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Miniaturized salting-out liquid–liquid extraction in a coupled-syringe system combined with HPLC–UV for extraction and determination of sulfanilamide

Hassan Sereshti [a,*], Marzieh Khosraviani [a], Mohammad Sadegh Amini-Fazl [b]

[a] Department of Chemistry, Faculty of Science, University of Tehran, P.O. Box 14155-64555, Tehran, Iran
[b] Polymer Research Laboratory, Department of Chemical and Petroleum Engineering, Sharif University of Technology, P.O. Box 11365-11155, Tehran, Iran.

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ABSTRACT

In salting-out liquid–liquid extraction (SALLE) technique, water-miscible organic solvents are used for extraction of polar analytes from saline solutions. In this study, for the first time, a coupled 1-mL syringes system was utilized to perform a miniaturized SALLE method. Sulfanilamide antibiotic was extracted and determined via the developed method followed by high performance liquid chromatography–ultraviolet detection (HPLC–UV). The extraction process was carried out by rapid shooting of acetonitrile as extraction solvent (syringe B) into saline aqueous sample solution (syringe A), and then the shooting was repeated several times at a rate of 1 cycle s^{-1}. Thereby, an extremely large contact surface area was created between phases and led to a rapid equilibrium and mass transfer. In order to improve the efficiency of the method, the effect of extraction solvent (type and volume), shooting times, salt concentration, and pH on the extraction efficiency was investigated. The best performance of the method was achieved with 250 μL of acetonitrile, salt concentration of 250 mg mL^{-1}, pH of 7, and shooting times of 5. The linear dynamic range was 0.001–10 μg mL^{-1} with the determination coefficient of 0.9999. The relative standard deviation (RSD; $n=3$, $C=5$ μg mL^{-1}), and the limit of detection (LOD) were 1.55% and 0.3 ng mL^{-1}, respectively. The developed technique was successfully applied to genuine samples of tea, water, milk, honey, human urine, plasma and blood.

1. Introduction

During recent years, considerable advances have been achieved in technologies related to analytical instruments. However, sample preparation is still a critical step. Removing potential interferences, isolation and/or preconcentration of analyte(s), and rendering them in a compatible form with analytical systems, are the main aims of this step [1]. One of the most common sample preparation methods is liquid–liquid extraction (LLE). It is a basic separation technique for a diverse range of water samples, but is a time-consuming and tedious process that requires large volumes of organic solvents. The development of miniaturized liquid–liquid extraction methods such as liquid-phase microextraction (LPME) [2–5], single-drop microextraction (SDME) [6,7], solvent bar microextraction [8], continuous microextraction [9] and drop-to-drop solvent microextraction (DDME) [7] has led to the improvement of extraction rate and considerably reduced the consumption of organic solvents. However, these techniques are limited to the use of water-immiscible nonpolar solvents which are typically suitable for extraction of nonpolar to moderately polar compounds. Therefore, polar and charged analytes such as highly water soluble pharmaceuticals cannot be quantitatively extracted by these techniques. The polar solvents like acetonitrile that are suitable for these compounds are mostly water miscible and cannot be used in these methods.

However, in another development, the addition of an inorganic salt into a mixture of water and an organic water miscible solvent induces a phase separation via the salting-out effect [10–12]. This method that was developed by Rustum is known as salting-out liquid–liquid extraction (SALLE) [13]. The SALLE technique has been used for extraction of a variety of compounds like drugs [14–16] and metals [17,18] in various sample matrices such as biological [19–21], environmental [22], foods [12,23], plants [15] and industrial products [24]. In a miniaturized SALLE method, the extraction process is carried out in a simple and small scaled device based on either the primary platform or a new setup. Accordingly, the consumption of both extractant and sample solution is considerably decreased. Therefore, the system is eco-friendly, very simple, inexpensive, convenient in operation, and in some cases can be automated to speed up the process and obtaining improved repeatability.

Sulfanilamide with the chemical name of *p*-Aminobenzenesulfonamide ($C_6H_8N_2O_2S$) is a sulfonamide antibacterial that is widely used as veterinary medicine for the treatment of infections.

* Corresponding author. Tel.: +98 21 61113632; Fax: +98 21 66495291.
E-mail address: sereshti@khayam.ut.ac.ir (H. Sereshti).

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Since some sulfonamides are known to be carcinogenic, their residue in food products can be a healthy risk for human. Therefore, many countries have established 100 ng g^{-1} of maximum residue limit (MRL) for most sulfonamides in edible animal tissues to minimize the healthy risk of them [25]. Sulfonamides residues in environmental and food samples have been extracted and analyzed with various methods such as solid phase extraction (SPE) coupled with liquid chromatography-electrospray tandem mass spectrometry (LC/ESI-MS) [26], SALLE combined with HPLC–UV and thin layer chromatography (TLC) [25,27,28], UV–vis spectrophotometry [29], capillary supercritical fluid chromatography–Fourier transform infrared spectroscopy (cSFC–FT-IR) [30], HPLC–FD (fluorescence detector) [31,32], pressurized liquid extraction (PLE) followed by LC/ESI-MS [33], HPLC–UV–vis [34], SPE-capillary electrophoresis (CE) [35], flow injection HPLC–DAD (diode array detector) [36], hollow fiber supported liquid phase microextraction (HF-LPME)–HPLC–UV [37], and stir bar sorptive extraction (SBSE)–HPLC–DAD [38].

This work was aimed at the development of a miniaturized SALLE method for extraction of sulfanilamide as polar pharmaceuticals from complex water samples. The whole extraction process is performed within a simple system consisted of two specially designed syringes that at the time of extraction they are coupled to each other via their tips (Fig. 1). Then, the determination of the extracted analyte is carried out using the HPLC–UV technique. In order to enhance the efficiency of the method, the effective parameters on the performance of SALLE are investigated and optimized by the traditional method of one at a time.

2. Experimental

2.1. Chemicals and reagents

The HPLC grade acetonitrile (ACN), methanol (MeOH) and water were purchased from Duksan Pure Chemicals (Seoul, Korea) and used as the mobile phase in HPLC. Sulfanilamide, acetone, ethanol, diethyl ether, isopropanol, perchloric acid, glacial acetic acid (HOAC), sodium chloride (NaCl), and sodium hydroxide (NaOH) with the purity higher than 99% were purchased from Merck Chemicals (Darmstadt, Germany). The sulfanilamide standard stock solution of 1000 μg mL^{-1} was prepared in double distilled water. The appropriate working standard solutions were prepared by diluting the standard stock solution.

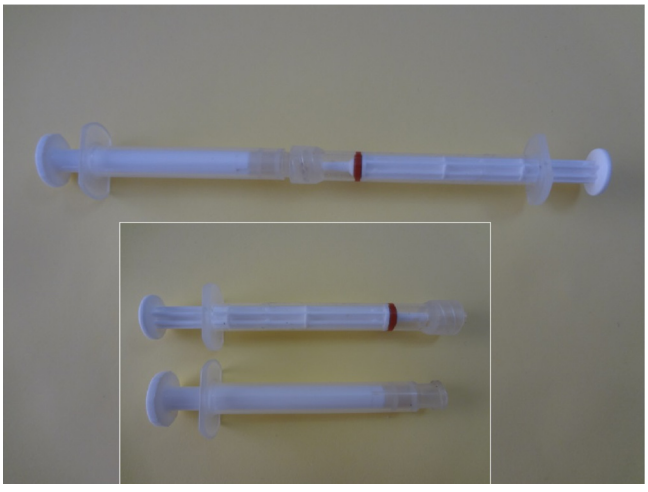

Fig. 1. The image syringes that were used in the proposed miniaturized SALLE method.

2.2. HPLC system

The HPLC analyses with isocratic elution were performed using an Agilent Technologies 1200 series HPLC system (Santa Clara, CA 95051, USA) equipped with an isocratic pump (Iso Pump, G1310A), UV detector (VWD, G1314B) and a manual injector (Man. Inj., G1328B). The HPLC–UV data were collected and processed using Chemstation software (B.02.01 version). Chromatographic separations were achieved using a Hypersil ODS C_{18} column (Hichrom, USA; length, 250 mm; internal diameter, 4.6 mm; particle size, 5 μm) at ambient temperature. The optimized mobile phase composition consisted of an isocratic solvent mixture of ACN: H_2O:HOAC (60:39:1, v:v:v). The flow rate was 0.8 mL min^{-1}, and the analyte was detected using UV detector at the wavelength of 260 nm. The injection volume to HPLC system was 20 μL.

2.3. Apparatus

All solvent used in HPLC as the mobile phase were degassed with an ultrasonic water bath (Digital Ultrasonic Cleaner, CD-4820, Korea). Both a vortex mixer (Dragon Lab, MX-S, Connecticut, USA) and the ultrasonic water bath were used for homogenization of the mixtures. The solutions pH values were measured using pH-indicator strips (Merck, Darmstadt, Germany). Specially designed syringes consisted of syringe A (Luer lock female, 1 mL, NJ, USA) and syringe B (Luer lock male syringe, 1 mL, IL, USA) were employed to perform the extraction process.

2.4. Extraction procedure

At first, 0.5 mL of sample solution was taken by syringe A, and a certain amount of NaCl (250 mg mL^{-1}) was added to it. Then, the mixture was vortexed for 20 s to obtain a homogenous solution. Afterward, the pH value of the solution was adjusted to 7 by adding appropriate amounts of 0.1 M NaOH. In the next step, syringe B was loaded with 250 μL ACN (extractant), then the syringes A and B were assembled through their tips. While the coupled-syringes system was held vertically with the syringe A at the bottom, the content of the syringe B (ACN) was rapidly injected into the syringe A (sample saline solution). In this stage, a cloudy solution was formed in the syringe A. The coupled-syringes system was then held horizontally and the content of the syringe A was injected into the syringe B and vice versa. In order to enhance the extraction efficiency, this cycle was repeated with pulling the plungers back and forth constantly (five cycles). When the last cycle was finished, the mixture will be in the syringe B. Afterwards, the coupled-syringes system was turned back to the vertical position with the syringe B at the bottom. The syringes were then disassembled and the syringe B was left statically for 2 min until two phases separated. Then, the plunger of syringe B was carefully pushed upward to move the upper layer (extracted sulfanilamide in ACN) into the narrow tip of the syringe. Finally, 20 μL of the acetonitrile phase was withdrawn by a Hamilton syringe and injected to HPLC. The procedure is schematically shown in Fig. 2.

3. Result and discussion

3.1. Influence of extraction solvent type

The organic solvents with the characteristics such as high capability to dissolve the analyte, miscibility with water, easily separable from water by adding salt, and having good chromatographic behavior were tested as extraction solvent. Moreover, the solvent peak should not interfere with the analyte peak under the

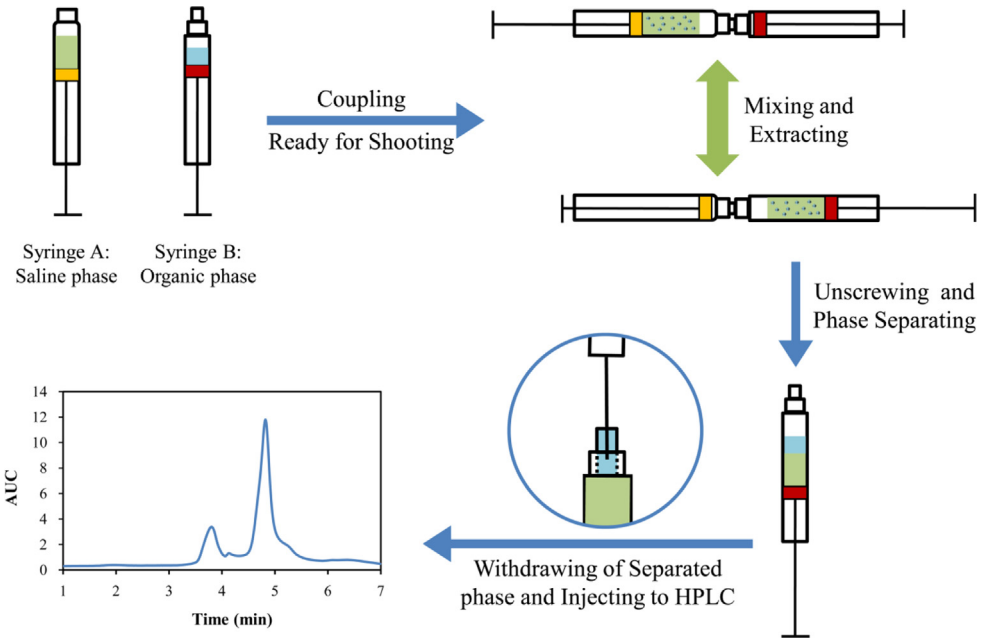

Fig. 2. Schematic procedure of miniaturized SALLE in coupled-syringes.

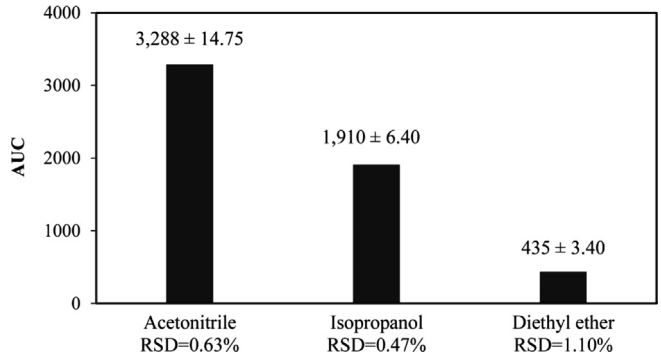

Fig. 3. Influence of various extraction solvents on the extraction efficiency. Extraction conditions: shooting times, 6; salt concentration, 300 mg mL^{-1}; extraction solvent volume, 300 μL; and pH, 5.

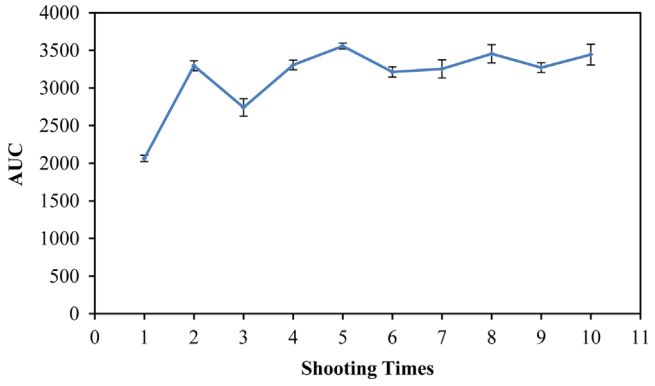

Fig. 4. Effect of shooting times on the extraction efficiency. Extraction conditions: salt concentration, 300 mg mL^{-1}; ACN volume, 300 μL; and pH, 5.

selected HPLC conditions. Hence, the solvents like isopropyl alcohol, acetonitrile, acetone, and diethyl ether were examined according to the procedure in Section 2.4. In the case of acetone, the minimum required volume for phase separation was 300 μL, but the repeatability at this point was not very good. Furthermore, the peak of sulfanilamide partially was overlapped with the acetone peak. Therefore, acetone was not chosen for further experiments. For diethyl ether, isopropyl alcohol and acetonitrile, the minimum needed volume for a clear phase separation was found to be 100, 200 and 210 μL, respectively. In each case, after the phase separation, the organic upper phase containing the extracted analyte was taken and injected into the HPLC system. In order to evaluate the efficiency of the method, the area under chromatographic peaks (AUC) was measured as the response. Fig. 3 illustrates that the maximum peak area of sulfanilamide with the least peak interference was obtained using acetonitrile as the extractant. Therefore, it was selected as the extraction solvent in the proposed method.

3.2. Influence of shooting times

In this work, shooting is defined as the rapid injection of syringe A content into syringe B and vice versa by pushing the plungers forward and backward. In this process, equilibrium is attained immediately due to the rapid dispersion of organic extraction solvent into saline aqueous sample solution. The infinitely large contact surface area between two phases results in the rapid extraction of the analyte. The effect of shooting times on the extraction efficiency was investigated for 1–10 shootings. The results in Fig. 4 show that the maximum efficiency with the least standard deviation was obtained at the fifth shooting, thus it was considered as the optimum shooting times.

3.3. Influence of salt concentration

The addition of an inorganic salt such as sodium chloride into a mixture of water and water-miscible organic solvent induces separation of the solvent from the mixture and formation of a two-phase solvent system [39]. Therefore, in the SALLE method, the salt concentration has a great influence on the phase separation. The effect of salt concentration on the performance of the proposed method was studied in the range of 100–400 mg mL^{-1}. The experiments indicated that at the concentrations higher than 350 mg mL^{-1}, the saline phase was oversaturated with sodium chloride. Fig. 5 displays the influence of salt concentration on the extraction performance. The addition of salt in the 100–250 mg mL^{-1} range led to

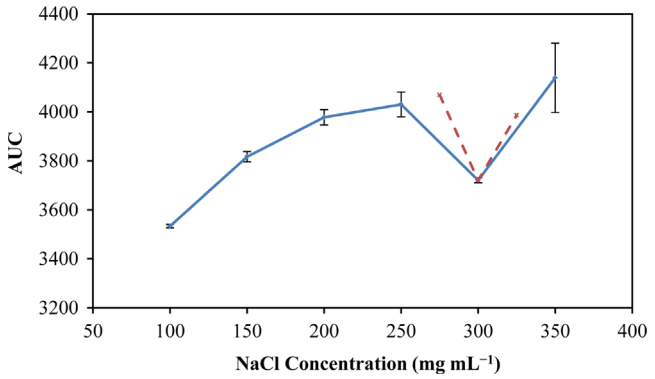

Fig. 5. Effect of salt concentration on the extraction recovery of sulfanilamide. Extraction conditions: shooting times, 5; ACN volume, 300 μL; and pH, 5. The procedure was repeated with 275, 300 and 325 mg mL^{-1} of salt concentration (shown by solid-dotted line).

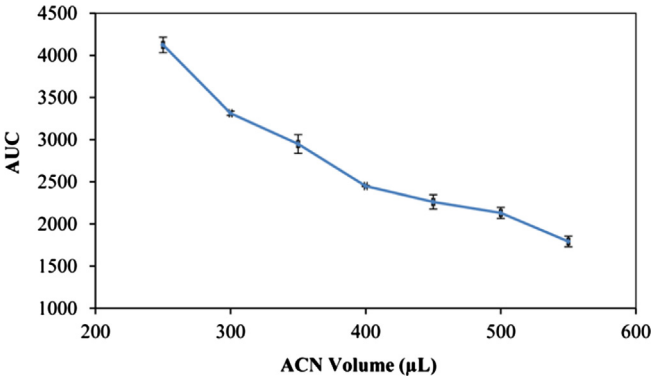

Fig. 6. Influence of ACN volume on the extraction efficiency. Extraction conditions: shooting times, 5; salt concentration, 250 mg mL^{-1}; and pH, 5.

increase the response via the salting-out effect. The decrease in chromatographic signal at the salt concentration of 300 mg mL^{-1} may be due to the increased viscosity of aqueous solution that overcame the salting-out effect and resulted in difficult mass transfer and low extraction efficiency [40]. However, the response was increased at the concentration of 350 mg mL^{-1} with a relatively poor repeatability. To ensure the changes in the last part of the curve, the procedure was repeated once more at the concentration levels of 275, 300 and 325 mg mL^{-1}, and the same trend was observed again. Therefore, according to the above explanations, the salt concentration of 250 mg mL^{-1} was chosen as the optimum point for this parameter.

3.4. Influence of extraction solvent volume

The effect of acetonitrile volume on the extraction performance was investigated in the range of 250–550 μL. With the volumes lower than 250 μL the phase boundary between acetonitrile and saline media was unclear and thus the removal of the upper organic layer for the analysis was difficult. The results illustrated in Fig. 6 show that the response decreases with increasing the acetonitrile volume. With increasing volume of ACN, the mass transfer is intensified and more sulfanilamide is extracted from the saline phase; however the dilution effect reduces the sulfanilamide concentration in ACN. Therefore, 250 μL was selected as the optimum volume for the extraction.

3.5. Influence of pH

Sulfanilamide contains an aniline group with pK_a=2.0 (weak base) and a sulfonamide group with pK_a=10.5 (weak acid) [28,40]. Therefore, the ionization of sulfanilamide and consequently its solubility are intensively affected by the pH value. The effect of pH of sample solution on the extraction recovery of sulfanilamide was investigated in the pH range of 3–10. The results depicted in Fig. 7 indicate that the pH values in this range have no significant effect on the extraction efficiency of sulfanilamide. This behavior can be attributed to its pK_a values. Moreover, it has been reported that sulfanilamide under both acidic and alkaline conditions is relatively unstable [40,41]. Therefore, the pH value of 7 was considered as the optimum pH for the extraction.

3.6. Method evaluation

The analytical characteristics of the proposed method were determined under the optimal conditions (acetonitrile (extraction solvent),

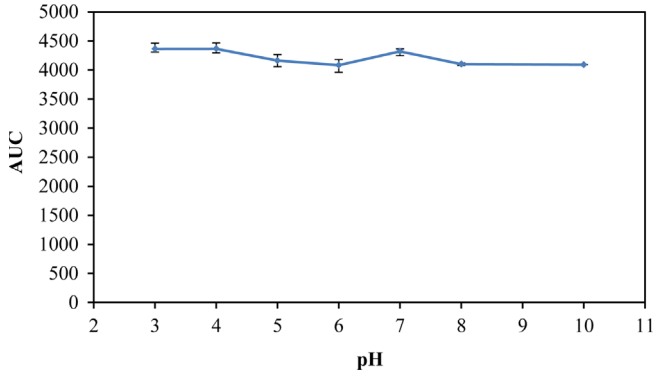

Fig. 7. Influence of pH on the extraction recovery of sulfanilamide. Extraction conditions: salt concentration, 250 mg mL^{-1}; shooting times, 5; and ACN volume, 250 μL.

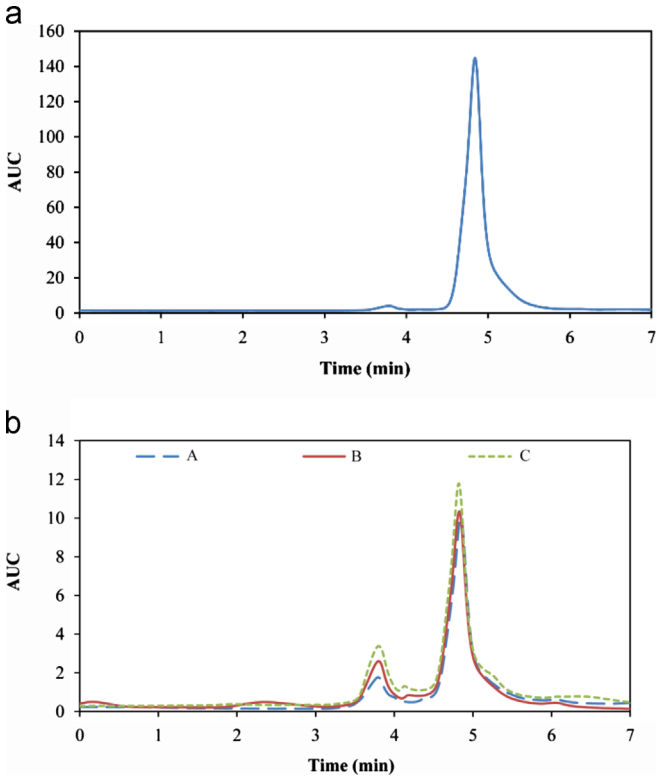

Fig. 8. The representative chromatograms resulted from analysis of (a) standard solution of sulfanilamide (10 mg L^{-1}); and (b) the real samples including tea (A), river water (B) and tap water (C) spiked with sulfanilamide after performing the extraction procedure at the optimal conditions. The retention time of sulfanilamide is equal to 4.8 min.

250 μL; shooting times, 5; salt concentration, 250 mg mL^{-1}; and pH, 7). The calibration graph was constructed by plotting the sulfanilamide peak area versus the corresponding concentrations with 10 levels in the range of 0.001–10 μg mL^{-1}. The linearity was characterized with a good determination coefficient (R^2) of 0.9999 and described with the equation of $y=431.3x+8.8$. Limit of detection (LOD) and limit of quantification (LOQ) were calculated based on the signal to noise ratio (S/N) of 3 and 10, respectively. Therefore, LOD was equal to 0.3 ng mL^{-1} and the obtained LOQ was 1.0 ng mL^{-1}. The precision based on relative standard deviation ($n=3$ and $C=5$ μg mL^{-1}) was 1.55%. In addition, the within-day ($n=3$) and between-day ($n=5$) variations were measured equal to 1.47% and 1.58%, respectively.

3.7. Analysis of real samples

The previously reported levels of sulfonamides found in some real samples are: 0–22.2 μg kg^{-1} in sewage sludge [33], 9.3 μg kg^{-1} in chicken meat [35], 0.3–0.5 μg mL^{-1} in medicinal forms of sulfonamides (injection solutions or drops) [36], 4.26 and 10.4 ng mL^{-1} in milk [38]. To evaluate the applicability of the developed method, various matrices including river and tap waters, tea beverage, milk, honey, urine, plasma and blood as the genuine samples were investigated for determination of sulfanilamide under the optimal conditions. The river water sample was collected from Alman river (Alman village, Ahar, eastern Azarbayjan province, northwest of Iran). The tap water was obtained from our laboratory. Milk, honey and tea were purchased from a local supermarket in Tehran (Iran). Urine, plasma and blood were supplied from a volunteer person. River water and tea samples were centrifuged for separation and removal of solid particles from the solution before performing the extraction process. Then, 0.5 mL of the sample was spiked with 15 μL of sulfanilamide standard solution (10 μg mL^{-1}) and the extraction was carried out in accordance with the procedure in Section 2.4. The HPLC chromatograms of standard solution of sulfanilamide and the real samples are shown in Fig. 8(a) and (b) respectively, and the results are given Table 1.

Table 1
Determination of sulfanilamide in different real samples.

Sample	Added (μg mL^{-1})	Found[a] (μg mL^{-1})	Relative recovery (%)
Tea beverage	0.30	0.29 ± 0.01	96.66
River water	0.30	0.27 ± 0.03	90.00
Tap water	0.30	0.32 ± 0.01	106.66
Milk	0.30	0.54 ± 0.02	76.67
Honey	0.30	8.49 ± 0.02	43.33
Plasma	0.30	1.50 ± 0.04	43.30
Blood	0.30	0.60 ± 0.05	66.67
Urine	0.30	0.65 ± 0.04	83.33

[a] Mean ± SD% ($n=3$).

The relative recovery (RR) was calculated using the following equation:

$$RR(\%) = \frac{C_{found} - C_{real}}{C_{added}} \times 100 \quad (1)$$

where C_{found}, C_{real}, and C_{added} are the concentrations of analyte after addition of known amount of standard in the real sample, the concentration of analyte in real sample and the concentration of known amount of standard which was spiked to the real sample, respectively.

3.7.1. Pretreatment of milk

Before performing the extraction process, proteins of the milk sample were precipitated with the method developed by Tyczkowska et al. [42]. At first, 1 mL of milk sample was placed in a centrifuge tube, and then 1 mL of ACN:MeOH:H_2O (deionized) (40:20:20) mixture was added to it. After shaking vigorously by hand, the solution was centrifuged at 3000 rpm for 10 min. Then, 0.5 mL of the upper phase was removed for the extraction of sulfanilamide residues with the procedure in Section 2.4.

3.7.2. Pretreatment of honey

The honey sample was diluted with distilled water to about 0.1 g mL^{-1}, then the solution was homogenized in an ultrasonic bath and subsequently centrifuged at 4000 rpm for 20 min. Finally, 0.5 mL of the solution was used for performing the extraction process.

3.7.3. Pretreatment of plasma and blood samples

For precipitation of the protein and other impurities, 250 μL of perchloric acid (0.1 M) was added to 50 μL of the sample and then

Table 2
Comparison of the proposed method with other previously reported research for determination of sulfonamides.

Preparation	Analysis	LOD[a]	LDR[b]	R^2[c]	RSD%[d]	RR%[e]	Ref.
SALLE[f]	HPLC–UV	0.3 ng mL^{-1}	0.001–10 μg mL^{-1}	0.9999	1.55	43.30–106.66	This work
SALLE[g]	HPLC–DAD	0.2–1.0 ng g^{-1}	2–30 ng mL^{-1}	0.9978–0.9999	2.7–4.0	96.5–109.2	[25]
LLE and SPE	HPLC–FD[h]	1–2 ng g^{-1}	2–100 ng g^{-1}	< 0.997	1.27–12.41	–	[32]
SALLE	HPLC	4.7–9.0 ng mL^{-1}	0.025–10 μg mL^{-1}	0.9994–1.0	7.4–8.7	19.37–93.78	[27]
SBSE[i]	HPLC	1.29–1.85 ng mL^{-1}	10–1000 ng mL^{-1}	0.9963–0.9992	7.34–10.9	55–126	[43]
HF-LPME	HPLC	0.1–0.4 μg kg^{-1}	1–2000 ng mL^{-1}	0.999	5	82–100	[37]
PLE[j]	LC–MS[k]	0.03–48 ng g^{-1}	0.1–500, 10–5000 ng mL^{-1}	0.9994	0.77–5.06	27–95	[33]
SPE	LC–MS[k]	< 200 pg L^{-1}	50–70,000 μg mL^{-1}	0.99	< 9.2	62–102	[26]
SPE	CE	5–10 μg kg^{-1}	0.5–50 μg mL^{-1}	0.99	0.2–1.0	80–97	[44]
–	HPLC	0.05–0.34 mg L^{-1}	1–16 mg L^{-1}	0.9995–0.9999	0.8–2.2	39–100	[45]
–	UV	0.24–0.81 mg L^{-1}	1–20 mg L^{-1}	–	0.26–22.17	96–102	[46]
–	HP-TLC	8 ng/spot	50–250 ng/spot	0.997	3.38–6.25	> 90	[41]

[a] Limit of detection.
[b] Linear dynamic range.
[c] Determination coefficient.
[d] Relative standard deviation ($n=3$ and $C=5$ μg mL^{-1}).
[e] Relative recovery (%).
[f] Miniaturized.
[g] Coupled with back-extraction.
[h] Fluorescence detection.
[i] Stir bar sorptive extraction.
[j] Pressurized liquid extraction.
[k] Electrospray ionization-mass spectrometry.

the mixture diluted to 700 μL with distilled water. In the next step, the mixture was vortexed and then centrifuged at 4000 rpm for 10 min. Afterward, 0.5 mL of the solution was used for salting-out extraction.

3.7.4. Pretreatment of urine sample

Before extraction, the urine was diluted with distilled water (1:5, v:v). Then, the sample was centrifuged for 20 min at 4000 rpm to remove the suspended particles. Thereafter, 0.5 mL of the supernatant solution was subjected to the extraction procedure.

3.8. Comparison with other methods

A literature review for determination of sulfonamides for a comparative study was carried out and the results are summarized in Table 2. The LDR of the proposed method (10^4) with a good R^2 is wider than that of the other methods. The repeatability of the method based on RSD% is better than the average RSD% of the other methods. The LOD of this work is also better than the mean LOD of the methods given in Table 2. Therefore, the proposed miniaturized SALLE followed by HPLC–UV has a good and comparable analytical results compared with other applied methods for extraction and determination of sulfonamides.

4. Conclusions

The miniaturized SALLE in a coupled-syringes system followed by HPLC–UV was successfully used for extraction and determination of trace levels of sulfanilamide antibiotic in a variety of matrices. The proposed extraction system is very simple, inexpensive, and convenient in operation. The method was validated with a good linearity (10^4) and determination coefficient (0.9999), a low LOD (0.3 ng mL^{-1}) and a satisfactory precision (RSD = 1.55%). Moreover, low consumption of extraction solvent (250 μL) and sample solution (0.5 mL) make it an environmentally friendly method. The fast and effective extraction was carried out by rapid injection of the extraction solvent into saline sample solution. The frequent pushing of the plungers forward and backward, resulted in achieving higher efficiencies. In addition, the method has the potential to be automated for producing more repeatable results.

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