Microchemical Journal 144 (2019) 469–473

Contents lists available at ScienceDirect

Microchemical Journal

journal homepage: www.elsevier.com/locate/microc

An automated homogeneous liquid-liquid microextraction based on deep eutectic solvent for the HPLC-UV determination of caffeine in beverages

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ARTICLE INFO

Keywords:
Homogeneous liquid-liquid microextraction
Deep eutectic solvent
Automation
Flow analysis
HPLC-UV
Caffeine
Soft drinks

ABSTRACT

This work presents an automated homogeneous liquid-liquid microextraction procedure for separation of caffeine from beverages. The microextraction procedure involved mixing sample and water-miscible deep eutectic solvent (DES, choline chloride with phenol at a 1:3 molar ratio) into a mixing chamber of a flow system resulting formation of homogeneous solution. Injection of aprotic solvent (tetrahydrofuran) into homogeneous sample solution promoted the fine DES droplets formation and caffeine extraction into DES phase separated. The automated homogeneous liquid-liquid microextraction procedure was coupled with a HPLC-UV system. The conditions of caffeine microextraction and its HPLC-UV determination in DES phase were studied and optimized. Under optimal experimental conditions the linear detection range and limit of detection, calculated from a blank test, based on 3σ were found to be 0.1–200 mg L^{-1} and 0.03 mg L^{-1}, respectively. The application of the developed procedure was demonstrated in the determination of caffeine in commercial soft drinks samples.

1. Introduction

Caffeine (1,3,7-trimethyl-1*H*-purine-2,6 (3*H*,7*H*)-dione) (ESM Fig. 1) is a natural alkaloid widely used in food industry as the most favorable psychostimulant in beverages or foods for motor activation, mood changes, information processing and cognitive/motor performances [1]. Caffeine can have both positive and negative health effects. On the one hand, it is powerful stimulant of the central nervous system and also stimulates the cardiac muscle. On the other hand, its high amounts have noticeable irritation of gastrointestinal tract [2] and might cause the “caffeinism” syndrome resulting anxiety, insomnia, irritability and headaches [3]. Up to 300 mg of caffeine a day is considered safe for most healthy adults [4]. It can be consumed daily with coffee, tea and energy drinks and also with pharmaceuticals. Therefore, the monitoring of caffeine's content in foods and drinks is an important challenge of food quality control.

Various analytical techniques based on high-performance liquid chromatography (HPLC) with UV-detection [5] and MS-detection [6], capillary electrophoresis (CE) with UV-detection [7], gas chromatograph with flame ionization detection (GC-FID) [8], thin layer chromatography [9], voltammetry [10] and synchronous fluorescence [11] have been developed for the determination of caffeine in beverages. Taking into account the complexity of beverages matrixes containing high amounts of sugar, artificial flavors, dyes, food preservatives etc., the developed techniques usually include sample preparation procedures based on dispersive liquid-liquid microextraction [12], solid phase extraction [13], magnetic solid phase microextraction [14] and molecularly imprinted polymer-solid phase extraction [15].

How to develop a faster, simpler, more inexpensive and environmentally-friendly sample preparation technique is very important in modern analytical society [16]. The automation and miniaturization of sample preparation based on flow systems allow to reduce sample and reagents consumption, time of analysis as well as improve precision and accuracy [17].

Recently, a fully-automated dispersive liquid-liquid microextraction procedure has been developed for the fast and efficient separation and preconcentration of caffeine from beverages [18]. The procedure was automated based on lab-in-syringe approach. The developed automated technique has advantages such as quickness, low cost, simplicity, high sensitivity and selectivity. However, the developed microextraction procedure assumes analyte extraction into chlorinated solvent which is not compatible with analytical instrumentation such as the HPLC-UV, HPLC-MC/MC and CE-UV systems.

A search for alternative extrication solvents is of interest for sample pretreatment. Recently, new potentially effective extractants – deep eutectic solvents (DESs) have appeared in analytical chemistry [19]. DESs are generally composed of two or three cheap components that are capable of self-association, often through hydrogen bond interactions,

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https://doi.org/10.1016/j.microc.2018.10.014
Received 13 September 2018; Accepted 5 October 2018
Available online 06 October 2018
0026-265X/

to form a eutectic mixture with a melting point lower than that of each individual component [20]. Recently, water-soluble DES based on choline chloride with phenol was proposed for preconcentration of analytes from aqueous sample phase [21–24]. This DES can be dissolved in aqueous phase resulting homogeneous solution formation. Addition of aprotic solvent into DES aqueous solution can promote DES phase separation. This phenomenon was used for the extraction of malachite green [21], rhodamine B in cosmetic products [22], cobalt from water [23] and speciation of chromium(III/VI) in environmental samples [24]. To the best of our knowledge, the microextraction of caffeine into DESs has not been studied and presented in literature.

In this research an automated homogeneous liquid-liquid microextraction (A-HLLME) of caffeine from beverage using DES is presented. We found that DES based on choline chloride with phenol provided fast and efficient extraction of caffeine from aqueous phase for the first time. The proposed A-HLLME procedure assumes mixing beverage sample and DES into a mixing chamber of a flow system resulting formation of homogeneous solution, injection of aprotic solvent followed by the fine DES droplets formation and caffeine extraction into DES phase separated. The DES phase obtained can be directly introduced into a HPLC-UV system. The A-HLLME procedure was coupled with a HPLC-UV system for the determination of caffeine. Taking into account that phenol is hazardous component of DES, miniaturization of microextraction procedure was successfully implemented based on the flow system.

2. Experimental

2.1. Reagents and solutions

All chemicals were of analytical reagent grade. Caffeine was purchased from Ecolan (Russia). Stock solution of analyte (1 g L^{-1}) was prepared by dissolving an appropriate amount in ultra-pure water from Millipore Milli-Q RG (Millipore, USA) and stored in a refrigerator at 4 °C. Working caffeine solutions were prepared immediately before the experiments by dilution of the stock solutions with ultra pure water. Phenol, tetrahydrofuran, acetone, dioxane, ethyl acetate, NaCl, HCl, NaOH, sucrose and choline chloride were purchased from Vecton (Russia).

2.2. Samples

Five samples of beverages (cola, two energy drinks and two samples of ice-tea) were purchased from a local supermarket (St. Petersburg, Russia) and analyzed. Spiked beverage samples were prepared by addition of calculated volumes of working caffeine solutions to samples.

2.3. Synthesis of DES

DESs were prepared according to the presented in literature procedure [23]. Choline chloride was mixed with phenol in a 15 mL screw-cap tube at molar ratios of 1:1, 1:2, 1:3 and 1:4, respectively. The mixture was vortexed and then kept at room temperature until a clear liquid was formed about 15 min.

2.4. Manifold and apparatus

The flow system (Fig. 1) consisted of eight-port selection valve (1) (Sciware Systems SL, Spain), syringe pump (Sciware Systems SL, Spain) (flow rate is from 0.1 to 10 mL min^{-1}) with 10 mL glass syringe equipped with a selection valve (2), peristaltic pump (Masterflex, USA) with PVC pumping tube (Watson-Marlow, Russia), mixing chamber (a pipette tip, 1.0 mL volume), PTFE holding coil (2 mL). PTFE tubs of 0.8 mm in i.d. were used for the entire manifold. The flow system was coupled with a LC-20 Prominence liquid chromatograph system (Shimadzu, Japan).

A gas chromatograph with a NPD (GC-2014, Shimadzu, Japan) was used for the GC-NPD determination of caffeine as a referent method.

2.5. The automated procedure for the caffeine determination

The first step of the automated procedure (Fig. 1) included setting the syringe pump to the “Out” position and then aspiration 1 mL of sample (1) and 50 μL of DES (choline chloride with phenol at a 1:3 molar ratio) (2) through the multiport valve into the holding coil by backward movement of the syringe pump plunger. The mixture obtained was then transferred by forward movement of the syringe pump from the holding coil into the mixing chamber. To promote the DES dissolution in sample, the syringe pump was switched to the air port (On), and 10 mL of air was aspirated into it. The air was then transferred into the mixing chamber at 10 mL min^{-1} flow rate by forward movement of the syringe pump through port 8.

Then 50 μL of tetrahydrofuran was injected by the peristaltic pump into the mixing chamber resulting DES phase separation and analyte microextraction. To promote extraction process and final phase separation, the syringe pump was switched to the air port (On), and 10 mL of air was aspirated into it. The air was then transferred into the mixing chamber at 10 mL min^{-1} flow rate by forward movement of the syringe pump through port 8. After final phase separation (30 s) the bottom sample phase was transferred to the waste (5) and the top DES phase was mixed with 50 μL of water (4) and transferred to an autosampler of the HPLC-UV system (6). The flow system was washed with water (4) to prevent any cross-contamination.

Chromatographic separation was performed using a Zorbax Bonus-RP column (Agilent, 2500 × 2.1 mm, 3.5 μm). Mobile phase was deionized water-acetonitrile (9:1, v/v). The analyte was eluted with a flow rate of 1 mL min^{-1}. The analytical wavelength was 220 nm.

2.6. GC-NPD determination of caffeine

10 mL of sample was mixed with 0.5 mL of chloroform for 10 min. Then the solution was centrifuged for 10 min at 5000 rpm. After that chloroform phase was analyzed by GC-NPD method [12]. The volume of injected sample was 1 μL. Separation was carried out on a CP-Sil 8 capillary column (20 m × 0.25 mm i.d. and film thickness 0.25 μm) (Supelco, Bellefonte, USA). Nitrogen (99.999%, Russia) was used as the carrier gas at a constant linear velocity of 30 cm s^{-1}. The oven temperature was programmed as follows: initial temperature 100 °C (held 2 min), from 100 to 290 °C at a rate of 15 °C min^{-1} and held at 290 °C for 6 min. The injector and FID temperatures were maintained at 250 °C. Hydrogen gas was generated with a hydrogen generator (OPGU-1500S, Shimadzu, Japan) for FID at a flow rate of 40 mL min^{-1}. The flow rate of air for FID was 300 mL min^{-1}.

3. Results and discussion

3.1. Preliminary studies

The A-HLLME procedure using DES prior to the HPLC-UV caffeine determination was used to remove matrix present in beverages to minimize the risk that the matrix might block the column of the HPLC-UV system and impair the chromatographic performance. For caffeine separation from aqueous sample phase DESs based on choline chloride with phenol were studied. This type of DESs was chosen in this study due to complete solubilisation of the DESs in the aqueous sample provides the contact surface between phases infinitely large resulting high extraction efficiency. The extraction mechanism using DESs can be based on hydrophobic, electrostatic and π-π interactions with target analytes [23]. Caffeine contains two fused rings: pyrimidinedione and imidazole (ESM Fig. 1). Interactions between nitrogen of caffeine imidazole ring and proton of phenol can be considered as a main extraction mechanism.

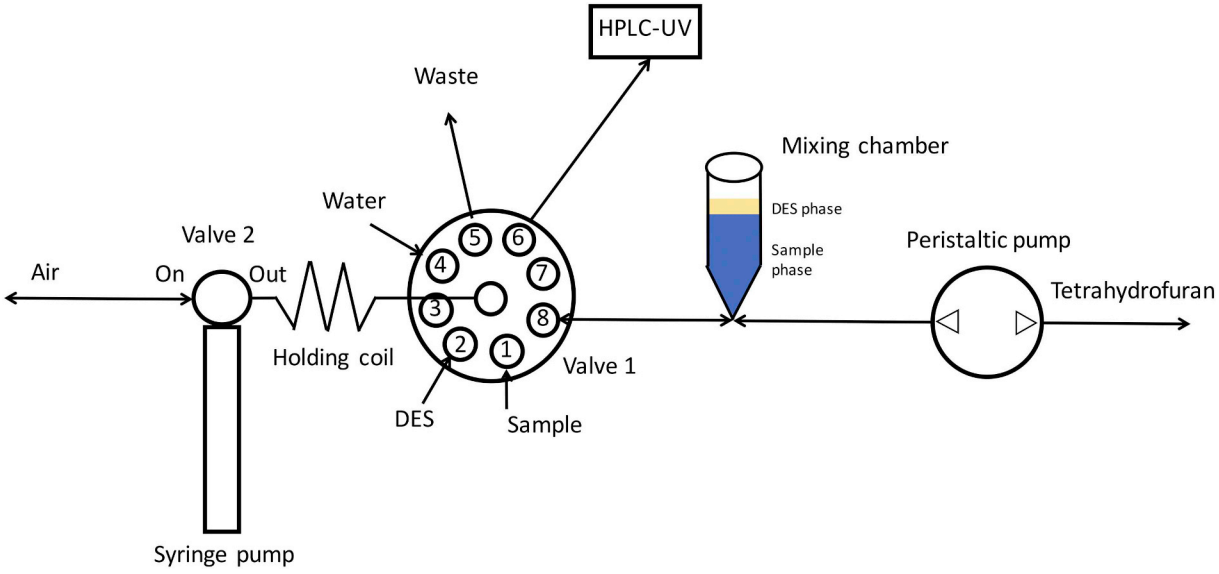

Fig. 1. The manifold of the A-HLLME procedure.

The extraction recovery (ER) values were determined by the concentrations of caffeine in the DES phase and in the aqueous phase after an establishment of the phase equilibrium (1 mL of caffeine solution (25 mg L^{-1}), 50 μL of DES, 50 μL of tetrahydrofuran). The estimated ER values were equal to 84 ± 3, 88 ± 3, 94 ± 3 and 94 ± 3 for DESs at 1:1, 1:2, 1:3 and 1:4 at molar ratios, respectively. From the results obtained choline chloride–phenol molar ratio of 1:3 was chosen because it provided maximum extraction efficiency and contains less phenol.

3.2. Optimization of conditions for chromatographic analysis

The Zorbax Bonus-RP column was used for the HPLC-UV determination of caffeine in DES phase. The mobile phase composition was optimized focused on the DES and analyte dissolution in mobile phase (1), efficiency their chromatographic separation (2) and analysis time (3). Water–acetonitrile mixture as a widely used mobile phase in HPLC-UV analysis provided DES and caffeine dissolution. To optimize chromatographic separation the water–acetonitrile ratio was varied in the range from 9:1 to 1:9. It was shown, that the water concentration increasing insignificantly influenced on retention time of caffeine (from 2.6 to 3.1 min) and increased retention times of DES (from 2.2 to 5.3 min). The minimum analysis time and satisfactory chromatogram peaks separation were achieved using the water–acetonitrile mixture (1:9) as mobile phase (ESM Fig. 2). The retention time values of caffeine and DES were 3.1 and 5.3 min, respectively.

3.3. A-HLLME optimization

3.3.1. Effect of aprotic solvent type

For separation of DES phase (choline chloride–phenol) from homogeneous sample solution addition of an aprotic solvent is required. The aprotic solvent is able to reduce the interactions between DES and water molecules promoting DES phase separation. However, the aprotic solvent used in the A-HLLME procedure can increase solubility of caffeine in an aqueous phase reducing the extraction efficiency. Several aprotic solvents (acetone, 1,4-dioxane, tetrahydrofuran and ethyl acetate) were studied as aprotic solvents. For this 1 mL of standard solution of caffeine (100 mg L^{-1}) was mixed with 100 μL of DES into the mixing chamber. Then 100 μL of aprotic solvent was added into the mixing chamber and mixed by air-bubbling. After mixing and phase separation the DES rich phase (top) was withdrawn and introduced into the HPLC-UV system. From the results showed in Fig. 2 A, it can be seen that tetrahydrofuran provided maximum peak area value using DES with various molar ratios of choline chloride and phenol (1:1, 1:2, 1:3 and 1:4).

3.3.2. Selection of sample volume

To reduce the limit of detection the influence of sample volume on extraction efficiency was investigated. The sample volume (100 mg L^{-1} solution of caffeine) was varied from 0.25 to 1.0 mL limited by volume of the mixing chamber, the DES and tetrahydrofuran volumes were same (100 μL). Fig. 2 B shows the relationship between sample volumes and peak area values obtained. The sample volume of 1.0 mL provided the maximum peak area value.

3.3.3. Selection of DES volume

The volume of the DES phase may result in preconcentration or dilution of the extracted analyte. On the one hand, the volume of the DES phase should be as small as possible to achieve high enrichment factor. On the other hand, the use small volume of the DES phase can give rise to poor reproducibility. The DES volume was changed from 25 to 200 μL, the sample volume was 1.0 mL. The injection of 100 μL of tetrahydrofuran promoted phase separation for all phase ratios studied. The results indicated the decrease of the peak area with the increase of the DES volume (Fig. 2 C). However, the use of the DES volume < 50 μL led to high RSD value. Consequently, 50 μL of DES was selected as the optimal extraction solvent volume.

3.3.4. Selection of tetrahydrofuran volume

The addition tetrahydrofuran into sample and DES solution is required to obtain the phase separation from homogeneous solution and analyte microextraction. Tetrahydrofuran is water-soluble solvent and caffeine is soluble in tetrahydrofuran-water mixtures. From this point of view high volume of aprotic solvent can be critical for caffeine microextraction. The tetrahydrofuran volume was changed from 25 to 200 μL, the sample and DES volumes were 1.0 mL and 50 μL, respectively. The tetrahydrofuran volume higher than 50 μL promoted the DES phase separation. The peak area values were significantly decreased with increasing tetrahydrofuran volume. Minimum tetrahydrofuran volume (50 μL) required for phase separation was selected for further experiments.

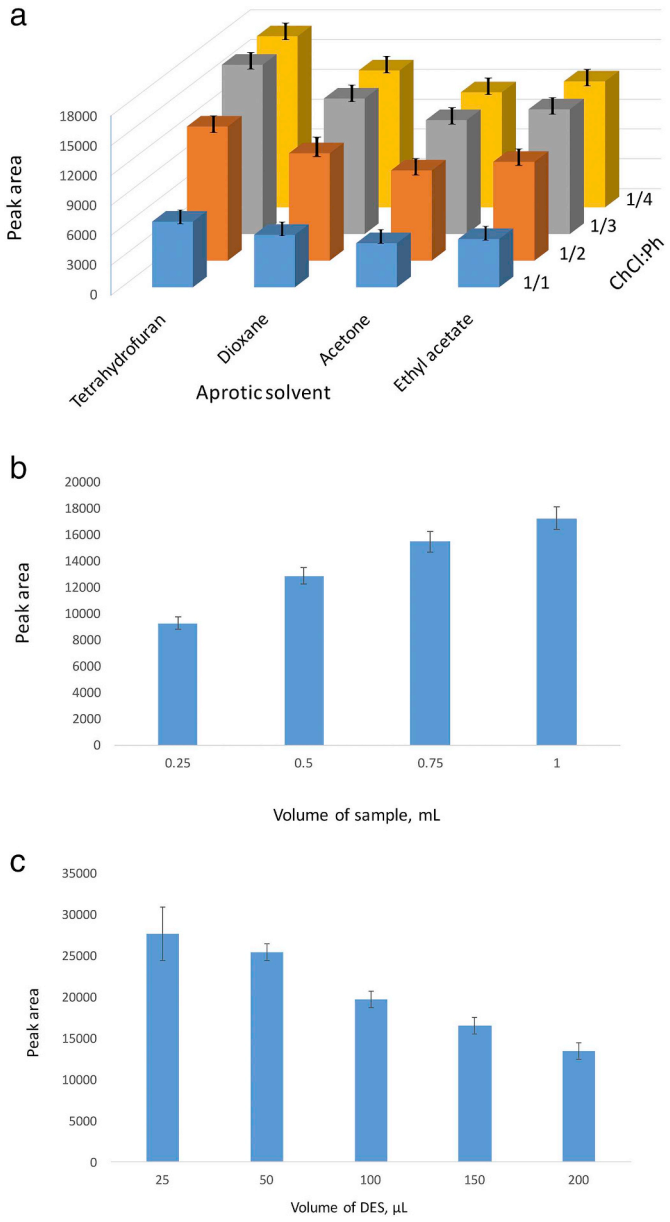

Fig. 2. Investigation of appropriate experimental conditions of A-HLLME (100 mg L^{-1} of caffeine): A. Effect of aprotic solvent type (1 mL of sample, 100 µL of DES, 100 µL of aprotic solvent); B. effect of sample volume (100 µL of DES, 100 µL of tetrahydrofuran); C. effect of DES volume (1 mL of sample, 100 µL of tetrahydrofuran).

3.3.5. Effect of pH

Phenol as component of DES is a weak acid (pK_a = 9.89) [25] and it is ionized in alkaline solutions. Phenol ionization can give rise to DES destruction. Effect of the pH on caffeine microextraction was studied in the range from 1 to 10. No significant influence of the pH value was found (ESM Fig. 3). Thus, beverages containing acids are not required a pH adjustment.

3.4. Interference effect

The effects of such compounds as glucose and sucrose, 4-hydroxy-3-methoxybenzaldehyde (vanillin), dyes (beta-carotene, ponceau 4R, ammonia caramel) and food preservatives (benzoic and sorbic acids) that can be found in beverages, on the determination of caffeine by the developed method were investigated. The tolerable concentration of each interfering compound is considered to be < 5% of relative error in the signal. The most interference was observed at the addition of > 30% of glucose and sucrose. To exclude this interference samples containing high glucose and sucrose concentration (> 30%) should be diluted with water. All other compounds studied did not interfere at the concentrations in which they can present in commercial soft drinks samples.

3.5. Analytical performance

Under the optimal conditions the linear calibration range of 0.1–200 mg L^{-1} and LOD, calculated from a blank test, based on 3σ, found to be 0.03 mg L^{-1} for caffeine with the coefficient of determination > 0.995. The LOQ, equal to 0.1 mg L^{-1}, was calculated based on the analyte peak with 10 times signal-to-noise ratio.

The within-day precision of the method was investigated in standard solutions at the concentration levels of 0.1 and 200 mg L^{-1} of caffeine, by performing three replicates daily. The same solutions were analyzed three times each day, for a period of five days, for the day-to-day precision evaluation. The obtained relative standard deviation (RSD) values were in the range from 3 to 5% and from 4 to 6%, respectively.

Under optimal experimental conditions ER and enrichment factor were also established to be 94 ± 3% and 18, respectively. The time required for the A-HLLME procedure was 5 min. Duration of the HPLC-UV analysis was 10 min.

3.6. Real samples analysis

The developed procedure was applied for the determination of caffeine in 2 green tea samples, cola and 2 energy drinks samples. Carbonated beverages were not degassed and all samples were used without any pretreatment. The concentration of caffeine was determined using the calibration curve. Caffeine was found in all samples.

Recovery values were varied from 101 to 103%. The results demonstrated that the precision and accuracy of the present method are acceptable.

Accuracy and reliability of the resulting information were also studied by analyzing the mentioned samples using referent method described in Section 2.6. As it can be seen from Table 1, the analytical results agreed well with the results obtained with reference GC-NPD method [12]. F-values ≤ 9.28 indicate insignificant difference in precision between both methods at the 95% confidence level. t-Values ≤ 3.18 indicate insignificant difference between the results obtained using these methods (n = 4).

3.7. Comparison of the developed method with other methods

The performance of the proposed extraction method based on the A-HLLME was compared with the previously reported extraction methods

Table 1
The results of caffeine determination in beverages (n = 4; P = 0.95; t_k = 3.18; F_k = 9.28).

Sample	Concentration, mg L^{-1}			t-Value	F-Value	Recovery, %
	Added	A-HLLME/ HPLC-UV	GC-NPD			
Green tea 1	0	89 ± 5	91 ± 4	1.9	2.6	–
	10	102 ± 6	101 ± 4	1.6	4.3	103
Green tea 2	0	67 ± 3	62 ± 2	2.1	3.4	–
	20	91 ± 4	84 ± 5	2.6	3.1	104
Cola	0	76 ± 4	73 ± 3	1.4	2.4	–
	10	88 ± 4	85 ± 3	1.3	3.5	102
Energy drink 1	0	270 ± 7	292 ± 8	2.2	1.8	–
	40	314 ± 8	321 ± 9	1.2	1.9	101
Energy drink 2	0	301 ± 9	296 ± 4	1.3	5.1	–
	20	325 ± 7	312 ± 9	1.2	3.4	101

Table 2
Comparison of the suggested method with the over methods for the determination of caffeine in beverages.

Method of detection	Sample preparation	Extraction solvent (volume, μL)	Automated	Linear range, mg L^{-1}	LOD, mg L^{-1}	RSD, %	Enrichment factor	Sample volume, mL	Ref.
GC-NPD	DLLME	Ethanol/chloroform (220)	No	0.05–500	0.02	3.2	16	1	[12]
UV–Vis	DLLME	Methanol/dichloromethane (1500)	Yes	2–75	0.46	2.1	–	1.5	[18]
HPLC-UV	DLLME	Ethanol/octanol-1 (530)	No	0.001–0.2	0.001	3.8	109	1	[26]
HPLC-UV	SAAHLLE	Acetonitrile (800)	No	1–50	0.013	4	–	5	[27]
HPLC-UV	A-HLLME	DES (50)	Yes	0.1–200	0.03	5	18	1	This work

HPLC-UV – high performance liquid chromatography with UV-detection, GC-NPD – gas chromatography with nitrogen–phosphorus detector, UV–Vis – UV–visible spectrophotometry, DLLME – dispersive liquid-liquid microextraction, SAAHLLE – salt and air-assisted homogeneous liquid-liquid extraction, A-HLLME – automated homogeneous liquid-liquid microextraction.

for the determination of caffeine in various beverage samples (Table 2). As it can be seen, LOD and linear range of the proposed method are comparable with those reported for the other methods. Unlike the previously proposed techniques, this developed technique includes a simple and fully automated sample preparation procedure before chromatographic analysis, which completely eliminates the interfering effect of a complex food product matrix. Moreover, the proposed procedure is characterized by a lower consumption of extraction solvent.

4. Conclusions

A fully-automated homogeneous liquid-liquid microextraction procedure for the HPLC-UV determination of caffeine in beverages has been developed for the first time. In this paper, the DES based on choline chloride with phenol was investigated as an extractant for caffeine extraction for the first time. It was established, that caffeine can be extracted into the DES phase with extraction recovery of 94 ± 3%. The automated homogeneous liquid-liquid microextraction procedure was coupled with a HPLC-UV system. An applicability of the procedure developed was demonstrated on the analysis of real beverages samples. In comparison with the extraction procedures described in literature [26] the procedure proposed requires less extraction solvent and does not require centrifugation for phase separation. The proposed method has the potential to be used as one of the alternatives to conventional methods for extraction of organic analytes from aqueous samples and can be coupled with other instrumental methods (UV–VIS, gas-chromatography, etc.).

Supplementary data to this article can be found online at https://doi.org/10.1016/j.microc.2018.10.014.

Acknowledgements

Andrey Shishov gratefully acknowledges financial support for research from Russian Science Foundation (project no. 18-73-00111). HPLC-UV assay was performed at the Chemistry Educational Centre of Research Park of St. Petersburg State University.

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