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Determination of sulfonamides in swine muscle after salting-out assisted liquid extraction with acetonitrile coupled with back-extraction by a water/acetonitrile/dichloromethane ternary component system prior to high-performance liquid chromatography

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ABSTRACT

A salting-out assisted liquid extraction coupled with back-extraction by a water/acetonitrile/dichloromethane ternary component system combined with high-performance liquid chromatography with diode-array detection (HPLC–DAD) was developed for the extraction and determination of sulfonamides in solid tissue samples. After the homogenization of the swine muscle with acetonitrile and salt-promoted partitioning, an aliquot of 1 mL of the acetonitrile extract containing a small amount of dichloromethane (250–400 μL) was alkalinized with diethylamine. The clear organic extract obtained by centrifugation was used as a donor phase and then a small amount of water (40–55 μL) could be used as an acceptor phase to back-extract the analytes in the water/acetonitrile/dichloromethane ternary component system. In the back-extraction procedure, after mixing and centrifuging, the sedimented phase would be water and could be withdrawn easily into a microsyringe and directly injected into the HPLC system. Under the optimal conditions, recoveries were determined for swine muscle fortified at 10 ng/g and quantification was achieved by matrix-matched calibration. The calibration curves of five sulfonamides showed linearity with the coefficient of estimation above 0.998. Relative recoveries for the analytes were all from 96.5 to 109.2% with relative standard deviation of 2.7–4.0%. Preconcentration factors ranged from 16.8 to 30.6 for 1 mL of the acetonitrile extract. Limits of detection ranged from 0.2 to 1.0 ng/g.

1. Introduction

Sample preparation including both clean-up and preconcentration is usually a bottle-neck for the analytical procedures. Liquid–liquid extraction (LLE) is one of the oldest of the preconcentration and matrix isolation techniques in analytical chemistry and it remains a popular choice. However, LLE is time-consuming, tedious and requires large amounts of organic solvent. Recently, liquid-phase microextraction (LPME) has attracted increasing attention as a novel sample preparation technique which is simple, low-cost, rapid, and requires only very small sample and solvent consumption [1,2]. In LPME, extraction normally takes place between a small amount of a water-immiscible solvent and an aqueous phase containing the analytes of interest. The volume of the acceptor phase is in the microliter or submicroliter range. Single-drop microextraction (SDME) has evolved from this technique, in which the extraction phase is in the form of a single drop suspended in the stirred aqueous solution [3,4]. After that, several different operational methods including static and dynamic LPME [5,6], hollow fiber membrane LPME [7], solvent bar microextraction [8], continuous microextraction [9] and drop-to-drop solvent microextraction [10] have been developed.

Since water-immiscible solvents are generally used in LPME, the preferred technique for the analysis of extracts is gas chromatography (GC). Most of the published applications of LPME are coupled with GC for aqueous samples, especially environmental samples. In general, HPLC is a widely used, versatile separation and quantification technology. However, the applicability of LPME

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to HPLC has been restricted because the solvents commonly used in LPME and the extraction volumes typically used are too low for HPLC analysis [11,12]. To overcome those drawbacks, different approaches have been developed. The compatibility of SDME with HPLC can be achieved by using single-drop liquid–liquid–liquid microextraction (SD-LLLME) [13–15], which involves the use of three phases, namely the aqueous donor (sample), organic (transferring or intermediary phase) and final aqueous acceptor phases. Another alternative is to use ionic liquids (ILs) or coacervates as solvents [12,16–18]. Compared to organic solvent (e.g. n-octanol) used in LPME, for example, a larger volume drop of the IL could be utilized and led to better extraction efficiency. Moreover, the extract could be directly analyzed by HPLC.

Another problem for LPME applications is that the scientific literature has been mostly focused on liquid samples, whereas solid samples have received only limited attention. This fact could be attributed mainly to the necessity of the first-step employment for the homogenization of the solid samples with water-miscible organic solvent to obtain a better extraction efficiency of target analytes from the solid samples. To obtain a final "aqueous" donor phase or to diminish matrix effect during LPME procedures for GC [19–22] or HPLC [15,23–25] analysis, a dilution step with water is usually necessary for solid food samples or biological fluid samples.

Recently, homogeneous liquid–liquid extraction (HLLE) and dispersive liquid–liquid microextraction (DLLME) with special emphasis on its simplicity and short extraction time have been developed for the extraction of some organic analytes in water samples [26–28]. Moreover, DLLME has also been successfully utilized for the determination of pesticides in solid samples (e.g. vegetable [29] and tea [30]). In both methods, the small sedimented organic phase formed after centrifuging is not suitable for directly injecting into the conventional HPLC. In the present work, based on a ternary component solvent system (water/solvent/organic modifier) similar to DLLME and HLLE, we propose a novel extraction technique that when a small volume of water was used as an extractant, the final sedimented phase would be aqueous phase and could be withdrawn easily into a microsyringe and directly injected into the HPLC system.

Sulfonamides are widely used as veterinary drugs for the treatment of infections and the promotion of growth of livestock. The presence of sulfonamide residue in food is of concern because some of the compounds are known to be carcinogenic and they generally enhance the risk of developing antibiotic resistance. To minimize the risks to human health from consumption of sulfonamides' residues in foods, many countries have established 100 ng/g of maximum residue limit (MRL) for most sulfonamides in edible animal tissues. Numerous methods such as GC, GC–MS, LC and LC–MS have been developed to analyze sulfonamide residue in environmental and food samples [31–37]. Among them, due to its high sensitivity and selectivity, liquid chromatography (LC) coupled to mass (MS) or tandem mass (MS–MS) spectrometry has been successfully applied for the determination of sulfonamides at trace levels in food samples [31,35–37]. However, mass instruments are still quite expensive and not readily available to chemists in most laboratories.

For most routine analytical laboratories, HPLC is still the most commonly used versatile separation and quantification technology, while the solvent extract obtained from the homogenization of tissue sample usually was not suitable for directly injecting into HPLC. An extra step of preconcentration and solvent exchange is usually needed for the extract prior to HPLC analysis. The aim of this study was to assess whether the proposed method could be used as a valuable sample concentration approach to determine the trace residues of sulfonamides in swine muscle sample by HPLC–DAD. Using the organic extract obtained from the homogenization of the swine muscle as a donor phase, here, we report how water could be used as an acceptor phase for the preconcentration of sulfonamides. The results indicated that the proposed two-step sample preparation method could be applied well to determine the trace levels of sulfonamides in swine muscle by HPLC–DAD.

2. Experimental

2.1. Reagents and materials

Sulfadiazine (SDZ), sulfathiazole (STZ), sulfapyridine (SPY), sulfamerazine (SMZ) and sulfamethazine (SMT) were purchased from Riedel-de Haën (Sigma–Aldrich, Seelze, Germany). Diethylamine was obtained from Alfa Aesar (Johnson Matthey, Germany). HPLC-grade acetonitrile (MeCN), and perchloric acid (70–72%) were purchased from Merck (Darmstadt, Germany). Magnesium sulfate anhydrous was from J.T. Baker (Phillipsburg, NJ, USA) and sodium chloride was form Nihon Shiyaku Reagent (Tokyo, Japan). Glacial acetic acid was purchased from Mallinckrodt Chemicals (Phillipsburg, NJ, USA). Deionized water was purified by a Direct-Q system (Millipore, Bedford, MA, USA). The stock solutions of sulfonamides were each prepared by dissolving in acetonitrile at the concentration of 0.1 mg/mL and stored at 4 °C. The structures, molecular weights and pK_a values of the sulfonamide compounds studied are presented in Table 1.

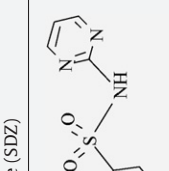
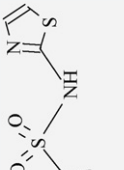
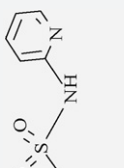
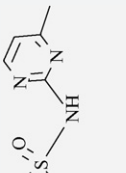
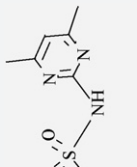
2.2. Instrumentation

Tissue was homogenized with an Omni TH homogenizer (Omni International, Warrenton, VA, USA). The pH values were measured by Cyberscan 2000 pH meter (Eutech Cybernetics, Singapore, Singapore). Considering the effect of MeCN on pH meter reading, MeCN solutions were diluted 4-fold with deionized water prior to making measurements according to the method described by Lehotay et al. [38]. A Kubota 3700 centrifuge (Tokyo, Japan) and a Minicentrifuge GMC-060 (LMS Co., Tokyo, Japan) were utilized for the 50- and 2-mL centrifuge tubes, respectively. LC analysis was performed using a Hitachi HPLC system (Hitachi, Tokyo, Japan) consisting of an L2130 LC pump and an L2455 diode-array detector. The chromatographic separation was performed on a Mightysil RP-18 analytical column (250 mm × 4.6 mm, particle size 5 μm) operated at 40 °C. A 20 μL injector loop was used. The photodiode-array detector was set at 280 nm. Mobile phase A was a 90:10 (v/v) 1% glacial acetic acid:MeCN mixture and mobile phase B was MeCN with a total flow of 1 mL/min. The separation gradient was an initial isocratic step 100% A for 2 min, from 2 to 10 min linearly change to 8% B, and from 10 to 16 min linearly change to 42% B. Between one injection and the next, a 70% MeCN solution was used to clean the column for 5 min. The initial condition was then reestablished and the equilibrium time was no less than 10 min for the next injection. The direct sample introduction was carried out using a Rheodyne six-port switching valve (Rohnert Park, CA, USA) with a 20 μL loop.

2.3. Sample preparation

A 5 g swine muscle tissue was weighed into a 50-mL tube. For spiked samples for recovery experiments, an appropriate volume of standard was added directly to the tissue for 20 min before homogenizing. A 5 mL of MeCN with 10 μL of 70–72% perchloric acid was then added and the sample was homogenized with an Omni TH homogenizer. After adding of 2 g anhydrous magnesium sulfate and 1 g sodium chloride, the mixture was mixed by vortex mixer for 1 min, and then centrifuged for 4 min at 10,000 rpm. A 1 mL aliquot of organic extract layer was transferred into a 2-mL vial containing 350 μL dichloromethane and mix thoroughly by vortex mixer for 30 s. After adding 8 μL of DEA, the mixture was mixed thoroughly by vortex mixer for 30 s and then centrifuged for 1 min at

Table 1
Structures, molecular weights, pK_a values and CAS numbers for the sulfonamide compounds [43].

	Sulfadiazine (SDZ)	Sulfathiazole (STZ)	Sulfapyridine (SPY)	Sulfamerazine (SMZ)	Sulfamethazine (SMT)
Molecular structure					
CAS No.	68-35-9	72-14-0	144-83-2	127-79-7	57-68-1
Molecular weight	250.3	255.3	249.3	264.3	278.3
pK_{a_1}	1.6 ± 0.1	0.7 ± 0.1	0.8 ± 0.1	1.6 ± 0.1	0.4 ± 0.1
pK_{a_2}	6.8 ± 0.5	7.8 ± 0.5	8.0 ± 0.5	6.9 ± 0.5	7.0 ± 0.5

3000 rpm. The liquid phase was transferred into a small vial with a glass pipette and then 50 μL of deionized water was added. The solution was then mixed thoroughly by vortex mixer for 30 s. After centrifugation for 1 min at 3000 rpm, the settled water phase (about 21 μL) was withdrawn into the 50-μL microsyringe and injected into the HPLC system for analysis. All experiments were carried out at room temperature, 22 ± 0.5 °C.

3. Results and discussion

3.1. Optimization of solvent extraction

Our objective was to develop a fast method for analysis of sulfonamides in solid samples that could be compatible with HPLC. Generally, for solid tissue samples, the first step of sample preparation is the homogenization step with organic solvent. In this work, MeCN was used in the homogenization step to extract analytes from tissue samples which could then be used as the organic donor phase in the following procedures. In 2003, Anastassiades et al. reported a rapid and inexpensive method involved the extraction of the residual pesticides in fruits and vegetables with MeCN followed by a liquid–liquid partitioning step formed by salting-out with sodium chloride and magnesium sulfate [39]. In our previous work, tetracyclines could also be extracted from liquid samples to MeCN layer after the partition step with the similar approach [40]. In this study, for the first-step extraction, 5 g swine muscle spiked with a high concentration of sulfonamides (0.4 μg/g), 5 mL MeCN with different amounts of perchloroic acid, 2 g magnesium sulfate and 1 g sodium chloride were used for this step. After homogenization, magnesium sulfate and sodium chloride were added to prompt phase separation. After centrifugation, the MeCN solutions were diluted 4-fold with deionized water prior to making pH measurements. To avoid loss of sulfonamides during the solvent evaporation step of the reconstituted procedure, the sulfonamides in the MeCN layer were detected by HPLC–DAD after directly diluting the crude MeCN extract. When different amounts of perchloroic acid were used to acidify the extraction solvent, followed by liquid–liquid partitioning formed by addition of magnesium sulfate and sodium chloride, the recoveries were more than 90% for all the five sulfonamides when the pH meter reading was 3.8–4.2. Therefore, 10 μL of 70–72% perchloric acid was chosen to get the pH meter reading of the MeCN extract approximately 4.0 after partitioning.

3.2. Adjusting pH of donor phase

The pH of donor phase was expected to be an important factor for the back-extraction of sulfonamides. Sulfonamides are ordinary ampholytes, so the acceptor solution must be either sufficiently alkaline or acidic to extract sulfonamides from the donor phase to aqueous acceptor phase. An alkaline acceptor phase is more advantageous than an acidic acceptor phase because isoelectric pH is less than 7 [41]. However, unlike the environmental water sample, when an alkaline acceptor phase was used, the precipitation phenomena occurred in the donor phase preparation from the muscle sample, and it was hard to perform the proposed back-extraction procedure. Therefore, the clear MeCN extract obtained after alkalinization and centrifugation was used as a donor phase and then water could be used as an acceptor phase to extract sulfonamides from the clear donor phase. Furthermore, when water was used as an acceptor phase, other sources of water should be avoided in this adjusting pH step. Therefore, an organic base was used instead of an aqueous alkalize solution (e.g. $NaOH_{aq}$). In this experiment, the alkalinization step of the MeCN extract was optimized by testing different amounts of diethylamine. As seen in Fig. 1, the peak areas of all the analytes increased with increase of the concen-

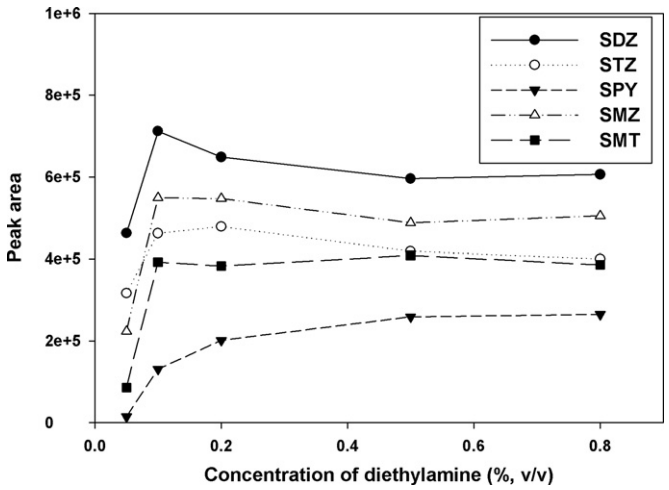


Fig. 1. Effect of the concentration of diethylamine on the peak areas of 100 ng/mL sulfonamides in the MeCN extract preparation from the swine muscle sample. *Conditions*: the MeCN extract volume, 1 mL; dichloromethane, 300 μL; water, 50 μL. SDZ: Sulfadiazine, STZ: sulfathiazole, SPY: sulfapyridine, SMZ: sulfamerazine, and SMT: sulfamethazine.

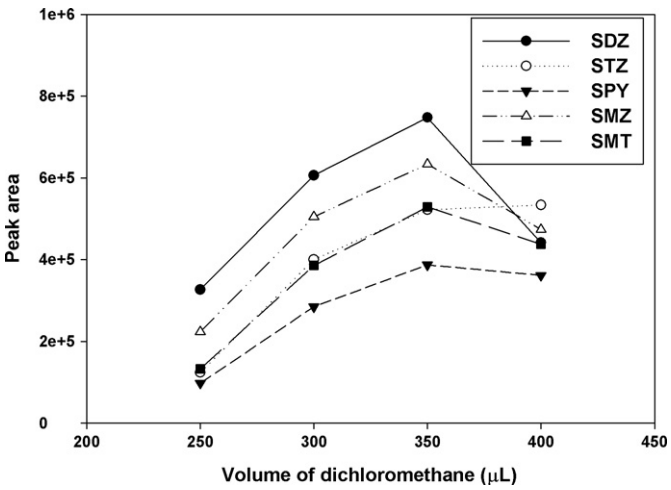


Fig. 2. Effect of the volume of dichloromethane on the peak areas of 100 ng/mL sulfonamides in the MeCN extract preparation from the swine muscle sample. *Conditions*: the MeCN extract volume, 1 mL; diethylamine, 8 μL; water, 50 μL. SDZ: Sulfadiazine, STZ: sulfathiazole, SPY: sulfapyridine, SMZ: sulfamerazine, and SMT: sulfamethazine.

tration of diethylamine, which was as expected. It along was also clear that when the concentration of diethylamine was >0.2%, further increase in its concentration did not result in the increase of peak areas significantly for the analytes, except for sulfapyridine. This was because the sulfapyridine molecule has a higher pK_a value and further increasing the concentration of diethylamine is needed to facilitate its ionization. Therefore, a concentration of 0.8% (v/v) diethylamine was used in the following studies.

3.3. Addition of organic modifier

Since water-immiscible solvents were generally used as an acceptor phase in most of LPME, the donor phase should normally be aqueous. In our proposed method, however, water was used as an acceptor phase for the purpose of compatibility with HPLC analysis while the organic solvent extract was used for the donor phase. Because MeCN is water-miscible organic solvent, the addition of another water-immiscible organic modifier is needed to ensure to the phase formation between the acceptor (water) and donor (MeCN) phases. When used as an organic modifier, dichloromethane was similar in the phase diagram of ternary component solvent system (water/MeCN/organic modifier) to chloroform [42]; however, chloroform is more toxic. Therefore, dichloromethane was used in our study as the water-immiscible organic solvent. Our preliminarily result show that when 200–400 μL dichloromethane was solvated in 1 mL MeCN, the lower phase would be water if the amount of water used was <500 μL. Although the density of dichloromethane is more than water, the density of the dichloromethane/MeCN mixture would be less than water and the sedimented phase after centrifuging would then be water. However, if the amount of water (for example, >4 mL) used was large enough to exclude the solvation effect of MeCN molecules, the water-immiscible sedimented phase, which contains dichloromethane molecules, would appear (e.g. in DLLME or HLLE methods). This is because the density of the MeCN/water mixture would be less than dichloromethane. In other words, at the high ratio of the aqueous solution and the mixed solvent (a water-miscible solvent and a water-immiscible solvent), the sedimented phase is the water-immiscible solvent, while the sedimented phase would "reverse" and would be the water phase at the low ratio. In the present work, added water was kept to the minimum and the lower phase would then be water after centrifugation. Thus, the small volume of the sedimented water phase after extraction could be withdrawn easily into a microsyringe and directly injected into the HPLC system. As shown in Fig. 2, when 250–400 μL of dichloromethane was added to the MeCN extract, the peak areas of all the analytes increased by the increasing of volume up to 350 μL. At higher volumes of dichloromethane due to increasing of sedimented phase volume and dilution of the sulfonamides, peak areas of the analytes were decreased. Thus, 350 μL of dichloromethane was used in further experiments.

3.4. Effect of acceptor phase volume

The effect of the acceptor phase volume on the HPLC peak area for the proposed method was studied by adding different volumes of water in the range of 40–55 μL. Results shown in Fig. 3 indicate that the peak area increased along with increasing water volume up to 50 μL. At higher volumes of water due to increasing of sedimented phase volume and dilution of the sulfonamides, HPLC peak areas of the analytes were decreased. Thus, 50 μL of water was used

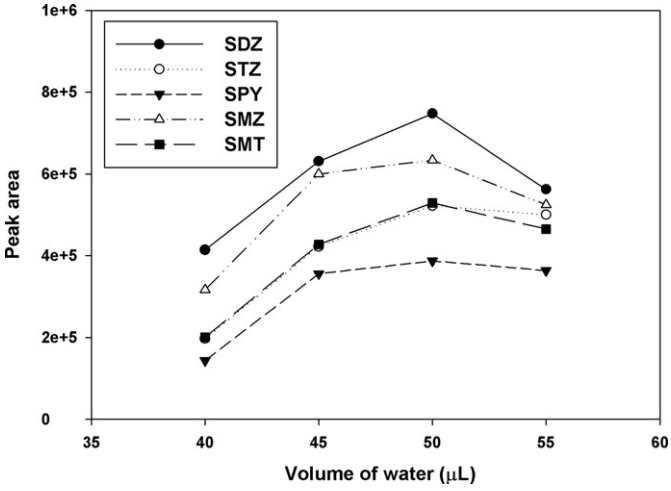


Fig. 3. Effect of the acceptor phase volume (water) on the peak areas of 100 ng/mL sulfonamides in the MeCN extract preparation from the swine muscle sample. *Conditions*: the MeCN extract volume, 1 mL; diethylamine, 8 μL; dichloromethane, 350 μL. SDZ: Sulfadiazine, STZ: sulfathiazole, SPY: sulfapyridine, SMZ: sulfamerazine, and SMT: sulfamethazine.

Table 2
Performance of the proposed method under optimized conditions.

Analyte[a]	Linearity range (ng/mL)	r^2	LOD (ng/g)	Swine muscle sample fortified at 10 ng/g (n = 5)		
				Recovery (%)	RSD (%)	Preconcentration factor
SDZ	2–30	0.9999	0.2	98.1	4.0	30.6
STZ	2–30	0.9982	0.7	96.5	3.9	16.8
SPY	2–30	0.9978	1.0	102.2	3.6	20.5
SMZ	2–30	0.9988	0.4	100.4	4.0	28.3
SMT	2–30	0.9986	0.7	109.6	2.7	25.2

[a] SDZ: Sulfadiazine, STZ: sulfathiazole, SPY: sulfapyridine, SMZ: sulfamerazine, and SMT: sulfamethazine.

and the volume of the sedimented water phase was about 21 μL (21 ± 0.5, n = 5). The sedimented water phase volume was about 40% of the initial water volume. As described in Section 3.3, the sedimented water phase volume will increase with the increase of the ratio of water-immiscible solvent (or the decrease of the ratio of water-miscible solvent). For a ternary component solvent system, the main point for the selection of dispersive or consolute solvents is the miscibility of the water-miscible solvents with the extracting solvent and aqueous phase in DLLME or HLLE. Thus, the increase of the ratio of water-miscible solvent will also result in the decrease of the sedimented organic phase volume. For example, compared to the conventional DLLME [27], the HLLE method has a higher ratio of water-miscible solvent and the sedimented organic phase volume was about 20% (60 → 11 μL) of the extraction solvent volume [28].

3.5. Method evaluation

For the two-step sample preparation method, sulfonamides were first isolated from the solid tissue sample using MeCN and then the extracted analytes can be transferred into the aqueous acceptor by the back-extraction method based on a water/acetonitrile/dichloromethane ternary component system. In the first extraction step, as described in Section 3.1, all sulfonamides could be extracted efficiently form the tissue sample to MeCN phase by the salt-promoted extraction procedure. However, in the second step, the following extraction efficiencies were obtained: 65.9% (SDZ), 35.4% (STZ), 42.3% (SPY), 58.0% (SMZ) and 52.5% (SMT) by the proposed back-extraction method under optimum conditions. Therefore, to provide reliable results, matrix-matched calibration curves prepared from the spiked MeCN extract of tissue sample were chosen as reference curves. To evaluate the proposed method, some parameters such as linearity, reproducibility, and preconcentration factor were determined under the above optimized conditions. Chromatograms of swine muscle samples spiked at 10 ng/g are shown in Fig. 4 using the proposed method. The calibration curves of sulfonamides isolated from spiked MeCN extract preparation from the swine muscle sample were linear over the range 2–30 ng/mL for all sulfonamides (the coefficients of estimation >0.998). Results shown in Table 2 indicate that, for swine muscle sample spiked at 10 ng/g of each compound, the recoveries were in the ranges 96.5–109.6% and the relative standard deviations (RSD, n = 5) were from 2.7 to 4.0%. The limits of detection (LODs, ranged from 0.2 to 1.0 ng/g) of the proposed method, were calculated from swine tissue sample spiked level at 2 ng/g at a signal-to-noise ratio (S/N) of 3. The preconcentration factors of sulfonamides, calculated as the ratio of the final concentration of analytes in the sedimented phase and its concentration in the initial solution, were obtained in the range of 16.8–30.6 for 1 mL of the MeCN extract. Higher preconcentration factors were usually obtainable owing to the higher sample volume-to-acceptor phase volume ratio as described in literature reports on the environmental samples analysis. However, if a larger sample size is used, then larger tubes, centrifuges and a greater amount of solvents will be required, which results in higher cost, more space and labor needs, and lower sample throughput. Thus, for the purposes of cost and ease for sample handling, 1 mL of the MeCN extract preparation from swine muscle sample and disposable minicentrifuge vials were chosen for the current method.

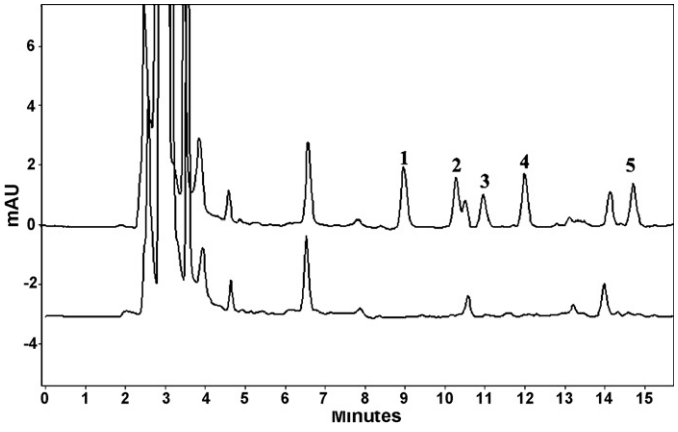


Fig. 4. HPLC chromatograms of blank swine muscle (bottom curve) and of a sample spiked with 10 ng/g of sulfonamides (top curve). The peaks were (1) SDZ; (2) STZ; (3) SPY; (4) SMZ and (5) SMT.

4. Conclusions

This study demonstrated that using the water/acetonitrile/dichloromethane ternary component system, water could be used as an acceptor phase to preconcentrate analytes from the MeCN solvent extract obtained from the homogenization step of solid tissue samples and then could be directly injected into the HPLC system for analysis. Using sulfonamides as a model, the two-step sample preparation procedure could be applied to the determination of sulfonamides at trace levels in swine muscle by HPLC–DAD. The proposed method is simple, inexpensive and highly sensitive with low limit of detection. Further, like conventional DLLME, it needs very short extraction time comparing to another report for pork muscle with SPME method (extraction time: 40 min; desorption time: 15 min) [37]. However, the proposed method is more difficult for automation. Additional work is in progress to assess whether water could also be used an acceptor phase to preconcentrate non-volatile ionizable compounds directly from the solvent extract of tissue samples by other LPME modes (e.g. SDME).

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