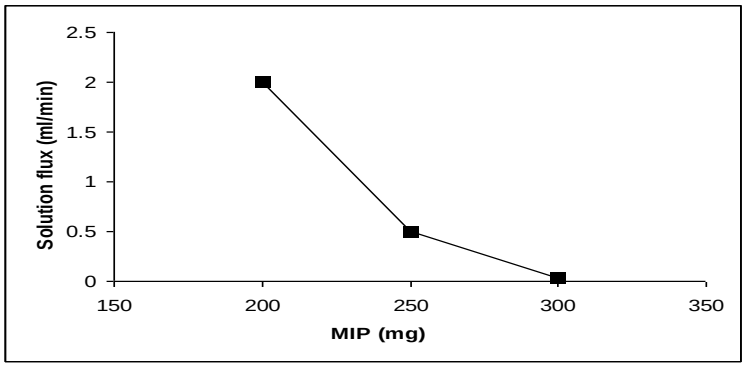

Figure 5: Effect of MIP amount on a rate of solution passage

As shown in Table 2, by increasing MIP content, the column efficiency was increased due to the increase in the number of detection holes, but increasing the amount above 250 mg of the polymer was not permitted due to the sharp decrease in sample passage rate.

Effect of VPA concentration

The prepared adsorbent adsorption capacity was studied BY an SPE column filled with 250 mg of VPA-imprinted polymer. Then, the solutions of 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4}, 10^{-3}, and 10^{-2} mM valproic acid were passed through the column, and the column was washed with sodium hydroxide (0.1 M). Next, it was adjusted to neutral pH and at specific time intervals (20 s), the potential of VPA solutions and detergents before and after passing the column against the Ag/AgCl control electrode was measured by a potentiometer. The solutions of 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4}, 10^{-3}, and 10^{-2} mM VPA were considered as standard solutions (Table 3 and Figure 6).

Table 3: Effect of VPA concentration on extraction efficiency

Sample concentration (mM)	E_{VPA} before passing through the column	E_{VPA} before passing through the column	E_{NaOH} (0. 1M) after passing through the column
10^{-7}	0.356	0.344	0.339
10^{-6}	0.424	0.422	0.42
10^{-5}	0.508	0.502	0.500
10^{-4}	0.603	0.570	0.603
10^{-3}	0.678	0.670	0.578
10^{-2}	0.712	0.7	0.650

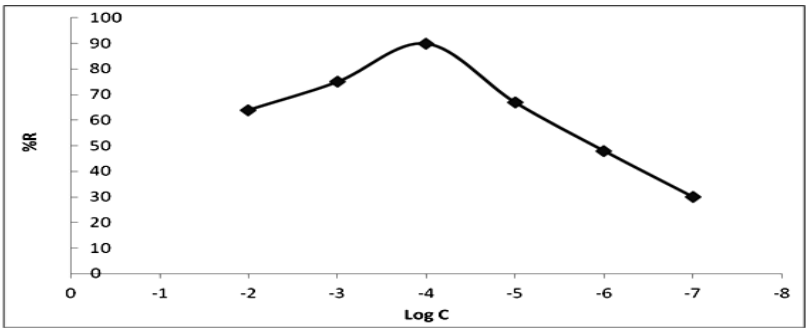

Figure 6: Effect of VPA concentration on extraction efficiency

pH effect

The sample pH effect on the efficiency of extraction was studied at the pH range of 2 to 10 (Figure 7 and Table 4).

Table 4: Effect of VPA solution pH on the extraction efficiency

pH	E_{VPA} before passing through the column	E_{VPA} after passing through the column	E_{NaOH} (0. 1M) after passing through the column
2	0.630	0.615	0.606
4	0.615	0.580	0.612
6	0.604	0.571	0.604
8	0.600	0.568	0.595
10	0.584	0.570	0.560

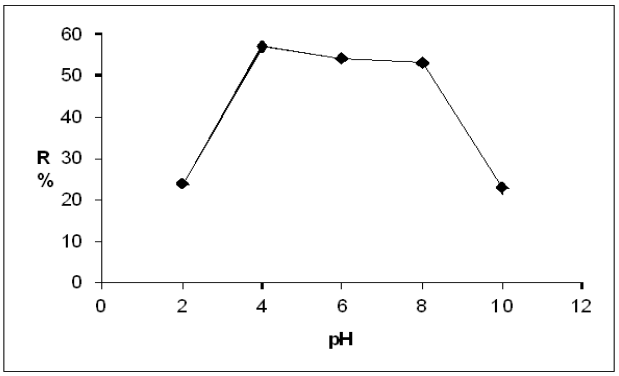

Figure 7: Effect of VPA solution pH on extraction efficiency

Salting effect

The effect of ambient ionic strength in the designed SPE column performance was evaluated (Figure 8).

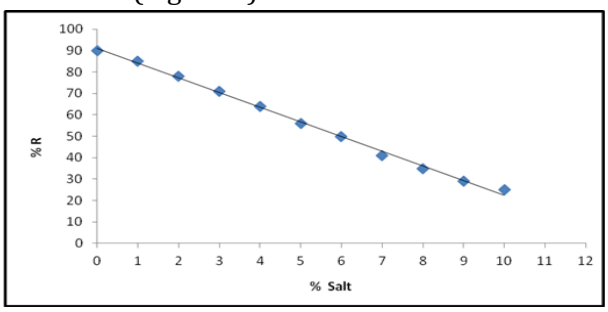

Figure 8: Salting effect on VPA extraction efficiency

As shown in Figure 8, the salt percentage increasing decreased the extraction efficiencies slightly.

Sample flow rate effect

The sample flow rate effect on the extraction of VPA was examined at the rate of 1, 2 and 5 ml min^{-1}. The results are shown in Figure 9.

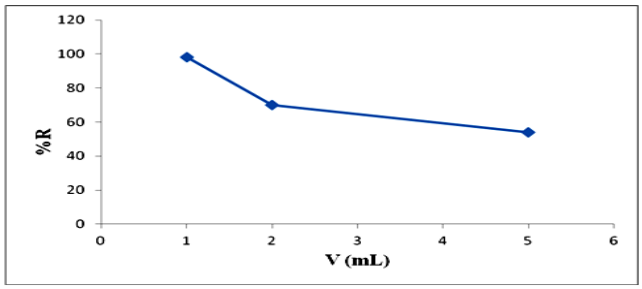

Figure 9: Effect of sample flow rate on VPA extraction efficiency

As shown in Figure 9, the optimized flow rates for VPA were up to 1 ml min^{-1} and higher flow rates have decreased the efficiency of VA extraction to 40%. The VPA solution was balanced faster with imprinted silica gel in the mean flow rate.

Column performance repeatability (relative standard deviation)

The reproducibility of the designed SPE column was investigated 6 times a week. The results indicated that the relative standard deviation obtained for the performance of this column was between 2–5, which was lower than that obtained for similar columns and indicated high performance of the designed column. Sustainable absorbent properties allowed it to decrease to more than 50 cycles with an average recovery of less than 6.6%.

Investigation of the selectivity coefficient of the surface imprinted polymer

The effect of interference on VPA surfaced MIP selectivity coefficient was investigated. The results are reported in Table 5.

Table 5: Effect of some species on the recoveries (%) of VPA

Interfering compound	Selectivity coefficient
Na^{+}	$6.5*10^{-3}$
K^{+}	$5.1*10^{-3}$
Mg^{2+}	$2.8*10^{-3}$
Ca^{2+}	$3.7*10^{-3}$
Glucose	$2.7*10^{-3}$
Uric acid	$1.9*10^{-3}$

As seen in Table 5, the prepared adsorbent showed high selectivity for VPA over the structurally similar compounds.

Application and analytical performance

The use of the developed method was investigated by determining the VPA in non-spiked and spiked samples. Using the *t*-test and *F*-test, the analysis showed no significant difference between the performances of these methods (95% confidence level). Three measurements were performed in every method, in which the proposed SPE process, the recoveries of samples, improved (from 94.6 to 98.1%, Table 6) with relative standard deviation (RSD) less than 5.78%. So, the prepared adsorbent could be directly used to determine and adsorb the VPA in samples.

Table 6: Investigation of the application of the SPE in tablet samples

Log C	E_1 (Tablet)	E_2(Standard solution)
-6	0.311	0.315
-5	0.337	0.382
-4	0.407	0.463
-3	0.467	0.542
-2	0.521	0.59

Finally, according to the findings, the results can be summarized in the following table.

Table 7: compression table to compare this work with other papers should be added

	VPA-SMIP	**other methods**
Organic solvent consumption	low	More
Convenience	more	Less
Recovery	good	Good
Extraction time	short	short
Cost	low	more
Selectivity	more	low

Silica gel containing siloxane (Si-O-Si) groups in the bulk and silanol (Si-OH) groups on the surface, is an amorphous inorganic polymer that facilitates the organic groups which are covalently bonded to it. This deficiency of hydroxyl groups can lead to low absorption capacity. Since the commercial silica gel contains a small concentration of surface silanol groups, silica gel surface activation is essential [28].

In this study, for silica gel activation, HCL was used. A complex between VPA, APS, and TEOS was formed, then co-hydrolyzed with the activated silica gel and co-condensed. After removal of residual APS and VPA, a functionalized silica gel adsorbent containing a cavity made for VPA was fabricated. It was shown that by a surface imprinting technique, a new ion-imprinted thiol-functionalized silica gel sorbent was synthesized in combination with a sol–gel process for selective online, solid-phase extraction of Cd(II) [29], and bisphenol-A[30]. Thus, surface molecularly imprinted polymers must be synthesized with specific carrier materials for better results in the pre-concentration process [31]. The nature of surface imprinted polymers directly affects the performance of extraction [32]. In recent years, due to the stable mesoporous structure, silica-based mesoporous materials have been reported as solid support with good chemical and mechanical properties as well as well-modified surface properties with abundant active SieOH bonds of the pore walls [33].

FTIR has been used to get VPA-imprinted silica gel adsorbents. The presence of 3200-3700 cm^{-1} absorption peaks (OH vibration) demonstrated that HCl activated the silica gel. As seen in the VPA spectrum, there were peaks at 1700-1710 cm^{-1} related to the carbonyl group and broad hydroxide absorption peak in the 2400-3400 cm^{-1}. For testing if the VPA would remove the ability from the adsorbent, various concentrations of sodium hydroxide were used and the difference in recovery was not significant. The FTIR spectrum demonstrated the decrease in carbonyl absorption in the imprinted polymer after passing the sodium hydroxide solution, showing its high performance.

The results indicated that the prepared silica gel amount in the SPE column increased extraction efficiency due to an increase in the cavity site number, but if the adsorbent is extracted more than 250 mg, the yield is reduced due to the slower passing rate of the sample [34].

10^{4-}mM valproic acids is a suitable concentration for crossing the column attributed to the slow kinetics of the adsorption, especially at a low concentration amount of analyte [35].

The optimized VPA extraction by SPE column was recorded at pH around 2-6 and the low efficiency was observed below pH 2 and more than 10. This is mainly due to pKa valproic acid, which is about 5. Thus, at pHs near 5, all valproic acid compounds cannot be decomposed. The decrease in recycling at pH= 2 may be due to high acidity. Free hydrogen competes with hydroxy valproic acid groups and forms stronger hydrogen bonds with nitrogen atoms, leading to the destruction of the analyte and adsorbent hydrogen bonds. When the pH of the sample was set to 10, potential ionic reactions took place between the valproic acid carbonate form and the nitrogen atoms, which reduced the recovery of valproic acid. These results indicate the important role of ionic reactions in the extraction process [36].

To investigate the ionic strength effect, the extraction was performed by solutions containing different amounts of NaCl (0-10%, w/v). With increasing NaCl concentration, the salting-out effect occurs, which is usually observed in the extraction process involving hydrophobic interaction. So, salt concentration had an unfavorable effect on the analytical signal. But because of the presence of salt in the real samples, the calibration graph and other analytical characterization of the method should be established in the presence of 4 % NaCl [37].

In this study, the sample flow rate was evaluated in the range of 1, 2, and 5 ml min^{-1}, and 1 ml min^{-1} was selected as the optimum sample rate due to the relatively higher extraction time and

extraction efficiency. Similar to the status of this study, the flow rate was adjusted to 10, 20, and 40 ml min^{-1}, and considering the extraction efficiency and sufficient time for extraction, the flow rate was chosen to be 40 ml min^{-1} [38]. Based on the evaluaiton, the synthesized VPA-surfaced imprinted polymer has the potential to pre-concentrate and separate a target ion in real samples that contain various ions. It has already been observed that lead ion-imprinted polymer had high selectivity to lead in presence of K^+, Na^+, Ca^{2+}, and another foreign ion [39].

In this study, the recoveries of tablet samples improved in the range from 94.6 to 98.1%. The relative standard deviation (RSD) was less than 5.78%. The statistical parameters evaluated in some validation experiments showed average recovery by 95% -106%, precision less than 17% [40].

Conclusion

In this paper, a simple method for the surface VPA imprinted adsorbent synthesis and its potential as an SPE adsorbent has been evaluated. The results indicated a simple, inexpensive, and accurate analytical technique to determine the VPA in tablets with satisfactory recoveries. Also, there is no need to remove other species in the sample as they do not affect VPA measurement.

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Author contributions

All the authors have contributed equally.

Conflict of Interest

We have no conflicts of interest to disclose.

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