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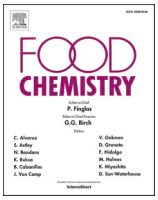

Chemometric design-based optimization of a green, selective and inexpensive switchable hydrophilicity solvent-based liquid phase microextraction procedure for pre-concentration and extraction of sulfadiazine in milk, honey and water samples

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A R T I C L E I N F O

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A B S T R A C T

In this research, a green, selective and inexpensive switchable hydrophilicity solvent-based liquid phase microextraction (SHS-LPME) procedure has been optimized for the extraction and preconcentration of sulfadiazine (SDZ) in milk, honey and water samples prior to spectrophotometric analysis. Five variables affecting the SHS-LPME procedure were optimized using chemometric-based central composite design. For the SHS-LPME procedure, analytical parameters such as linearity, limit of detection, extraction recovery and enrichment factor were 15–300 μg L^{-1}, 4.5 μg L^{-1}, 96 ± 3% and 113, respectively. The precision of the method was investigated by repeatability and reproducibility studies. The relative standard deviation from these studies was found in the range of 2.4–4.5%. The recovery of the SDZ in the samples was in the range of 94 ± 4–99 ± 2%. Collected samples were analyzed by both the SHS-LPME procedure and the reference method using flow injection-flame atomic absorption technique, and the results were compared. There was no statistically significant difference between the two methods. This showed that the SHS-LPME procedure can be safely applied to the analysis of real samples.

1. Introduction

Sulfadiazine (SDZ) is a broad-spectrum, rapid and effective synthetic antibiotic belonging to the sulfonamide antibiotic family, which has free amino and sulfonyl groups in its structure and is used in the treatment of bacterial diseases by inhibiting the dihydropteroate synthetase enzyme (Afsharipour, Shabani, Dadfarnia, & Kazemi, 2020). SDZ is used worldwide in the treatment of diseases caused by bacteria or fungi, such as urinary tract and ear infections, meningitis, malaria and toxoplasmosis, and in animal feed as a growth supplement (Dil, Ghaedi, Mehrabi, & Tayebi, 2021). However, prolonged exposure to trace residues of SDZ can lead to drug-resistant microbial strains that are difficult to control (Ait Errayess, Idrissi, & Amine, 2018; Zhang, Zheng, & Chen, 2009). For these reasons, it is clear that it is important to develop simple, selective, inexpensive, and rapid analytical techniques for the determination of SDZ in real samples, especially for routine quality control analysis.

Until now, several analytical techniques including capillary zone electrophoresis (Tong et al., 2013), UV–VIS spectrophotometry (Kazemi, Shabani, & Dadfarnia, 2017), differential pulse voltammetry (DPV) (Sriram et al., 2021), cyclic voltammetry (CV) (Ebrahimi et al., 2017), liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) (Jansomboon, Boontanon, Boontanon, Polprasert, & Da, 2016), high-performance liquid chromatography with diode-array detection (HPLC-DAD) (Shi & Ye, 2014), ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) (Wang et al., 2019), HPLC with UV detection (HPLC-UV) (Yao & Du, 2020), capillary zone electrophoresis with on-line chemiluminescence detection (CZE-CD) (Dai et al., 2017) and flow injection–chemiluminescence (Liu, Ren, Hao, He, & Fang, 2007) have been used for the determination of SDZ in different samples. These methods have their own specific applicability, but most of them, with the exception of the spectrophotometric technique, are time consuming, skilled user, inherently complex equipment, and involve expensive tools (Pourreza, Rastegarzadeh, & Larki, 2015; Hassoun et al., 2020). Contrary to these techniques, the use of the spectrophotometric technique for trace analysis of important compounds has always been of interest, given the simplicity, ease of use, easy accessibility, rapid measurement and sufficient sensitivity.

Since the SDZ is present at trace levels in real samples, a separation

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and preconcentration procedure should be applied before spectrophotometric determination to reduce interference and increase measuring capacity. During recent decades, several procedures such as emulsification liquid–liquid microextraction based on deep eutectic solvents (ELLME-DES) (Liu & Zhu, 2017), vortex-assisted liquid–liquid microextraction (Yu et al., 2014), hollow-fiber liquid-phase microextraction (HF-LPME) (Yang, Shi, Li, & Luan, 2018), in-syringe ionic liquid dispersive liquid–liquid microextraction (IL-DLLME) (Yu et al., 2014) and cloud point extraction (CPE) (Kazemi, Dadfarnia, Shabani, Fattahi, & Khodaveisi, 2017) have been used for separation and preconcentration of SDZ. Most of the above procedures are time consuming and complex, large amount of samples and very difficult to automate (Campillo, Gavazov, Viñas, Hagarova, & Andruch, 2020). Therefore, it is very important to develop new separation and preconcentration procedures in which simple, environmentally friendly, inexpensive and effective solvents are prepared. In this context, in recent years, switchable hydrophilic solvents (SHS) have attracted attention as an alternative extraction solvent to organic solvents, ionic liquids, surfactants and deep eutectic solvents (Pochivalov, Vakh, Garmonov, Moskvin, & Bulatov, 2020). The SHS is a solvent that can switch reversibly between a water-miscible form and another form that can form a biphasic mixture with water (Ezoddin, Abdi, & Lamei, 2016). These solvents are generally prepared by the fact that amidines and tertiary amines can be switched between the two forms by addition of CO_2 (dry ice) and then returned to its nonionic form by the addition of sodium hydroxide (Alshana, Hassan, Al-Nidawi, Yilmaz, & Soylak, 2020). Here, the addition of dry ice changes the miscibility of the amine in water and transforms the protonated amine into a water-soluble carbonate salt (Durelle et al., 2015). Dry ice is preferred as the triggering agent for the switching operation because it is not expensive, green and easily removed. Moreover, the SHSs have been recently used as green solvents for liquid-phase microextraction (LPME) due to their unique physicochemical properties (low toxicity, volatility, or flammability) and high degree of greenness. The most important advantage of using SHSs in LPME is that the extraction of target species is accomplished in a homogeneous phase without dispersing solvent. In addition, this procedure was more famous due to ease, cost-effective and flexibility. N,*N*-dimethylbutylamine (DMButA) has been reported as an extraction solvent for the extraction of organic and inorganic species from foods, biological samples, and environmental samples (Wang et al., 2019;.Wang et al., 2018; Alshana, Yilmaz, & Soylak, 2020).

The purpose of the current research was to develop an analytical method based on the switchable hydrophilicity solvent-based liquid phase microextraction (SHS-LPME) for the determination, preconcentration and extraction of sulfadiazine in milk, honey and water samples. The chemometric based central composite design was employed to optimize key the SHS-LPME conditions. The developed SHS-LPME procedure was investigated for quantitative analysis through the determination of main validation parameters including linearity, correlation coefficient, limit of detection, limit of quantification, enrichment factor, preconcentration factor, relative standard deviation, and extraction recoveries for the SDZ. The analytical features of the developed SHS-LPME procedure was compared with other analytical techniques (UV–VIS spectrophotometry, HPLC-UV, CZE-CD and UPLC-MS/MS) to evaluate its advantages and feasibility for determining of the SDZ in real samples. According to our research, this is the first application of the SHS-LPME procedure, based on DMButA as switchable hydrophilicity solvent, for the preconcentration and extraction of trace-level SDZ in milk, honey and water samples.

2. Materials and methods

2.1. Reagents and chemicals

Unless otherwise stated, all reagents were of analytical purity. The water used in the experimental studies was obtained using a Millipore Milli-Q purification system (Millipore, Bedford, MA, USA). Sulfadiazine (4-amino-*N*-pyridin-2-yl-benzene sulfonamide) (99%, SDZ) was purchased from Merck Company (Darmstadt, Germany). The stock of SDZ solution (1000 mg L^{-1}) was prepared by dissolving an appropriate amount of the reagent in methanol and stored in the dark at 4 °C. Calibration solutions were prepared at different concentrations by serial dilution of the stock solution in methanol. By using citrate, borate, phthalate and phosphate buffer solutions, the desired pH values in experimental studies were achieved. A 2.0 (w/v)% NaCl solution was prepared from its stock solid (Sigma-Aldrich, USA). N,*N*-dimethylbutylamine (99%, 0.721 g/mL at 25 °C, DMButA), N,*N*-dimethyl-*n*-octylamine (95%, 0.765 g/mL at 25 °C, DMOA) and triethylamine (≥99.5%, 0.726 g/mL at 25 °C, TEA) were purchased from Merck. These reagents were used for the preparation of switchable hydrophilicity solvents (SHS). A 5.0 (w/v)% of Na_2CO_3 solution (as alkaline agent) was prepared by dissolving appropriate amount of its solid in the water.

2.2. Instrumentation

UV–Visible Spectrophotometer (Shimadzu UV-1800 PC model) was used to carry out spectral analysis. Quartz cuvettes with a path length of 10 mm were used in the determination step. A model 692 digital pH-meter (Herisau, Switzerland) was applied for pH measurements. Centrifuge (Universal-320, Hettich, London, England), vortex (VG3 model, IKA GmbH, Germany) and ultrasonic bath (SK5210LHC Kudos, Shanghai, China) were used for microextraction processes.

2.3. Sample preparation

The developed SHS-LPME procedure was applied for the separation and preconcentration of SDZ from three different sample groups including milk, honey and water. Milk samples (whole milk, semi whole milk and daily milk) were collected from local markets in Sivas/Turkey. Honey samples were obtained directly from the producers in Sivas, Erzurum and Erzincan. The waste-water was collected in the hospital area in Sivas. Bottled water was purchased from the local grocery store. Well-water was collected from the agricultural area in Sivas. Water samples were filtered using a 0.45 millipore filter. Then, the SHS-LPME procedure was applied to 10 mL of the sample. The following procedure was applied for preparation of milk samples (Karami-Osboo, Miri, Javidnia, Shojaee, & Kobarfard, 2015). First, 5 mL of milk sample was transferred to a 50 mL centrifuge tube and 10.0 mL of acetonitrile was added to the tube. Then, the resulting mixture was vigorously vortexed for 3 min. After the mixture was centrifuged at 1968 g-force for 2 min, 2 mL of supernatant phase was taken into another tube and the final volume was diluted to 10 mL with water. Finally, the diluted solution was subjected to the SHS-LPME procedure.

The following procedure was applied for preparation of honey samples (Yu, Liu, Guo, & Yang, 2013). First, 10 mL of the water was added to a 50 mL conical tube containing 5 mL of honey. The resulting mixture was then vortexed for 2 min and filtered using a 0.45 millipore filter. The resulting filtrate was diluted to 50 mL with the water. The diluted solution was mixed and then centrifuged at 1968 g-force for 15 min. Finally, the SHS-LPME procedure was applied to 10 mL of the obtained supernatant.

2.4. Preparation of switchable hydrophilicity solvent

The SHSs were prepared according to the following method (Heydari & Ramezani, 2019). In this study, three SHSs were prepared in a mixture of equal volumes of DMButA/DMOA/TEA and water. First, 200 mL of water and 200 mL of DMButA/DMOA/TEA were added to three separate 1 L beakers on a magnetic stirrer. In this step, a two-phase system was obtained. Dry ice (~20 g) was then slowly added to the beakers with vigorous mixing by hand until the solution became cloudy. Addition of dry ice was done 20 times in succession to obtain a single protonated the

Table 1a
Symbol. factors. unit. runs and responses for CCD.

Symbol	Factors	Unit	Levels				
			−α	−1	0	+1	+α
A	pH		3.5	4	6.5	9	9.5
B	DMButA volume	μL	50	100	350	600	650
C	NaCI volume	μL	5	50	275	500	545
D	Na_2CO_3 volume	μL	140	200	500	800	860
E	Sonication time	min	0.1	1	5.5	10	10.9

Run	A	B	C	D	E	*Exp
1	4	600	50	800	10	34.5
2	4	100	500	800	10	59.2
3	4	600	500	800	1	26.4
4	6.5	350	5	500	5.5	46.5
5	9	100	500	200	10	18.2
6	9	100	500	800	1	39.1
7	6.5	350	275	500	5.5	58.4
8	9.5	350	275	500	5.5	60.0
9	6.5	50	275	500	5.5	66.4
10	4	100	500	200	1	75.2
11	9	100	50	800	10	44.8
12	6.5	350	275	500	0.1	42.1
13	3.5	350	275	500	5.5	51.7
14	6.5	650	275	500	5.5	65.2
15	6.5	350	275	500	5.5	57.8
16	6.5	350	275	860	5.5	77.5
17	9	600	500	800	10	54.5
18	6.5	350	275	140	5.5	73.2
19	6.5	350	275	500	10.9	15.7
20	4	600	500	200	10	15.1
21	9	600	50	800	1	79.2
22	9	600	500	200	1	99.2
23	9	600	50	200	10	21.1
24	6.5	350	545	500	5.5	48.5
25	9	100	50	200	1	48.4
26	4	600	50	200	1	40.4
27	6.5	350	275	500	5.5	57.8
28	6.5	350	275	500	5.5	57.2
29	6.5	350	275	500	5.5	57.6
30	4	100	50	200	10	42.8
31	6.5	350	275	500	5.5	57.0
32	4	100	50	800	1	53.7

*Recovery% (Exp.): experimental value.

SHSs. Then, the obtained solution was stirred for 2 h at room temperature to ensure the complete protonation of SHSs. And at the end of this step, 400 mL of protonated SHSs were prepared.

2.5. Chemometric design

Chemometric based central composite design (CCD) was applied for optimization of important variables of the SHS-LPME procedure. The CCD was used to evaluate main effects, interaction effects and quadratic effects of the important factors on the recovery of SDZ. A 5-factor, 3-level CCD was applied to identify quadratic response surfaces and generate quadratic polynomial models. The relationship between the coded values and the actual values for statistical calculations was expressed by the Eq. (1).

$$Xi = (Ai - Ao)/\Delta A \quad (1)$$

Where ΔA the step change of factor; Xi was a coded value of the factor; Ao the actual value of the Ai at the center point and Ai the actual value of factor.

The nonlinear quadratic model for the CCD design is expressed by Eq. (2).

$$y = b_0 + \sum_{i=1}^{k} b_i x_i + \sum_{i=1}^{k} b_{ii} x_i^2 + \sum_{1 \leqslant i \leqslant j}^{k} b_{ij}\, x_i x_j + \varepsilon \quad (2)$$

Where y is response, x_i was factors, k was factor number, b_0 was constant, b_i, b_{ij} and b_{ii} were regression parameters for the effects of linear, interaction and quadratic coefficients, respectively, and ε was residue. In addition, the terms X_iX_j and X_i^2 represent the interaction and quadratic terms, respectively. A summary of the design established for this study was presented in Table 1a. Data from studies were evaluated using the Design-Expert® trial version 12.0.1. (Stat-Ease Inc., Minneapolis). Experimental studies were carried out using triplicate measurements.

2.6. SHS-LPME procedure

An aliquot of 10 mL of sample solution containing 50 μg L^{-1} SDZ was spiked into a 15-mL grade centrifuge tube. Then, the pH of the solution was adjusted to pH 7.8 with TRIS-acetate buffer. To enable the extraction of SDZ, 540 μL of the prepared SHS (DMButA/water) and 315 μL of NaCI (2.0, w/v%) were added into the tube. Then, 250 μL of Na_2CO_3 solution (5.0 w/v%, as alkaline agent) was added to the obtained mixture. The tube was placed in an ultrasonic bath and sonicated for 2 min to remove CO_2 and cause the solution to turbid. At this stage, the SDZ in the solution was rapidly extracted into the fine droplets of DMButA phase. The resulting solution was centrifuged at 1968 g-force for 5 min to accelerate to the separation of the water and DMButA phase. The DMButA phase containing the SDZ was collected on top of the mixture. This phase (~400 μL) was transferred to microcuvette with the help of a syringe and absorbance measurements were made using spectrophotometer at 286 nm against solvent blank.

The analytical properties of the developed SHS-LPME procedure were compared with the different techniques and microextraction procedures previously reported in the literature. Here the analytical parameters to be compared are linearity, detection limit, relative standard deviation and enrichment factor and extraction time. The comparison made is only the analytical features of the methods. It is not the data obtained as a result of application to real samples. In this study, the results obtained from real samples were compared with the reference method.

3. Results and discussion

3.1. Preliminary studies before the CCD

Before the CCD optimization step, the most important factor in preliminary studies is the selection of the appropriate extraction solvent. In this regard, three SHSs such as DMButA, DMOA, TEA were prepared as described in section 2.4. Then, these prepared SHSs were tested for extraction of SDZ in model solution under the same extraction conditions. As can be seen from the results in Fig. S1, the best recovery of SDZ was obtained using DMButA. Based on these results, DMButA was chosen as the most suitable SHS for the extraction of SDZ. Then, the effect of extraction temperature on the recovery of SDZ was evaluated at temperatures ranging from room temperature (25 °C) to 65 °C. The results in Fig. S2 show that both effective phase separation and high recovery are achieved at room temperature. The decrease in the recovery of SDZ at high temperatures can be attributed to the decrease in the effectiveness of DMButA due to the increase in temperature.

3.2. Chemometric design results

3.2.1. ANOVA analysis

In order to perform ANOVA analysis, the recovery values of SDZ were entered into the Design-Expert® program. The ANOVA data obtained in the light of the data entered into the Design-Expert® program are presented in Table 1b. According to the ANOVA analysis, p-values should be<0.05 for the constructed model. When Table 1b is examined, it is seen that the p-values of the model and other interactions except DMButA volume* Na_2CO_3 volume are lower than < 0.0001. The numerical magnitude of the F-value of the variables indicates that it contributes more to the recovery of the SDZ. In this context, the most

Table 1b
Analysis of variance (ANOVA) for CCD.

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	11618.61	20	580.93	2674.83	<0.0001	significant
A	238.90	1	238.90	1100.00	<0.0001	
B	8.20	1	8.20	37.74	<0.0001	
C	31.53	1	31.53	145.19	<0.0001	
D	69.26	1	69.26	318.88	<0.0001	
E	2184.40	1	2184.40	10057.82	<0.0001	
AB	2970.25	1	2970.25	13676.17	<0.0001	
AC	10.56	1	10.56	48.63	<0.0001	
AD	57.76	1	57.76	265.95	<0.0001	
AE	432.64	1	432.64	1992.04	<0.0001	
BC	20.25	1	20.25	93.24	<0.0001	
BD	2.72	1	2.72	12.54	0.0046	
BE	294.12	1	294.12	1354.25	<0.0001	
CD	484.00	1	484.00	2228.52	<0.0001	
CE	12.96	1	12.96	59.67	<0.0001	
DE	1612.02	1	1612.02	7422.37	<0.0001	
A^2	8.83	1	8.83	40.65	<0.0001	
B^2	155.80	1	155.80	717.35	<0.0001	
C^2	254.08	1	254.08	1169.86	<0.0001	
D^2	746.05	1	746.05	3435.10	<0.0001	
E^2	2009.49	1	2009.49	9252.44	<0.0001	
Residual	2.39	11	0.2172			
Lack of Fit	1.16	6	0.1926	0.7809	0.6191	not significant
Pure Error	1.23	5	0.2467			
Cor Total	11621.00	31				
Quality of quadratic model						
Std. Dev.		0.4660		R^2	0.9998	
Mean		51.39		Adjusted R^2	0.9994	
C.V. %		0.9069		Predicted R^2	0.9936	

A: pH.
B:DMButA volume.
C:NaCI volume.
D:Na_2CO_3 volume.
E:Sonication time.
C.V: Coefficient of variation.

important for linear, binary and quadratic interactions affecting the recovery of SDZ are sonication time (F-value:10057.82), pH*DMButA volume (F-value:13676.17) and sonication time* sonication time (F-value:9252.44), respectively. The quality of the quadratic model is evaluated with the numerical values of the R^2 parameters (R^2, Adjusted-R^2 and Predicted-R^2). Here, it is desirable for R^2 values to be close to 1. Also, the difference between Adjusted-R^2 and Predicted-R^2 should be<0.2 for the validation of the model. In the light of the explanations, when Table 1b is examined, it is easily seen that the R^2 values (R^2: 0.9998, Adjusted-R^2:0.9994 and Predicted-R^2:0.9936) are close to 1 and the difference between the relevant R^2 values is much smaller than 0.2. These results indicate that the quality parameters of the model are validated. The lack of fit assessment determines the model's failure to represent data obtained in the study area at a point not included in the regression analysis. It is desirable that the p-value for lack of fit be greater than 0.05. The lack of fit p-value (0.6191) from the studies showed that the model used was significant and sufficient to represent the relationship between response and independent variables. Since all interactions are significant in the established model, a full quadratic Equation (3) of the recovery of SDZ depending on the variables.

$$\text{Recovery}(\%) = +57.70 + 3.56A - 0.6589B + 1.29C + 1.92D - 10.76E + 13.63AB + 0.8125AC + 1.90AD - 0.20AE + 1.13BC + 0.4125BD - 4.29BE - 5.50CD - 0.9000CE + 10.04DE - 1.33A^2 + 5.58B^2\ 7.13C^2 + 12.21D^2 - 20.04E^2 \quad (3)$$

One of the important statistical evaluations is the numerical value of the coefficient of variation (C.V%) obtained from the results. For the validity of the model, the C.V% value must be<20%. As can be seen from Table 1b, the C.V% obtained for this study was 0.9069. The harmony between the recovery values predicted by the model and the recovery value obtained from the experimental studies can be seen from Fig. S3.

3.2.2. *Effect of process variables*

3D response surfaces were plotted to obtain more details of micro-extraction variables related to recovery of the SDZ. These graphs simultaneously provide information about the response of two variables and the relationship between their levels, while the other variables are kept constant at their central level. The 3D response surface plots presented in Fig. S4(a-d) represent the relationship between recovery and five microextraction variables (pH, DMButA volume, NaCI volume, Na_2CO_3 volume and sonication time). Fig. S4a describes the 3D response surface for the effect of DMButA volume and pH on recovery of SDZ. The recovery of SDZ increased with increasing pH from 5.5 to 8.3 and DMButA volume from 350 μL to 600 μL. But, with a further increase in pH from 8.3 to 9 min and DMButA volume from 600 μL to 650 μL, the recovery of SDZ declined. Also, the recovery of SDZ was low at acidic pH and DMButA volumes<500 μL. Fig. S4b depicts the 3D response surface for the effect of DMButA volume and NaCI volume on recovery of the SDZ. The maximum recovery was observed in range of 380–450 μL NaCI volume and 450–600 μL DMButA volume. With further decreases in NaCI volume (≤250 μL) and DMButA volume (≤400 μL), the recovery decreased sharply. Fig. S4c shown the 3D response surface for the effect of DMButA volume and Na_2CO_3 volume on the recovery of SDZ. When the DMButA volume increased from 450 μL to 640 μL and the Na_2CO_3 volume increased from 150 to 350 μL, the recovery gradually increased. In particular, the recovery of SDZ decreased rapidly at high volumes of Na_2CO_3. Fig. S4d explains the 3D response surface for the effect of NaCI volume and sonication time on the recovery of SDZ. The recovery of SDZ increased with increasing sonication time from 0.5 to 4 min and NaCI volume from 290 μL to 420 μL. But, with a further increase in sonication

Table 2
Analytical characteristics of the SHS-LPME procedure.

Analytical characteristics	Obtained value
Linearity (μg L^{-1})	15–300
R^2	0.997
LOD (3 s/m. μg L^{-1})	4.5
LOQ (10 s/m. μg L^{-1})	15
RSD (for 50 μg L^{-1}N = 3)	2.7
Extraction recovery (%)	96 ± 3
EF	113

S_b/m (where S_b is the standard deviation of the blank and m is the slope of the calibration graph).
Regression coefficient (R^2). Limit of detection (LOD). Limit of quantification (LOQ). Enrichment factor (EF). Relative standard deviation (RSD).

Table 3a
Investigation of the effect of some chemical species on the determination and recovery of SDZ.

Chemical species	Tolerable limit*	Recover (%)
NH_4^+	2000	99 ± 3
Mn^{2+}	2000	97 ± 2
K^+	2000	98 ± 3
SO_4^{2-}	2000	99 ± 4
Pb^{2+}	1000	98 ± 2
F^-	1000	97 ± 2
Fe^{2+}	1000	97 ± 3
CO_3^{2-}	500	98 ± 6
Ni^{2+}	500	96 ± 4
Al^{3+}	500	96 ± 3
Co^{2+}	500	97 ± 5
Sulfamethoxypyridazine	250	96 ± 5
Sulfamethoxazole	250	95 ± 3
Sulfadoxine	250	95 ± 4
Sulfathiazole	100	94 ± 4

*[Chemical type amount] / [Sulfadiazine amount].

time from 5 to 9 min, the recovery of SDZ declined.

3.2.3. Determination of optimum conditions

It is important to determine the optimum values of the variables in order to provide easy phase separation and to obtain quantitative analytical data. In this context, optimum data for pH, DMButA volume, NaCI volume, Na_2CO_3 volume and sonication time were produced by the model established as 7.8, 540 μL, 315 μL, 250 μL, and 2 min respectively. As a result of three replications performed, a high agreement was observed between the experimental recovery for SDZ and the recovery predicted by the model. Therefore, these data for variables were optimally used in further experimental studies.

3.3. Analytical performance

The linearity, correlation coefficient (R^2), limit of detection (LOD), limit of quantification (LOQ), enrichment factor (EF), preconcentration factor (PF), relative standard deviation (RSD), and extraction recoveries were listed on Table 2. Linearity was investigated by adding standard SDZ solutions to the sample solutions, and excellent linearity in the range of 15–300 μg L^{-1} was obtained with a the R^2 above 0.997. The LOD and LOQ values were calculated according to the Equation (3) and (4), respectively.

$$LOD = 3 \cdot S_b/m \quad (4)$$

$$LOQ = 10 \cdot S_b/m \quad (5)$$

Where S_b was the standard deviation of the blank and m was the slope of the calibration graph. The LOD was 4.5 μg L^{-1}, while the LOQ was 15 μg L^{-1}. The EF was calculated from the ratio of the slopes of the calibration curves before and after the SHS-LPME procedure, while the PF was calculated from the ratio of the initial volume to the final volume. The EF and PF from the related calculations were found to be 113 and 150, respectively. The RSD and extraction recovery from 3 replicates of 50 μg L^{-1} SDZ were 2.7% and 96 ± 3, respectively.

Table 3b
Results of the intra-day repeatability and inter-day reproducibility studies of the SHS-LPME procedure.

Added (μg L^{-1})	Intra-day repeatability (N = 5)		Inter-day reproducibility (N = 5 × 5)	
	RSD (%)	Recovery (%)	RSD (%)	Recovery (%)
25	2.4	95 ± 2	3.2	93 ± 4
100	2.9	97 ± 3	3.8	95 ± 4
200	3.7	98 ± 3	4.5	96 ± 3

RSD: Relative standard deviation.

3.4. Selectivity

Since the optimization step was performed using standard solutions, the selectivity of the developed SHS-LPME procedure for SDZ should be examined. In this context, the developed SHS-LPME procedure was applied to the solutions in which different chemical species were added to standard solutions in varying proportions. Next, tolerance limits and recovery for the related chemical species were determined. The numerical data were presented in Table 3a. The tolerance limit and recovery values for the studied chemical species were 100–2000 and 94 ± 4%-99 ± 2%, respectively. These results showed that the optimized conditions exhibited high selectivity for the SDZ in the presence of other chemical species.

3.5. Precision

The precision of the developed SHS-LPME procedure was evaluated by intra-day repeatability and inter-day reproducibility studies. For these studies, 25, 100 and 200 μg L^{-1} concentrations of SDZ were used. For intra-day repeatability, these concentrations of SDZ were analysed for five replicates within one day, while for inter-day reproducibility, the same concentrations were analysed in five replicates for consecutive

Table 3c
The results of the SDZ determination in real samples (N = 4. P = 0.95; tk = 3.18).

Samples	Present method			Reference method	*t*-criterion*
	Added μg L^{-1}	Obtained concentration μg L^{-1}	Recovery (%)		
Whole milk	–	47.2 ± 1.7	–	45.6 ± 1.4	1.45
	50	95.7 ± 3.2	97 ± 4	–	–
Semi whole milk	–	11.6 ± 1.1	–	12.9 ± 1.1	1.18
	50	60.6 ± 2.4	98 ± 2	–	–
Daily milk	–	32.5 ± 2.0	–	36.7 ± 2.1	2.05
	50	80.0 ± 2.6	95 ± 6	–	–
Honey-1	–	24.7 ± 1.5	–	26.9 ± 1.8	1.36
	50	71.7 ± 2.3	94 ± 4	–	–
Honey-2	–	18.3 ± 1.2	–	19.5 ± 1.4	0.92
	50	66.3 ± 1.9	96 ± 3	–	–
Honey-3	–	78.1 ± 2.4	–	74.8 ± 2.5	1.35
	50	127.6 ± 4.2	99 ± 2	–	–
Waste-water	–	16.9 ± 1.3	–	18.4 ± 1.1	1.25
	50	65.4 ± 2.8	97 ± 2	–	–
Well-water	–	27.4 ± 1.9	–	29.2 ± 1.7	1.01
	50	74.4 ± 3.2	94 ± 4	–	–
Bottled water	–	36.2 ± 1.8	–	37.7 ± 2.0	0.89
	50	84.2 ± 2.6	96 ± 3	–	–

The criterion *t*-value established by two paired ANOVA analysis for 6-degree of freedom at 95% confidence limit where $t_{exp} = (m_a - m_b)/ S_{pooled} \times [(n_1 + n_2)/n_1 \times n_2]^{1/2}$ and $S_{pooled} = [(n_1\text{-}1)\ S^2_{m.1} + (n_2\text{-}1)\ S^2_{m.2}\ /(n_1 + n_2\text{-}2)]^{1/2}$.

five days. Recovery and RSD for intra-day repeatability studies were in the range of 95 ± 2–98 ± 3% and 2.4–3.7%, respectively, while recovery and RSD for inter-day reproducibility studies were in the range of 93 ± 4–96 ± 3% and 3.2–4.5%, respectively. Comprehensive data were presented in Table 3b.

3.6. Real sample analysis

The applicability of the developed SHS-LPME procedure was investigated by the extraction, preconcentration and determination of SDZ in milk, honey and water samples. In addition, to evaluate the accuracy of the developed SHS-LPME procedure, the selected samples were also analyzed with the reference method. The results found with both the developed SHS-LPME procedure and the reference method (Dadfarnia, Hajishabani, & Rad, 2011) were compared statistically. In this context, in the statistical evaluation using Student's *t*-test, it was seen that there was no significant difference at the 95% confidence level between the value obtained using the developed SHS-LPME procedure and the reference method. In addition to these, the accuracy of the developed SHS-LPME procedure was investigated by the recovery study. In this context, 50 μg L^{-1} of standard SDZ was added to the selected samples and then the developed SHS-LPME procedure was applied to the samples. Recovery values for the selected samples were found to be in the range of 94 ± 4–99 ± 2%. Comprehensive analytical results obtained in the analysis of milk, honey and water samples were presented in Table 3c.

3.7. Comparison of analytical features with reported some analytical approaches

The analytical features of developed SHS-LPME procedure was compared with other analytical approaches in terms of analytical data such as linearity, LOD, RSD, EF/PF and extraction time. The analytical features of the developed SHS-LPME procedure were compared with the CPE, MIL-DLLME, SS–MSPME, LLME, MSPE and d-SPE microextraction procedures using UV–VIS spectrophotometry, HPLC-UV, CZE-CD and UPLC-MS/MS techniques (See Table S1f or comprehensive results). As can be seen from the table presented, the developed SHS-LPME procedure exhibited shorter extraction time and higher EF/PF compared to other analytical approaches. Compared with the same detection technique, the developed SHS-LPME procedure exhibited greater linearity, lower LOD and lower RSD. Compared with the HPLC-UV detector detection technique, lower RSD was obtained with the developed SHS-LPME procedure, while linearity and LOD were comparable. In addition, compared to techniques such as CZE-CD and UPLC-MS/MS, the developed SHS-LPME procedure has a lower RSD value and a wide linear range, but the LODs of these techniques are lower than the developed SHS-LPME procedure. The developed SHS-LPME procedure was shown to be fast, inexpensive, and green when compared with microextraction procedures.

4. Conclusions

In this research, a green, selective and reliable the SHS-LPME procedure was developed for the extraction and preconcentration of the SDZ in milk, honey and water samples prior to spectrophotometric analysis. Chemometric-based central composite design were successfully employed to get the optimized parameters for extraction of the SDZ. Dry ice and Na_2CO_3 were used to switch SHS between the two phases. Compared to other triggers such as light and oxidants, dry ice has been used in the preparation of SHS because of its advantages such as being inexpensive, non-hazardous, not accumulating in the system and easily removed. The main advantage of SHS is that allows the extraction of SDZ in a homogeneous phase without dispersing solvent. The developed SHS-LPME procedure showed high selectivity and enrichment factor of the SDZ. In addition, the SHS-LPME procedure was sensitive, fast, simple and reproducible with a high PF of 150. The developed SHS-LPME procedure showed appropriate accuracy and precision. The SHS-LPME procedure was suitable for the determination and extraction of SDZ from complex matrices.

CRediT authorship contribution statement

Nail Altunay: Supervision, Investigation, Validation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.foodchem.2022.133540.

References

Afsharipour, R., Shabani, A. M. H., Dadfarnia, S., & Kazemi, E. (2020). Selective fluorometric determination of sulfadiazine based on the growth of silver nanoparticles on graphene quantum dots. *Microchimica Acta, 187*(1), 1–8. https://doi.org/10.1007/s00604-019-4001-9

Ait Errayess, S., Idrissi, L., & Amine, A. (2018). Smartphone-based colorimetric determination of sulfadiazine and sulfasalazine in pharmaceutical and veterinary formulations. *Instrumentation Science & Technology, 46*(6), 656–675. https://doi.org/10.1080/10739149.2018.1443943

Alshana, U., Hassan, M., Al-Nidawi, M., Yilmaz, E., & Soylak, M. (2020). Switchable-hydrophilicity solvent liquid-liquid microextraction. *TrAC Trends in Analytical Chemistry, 116025*. https://doi.org/10.1016/j.trac.2020.116025

Alshana, U., Yilmaz, E., & Soylak, M. (2020). Switchable solvents in separation and preconcentration of organic and inorganic species. In *New generation green solvents for separation and preconcentration of organic and inorganic species* (pp. 347–380). Elsevier. https://doi.org/10.1016/B978-0-12-818569-8.00008-5.

Campillo, N., Gavazov, K., Viñas, P., Hagarova, I., & Andruch, V. (2020). Liquid-phase microextraction: Update May 2016 to December 2018. *Applied Spectroscopy Reviews, 55*(4), 307–326. https://doi.org/10.1556/1326.2019.00636

Dadfarnia, S., Hajishabani, A. M., & Rad, H. F. (2011). Indirect Determination of Sulfadiazine by Cloud Point Extraction/Flow Injection-Flame Atomic Absorption (CPE/FI-FAAS) Spectrometry. *Journal of the Chinese Chemical Society., 58*(4), 503–508. https://doi.org/10.1002/jccs.201190013

Dai, T., Duan, J., Li, X., Xu, X., Shi, H., & Kang, W. (2017). Determination of sulfonamide residues in food by capillary zone electrophoresis with on-line chemiluminescence detection based on an Ag (III) complex. *International Journal of Molecular Sciences, 18*(6), 1286. https://doi.org/10.3390/ijms18061286

Dil, E. A., Ghaedi, M., Mehrabi, F., & Tayebi, L. (2021). Highly selective magnetic dual template molecularly imprinted polymer for simultaneous enrichment of sulfadiazine and sulfathiazole from milk samples based on syringe–to–syringe magnetic solid–phase microextraction. *Talanta, 232*, Article 122449. https://doi.org/10.1016/j.talanta.2021.122449

Durelle, J., Vanderveen, J. R., Quan, Y., Chalifoux, C. B., Kostin, J. E., & Jessop, P. G. (2015). Extending the range of switchable-hydrophilicity solvents. *Physical Chemistry Chemical Physics, 17*(7), 5308–5313. https://doi.org/10.1039/C4CP05313C

Ebrahimi, M., Nikoofard, H., Faridbod, F., Dezfuli, A. S., Beigizadeh, H., & Norouzi, P. (2017). A ceria NPs decorated graphene nano-composite sensor for sulfadiazine determination in pharmaceutical formulation. *Journal of Materials Science: Materials in Electronics, 28*(22), 16704–16712. https://doi.org/10.1007/s10854-017-7583-1

Ezoddin, M., Abdi, K., & Lamei, N. (2016). Development of air assisted liquid phase microextraction based on switchable-hydrophilicity solvent for the determination of palladium in environmental samples. *Talanta, 153*, 247–252. https://doi.org/10.1016/j.talanta.2016.03.018

Hassoun, A., Måge, I., Schmidt, W. F., Temiz, H. T., Li, L., Kim, H. Y., … Cozzolino, D. (2020). Fraud in animal origin food products: Advances in emerging spectroscopic detection methods over the past five years. *Foods, 9*(8), 1069. https://doi.org/10.3390/foods9081069

Heydari, F., & Ramezani, M. (2019). Application of response surface methodology for optimization of conditions for nickel determination in water and vegetables by switchable solvent based liquid phase microextraction. *Journal of Analytical Chemistry, 74*(11), 1081–1088. https://doi.org/10.1134/S1061934819110054

Jansomboon, W., Boontanon, S. K., Boontanon, N., Polprasert, C., & Da, C. T. (2016). Monitoring and determination of sulfonamide antibiotics (sulfamethoxydiazine, sulfamethazine, sulfamethoxazole and sulfadiazine) in imported Pangasius catfish products in Thailand using liquid chromatography coupled with tandem mass spectrometry. *Food Chemistry, 212*, 635–640. https://doi.org/10.1016/j.foodchem.2016.06.026

Karami-Osboo, R., Miri, R., Javidnia, K., Shojaee, M. H., & Kobarfard, F. (2015). Extraction and determination of sulfadiazine and sulfathiazole in milk using magnetic solid phase extraction-HPLC-UV. *Analytical Methods, 7*(4), 1586–1589. https://doi.org/10.1039/C4AY02503B

Kazemi, E., Dadfarnia, S., Shabani, A. M. H., Fattahi, M. R., & Khodaveisi, J. (2017). Indirect spectrophotometric determination of sulfadiazine based on localized surface plasmon resonance peak of silver nanoparticles after cloud point extraction. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 187*, 30–35. https://doi.org/10.1016/j.saa.2017.06.023

Kazemi, E., Shabani, A. M. H., & Dadfarnia, S. (2017). Application of graphene oxide-silica composite reinforced hollow fibers as a novel device for pseudo-stir bar solid phase microextraction of sulfadiazine in different matrices prior to its spectrophotometric determination. *Food Chemistry, 221*, 783–789. https://doi.org/10.1016/j.foodchem.2016.11.103

Liu, H., Ren, J., Hao, Y., He, P., & Fang, Y. (2007). Flow injection–chemiluminescence determination of sulfadiazine in compound naristillae. *Talanta, 72*(3), 1036–1041. https://doi.org/10.1016/j.talanta.2006.12.048

Liu, L., & Zhu, T. (2017). Emulsification liquid–liquid microextraction based on deep eutectic solvents: An extraction method for the determination of sulfonamides in water samples. *Analytical Methods, 9*(32), 4747–4753. https://doi.org/10.1039/C7AY01332A

Pochivalov, A., Vakh, C., Garmonov, S., Moskvin, L., & Bulatov, A. (2020). An automated in-syringe switchable hydrophilicity solvent-based microextraction. *Talanta, 209*, Article 120587. https://doi.org/10.1016/j.talanta.2019.120587

Pourreza, N., Rastegarzadeh, S., & Larki, A. (2015). Determination of fungicide carbendazim in water and soil samples using dispersive liquid-liquid microextraction and microvolume UV–vis spectrophotometry. *Talanta, 134*, 24–29. https://doi.org/10.1016/j.talanta.2014.10.056

Shi, P., & Ye, N. (2014). Magnetite–graphene oxide composites as a magnetic solid-phase extraction adsorbent for the determination of trace sulfonamides in water samples. *Analytical Methods, 6*(24), 9725–9730. https://doi.org/10.1039/C4AY02027H

Sriram, B., Baby, J. N., Hsu, Y. F., Wang, S. F., Benadict Joseph, X., George, M., … Lin, K. C. (2021). MnCo2O4 Microflowers anchored on P-doped g-C3N4 nanosheets as an electrocatalyst for voltammetric determination of the antibiotic drug sulfadiazine. *ACS Applied Electronic Materials, 3*(9), 3915–3926. https://doi.org/10.1021/acsaelm.1c00506

Tong, F., Zhang, Y., Chen, F., Li, Y., Ma, G., Chen, Y., … Chu, Q. (2013). Hollow-fiber liquid-phase microextraction combined with capillary electrophoresis for trace analysis of sulfonamide compounds. *Journal of Chromatography B, 942*, 134–140. https://doi.org/10.1016/j.jchromb.2013.10.038

Wang, H., Xia, M., Ling, Y., Qian, F., Xu, J., Wang, Z., … Wang, X. (2019). Switchable hydrophilicity solvent based and solidification-assisted liquid-phase microextraction combined with GFAAS for quantification of trace soluble lead in raw bovine and derivative milk products. *Food Additives & Contaminants: Part A, 36*(11), 1654–1666. https://doi.org/10.1080/19440049.2019.1644458. DOI: 10.1007/s12161-018-1187-0

Wang, X., Gao, M., Zhang, Z., Gu, H., Liu, T., Yu, N., … Wang, H. (2018). Development of CO2-mediated switchable hydrophilicity solvent-based microextraction combined with HPLC-UV for the determination of bisphenols in foods and drinks. *Food Analytical Methods, 11*(8), 2093–2104.

Wang, Z., Wang, X., Tian, H., Wei, Q., Liu, B., Bao, G., … Wang, L. (2019). High throughput determination of 28 veterinary antibiotic residues in swine wastewater by one-step dispersive solid phase extraction sample cleanup coupled with ultra-performance liquid chromatography-tandem mass spectrometry. *Chemosphere, 230*, 337–346. https://doi.org/10.1016/j.chemosphere.2019.05.047

Yang, L., Shi, Y., Li, J., & Luan, T. (2018). In situ derivatization and hollow-fiber liquid-phase microextraction to determine sulfonamides in water using UHPLC with fluorescence detection. *Journal of Separation Science, 41*(7), 1651–1662. https://doi.org/10.1002/jssc.201701041

Yao, T., & Du, K. (2020). Simultaneous determination of sulfonamides in milk: In-situ magnetic ionic liquid dispersive liquid-liquid microextraction coupled with HPLC. *Food Chemistry., 331*, Article 127342. https://doi.org/10.1016/j.foodchem.2020.127342

Yu, F., Liu, C., Guo, Y., & Yang, Y. (2013). Ultrasound-assisted cloud point extraction for the determination of sulfonamides in honey samples by fluorescence spectrophotometry. *Analytical Methods, 5*(16), 3920–3926. https://doi.org/10.1039/C3AY26587K

Yu, F., Liu, C., Guo, Y., & Yang, Y. (2014). Vortex-Assisted Liquid-Liquid Microextraction for the Determination of Residual Sulfonamides in Meat Samples with Spectrofluorophotometer. *Spectroscopy Letters, 47*(10), 761–770. https://doi.org/10.1080/00387010.2013.845576

Yu, W., Liu, Z., Cui, S., Zhang, S., Yang, X., Lei, L., … Yu, A. (2014). In-syringe ionic liquid dispersive liquid–liquid microextraction for the determination of sulfonamides in blood using high-performance liquid chromatography. *Analytical Methods, 6*(8), 2545–2552. https://doi.org/10.1039/C3AY41726C

Zhang, X. J., Zheng, B., & Chen, X. C. (2009). Simultaneous determination of 4 sulfonamide residues in fishery products by high performance liquid chromatography with fluorescence detection. *Food Science, 30*(8), 235–237.

Further readings

Ibarra, I. S., Miranda, J. M., Rodriguez, J. A., Nebot, C., & Cepeda, A. (2014). Magnetic solid phase extraction followed by high-performance liquid chromatography for the determination of sulphonamides in milk samples. *Food Chemistry., 157*, 511–517. https://doi.org/10.1016/j.foodchem.2014.02.069

Pochivalov, A., Cherkashina, K., Shishov, A., & Bulatov, A. (2021). Microextraction of sulfonamides from milk samples based on hydrophobic deep eutectic solvent formation by pH adjusting. *Journal of Molecular Liquids, 339*, Article 116827. https://doi.org/10.1016/j.molliq.2021.116827