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Response surface methodology optimized dispersive liquid–liquid microextraction coupled with UV-Vis spectrophotometry for determination of quinine

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Dispersive liquid–liquid microextraction (DLLME) followed by UV-Vis spectrophotometry was applied for extraction/preconcentration and determination of trace levels of quinine (QN). Chloroform and methanol were chosen as the extraction solvent and the disperser solvent, respectively. A central composite design (CCD) was applied to optimize the effective parameters of DLLME including volume of extraction solvent, pH, and salt concentration. The optimal conditions were obtained as 160 μL for the volume of extraction solvent, 9.88 for pH, and 2.2% (w/v) for salt concentration. The linear dynamic range (LDR) was 25–700 μg L^{-1} with a correlation coefficient of 0.994. The limit of detection (LOD) and relative standard deviation (RSD) were 14.71 μg L^{-1} and 1.13%, respectively. The method was successfully applied for the determination of QN in real samples and satisfactory relative recoveries (101.51–108.02%) were obtained.

Introduction

Quinine (QN), with the chemical name of (6-methoxyquinolin-4-yl-8-vinylquinuclidin-2-yl)methanol, is an important plant alkaloid isolated from the bark of *Cinchona*, a plant of South America. Historically, it was an important anti-malaria drug for more than 300 years. The drug is also used for the treatment of muscle cramps and reversal of multi-drug resistance during chemotherapy. In food and beverage industries, it is applied as a bitter flavoring agent in tonic water or tonic-containing mixed beverages.[1] However, owing to its side effects, except in some complicated and resistant cases, it has been replaced by other drugs.[2] Despite multiple cautions from the US Food and Drug Administration (FDA) about the risks and limited effectiveness, since the 1940s, QN and its derivatives, based on a series of uncontrolled studies, have been commonly prescribed for treating nocturnal leg cramps.[3] The drug is also applied as an additive in some anti-hair-loss lotions and in beverage industries – it is commonly used as a bitter flavoring agent in tonic water. Quinine tea is also produced in Guatemala. In some parts of Iran, quinine is commonly used to treat nocturnal leg cramps in folk-medicine, mixed with some inert powder and subsequently treated with some type of natural oil. This is then placed topically on the area of the pain.

Owing to its high toxicity, which in some cases of overdosing might result in death,[4] the determination of QN in biological, pharmaceuticals, and food samples is critical. QN is mainly determined by chromatographic techniques including high performance liquid chromatography (HPLC),[5,6] reversed phase ion-pair chromatography[7] and gas chromatography-mass spectrometry (GC-MS).[8] Some other techniques like capillary electrophoresis (CE),[9] flow-injection chemiluminescence (FIC),[10,11] electrochemical methods,[1] mass spectrometry[12] and atomic absorption spectrometry (indirect approach)[13] have been also reported for the analysis of QN.

However, due to insufficient sensitivity and matrix interferences, the direct determination of QN at trace levels using these techniques is limited. Therefore, a separation and/or a preconcentration step prior to analysis are necessary. Several techniques such as dynamic drop-to-drop solvent microextraction (DDSME),[12] solid phase extraction (SPE),[14,8] solid phase microextraction (SPME),[15] and single drop microextraction (SDME)[16] have been used for the separation and preconcentration of QN. Nevertheless, most of these methods suffer from some disadvantages such as high expense, and having a tedious and time-consuming procedure.

In order to enhance the sensitivity of the method and enrichment factor, extraction has been followed by using the preconcentration method of dispersive liquid–liquid microextraction (DLLME).[17] This method is a very simple, fast and efficient preconcentration technique with a high recovery and enrichment factor.[18]

In this study, DLLME combined with UV-Vis spectrophotometry was applied for the determination of trace amounts of quinine in a type of quinine folk-medicine, which is used for treating nocturnal leg cramps, and a type of shampoo. The effective parameters of DLLME, including the volume of

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extraction solvent, pH and salt concentration were investigated and optimized using a fractional central composite design (CCD).

Experimental

Reagents and materials

Methanol, acetone, acetonitrile, ethanol, chloroform, chlorobenzene, carbon tetrachloride, *m*-xylene, toluene, boric acid, potassium chloride, sodium hydroxide and sodium chloride with the purity higher than 99% were purchased from Merck Chemicals (Darmstadt, Germany). A stock standard solution of quinine (1000 mg L^{-1}) was prepared by dissolving a suitable amount of quinine hydrochloride dehydrate (obtained from Sigma-Aldrich) in methanol and was stored at 4 °C until use. The working solutions were prepared daily by subsequent dilution of the standard solution. In order to prepare the buffer solution, an appropriate amount of boric acid and potassium chloride were dissolved in double distilled water and pH adjustment was achieved by dropwise addition of sodium hydroxide solution.

Instrumentation

A Lambda 850 ultra-high performance UV-Vis spectrophotometer (Perkin Elmer, Life and Analytical Sciences, Waltham, Mass, USA) with 1 cm optical path, micro-cuvettes (Fischer Scientific, USA) with a sample volume of 0.1 mL was used to record the absorbance data. Centrifugation was performed using a Hermel Z200A centrifuge (Hemel Labortechnik, Wehingen, Germany). The pH values were measured by using a Metrohm 691 pH-meter (Herisau, Switzerland) with a combined glass electrode. In order to homogenize real sample solutions, a vortex mixer, ZX classic model (Velp scientifica, Milan, Italy) was used.

The procedure

Firstly, 10 mL of a buffered solution of quinine with a pH of 9.88 containing 2.2% (w/v) of NaCl was placed in a conical glass test tube. Then, 1 mL methanol (disperser solvent) containing 160 μL chloroform (extraction solvent) was rapidly injected into the solution using a 2 mL syringe. In this step, a cloudy solution, which consisted of suspended fine droplets of chloroform dispersed throughout the aqueous phase, was formed. The extraction was completed in 10 min at ambient temperature. In the next step, the emulsion was disrupted by centrifugation for 5 min at 3250 rpm. Afterward, the organic phase was sedimented at the bottom of the tube. The sedimented phase was completely removed using a 100 μL microsyringe, and then transferred to a micro-cuvette of the spectrophotometer. The absorbance was measured in the range of 300–400 nm against the blank.

Data analysis

The Perkin Elmer UV Winlab software package was used for all absorbance measurements and recording the spectra. Designing the experiments for CCD, analysing and modeling the data, analysis of variance and constructing the related plots were performed by using a trial version of the "Design-Expert 7.1.3" software package (Stat-Ease Inc., Minneapolis, USA).

Result and discussion

Selection of extraction solvent

Organic solvents with extraction capability for the target analyte (quinine), immiscibility with water, and having higher density than water were considered for the extraction solvent. Therefore, chloroform (density: 1.48 g mL^{-1}), carbon tetrachloride (density: 1.59 g mL^{-1}) chlorobenzene (density: 1.11 g mL^{-1}), toluene–chloroform (1 : 1, v/v) and *m*-xylene–chloroform (1 : 1, v/v) were examined. The results presented in Fig. 1 indicate clearly that the highest extraction efficiency was obtained using chloroform. Therefore, it was chosen as the extraction solvent in the subsequent experiments.

Selection of disperser solvent

To achieve maximum extraction efficiency in DLLME, the selection of an appropriate disperser solvent is important. The most critical point for selection of the disperser solvent is its miscibility in both organic and aqueous phases. Therefore, acetone, methanol, ethanol and acetonitrile were tested for this purpose. The results suggested that, among these solvents, methanol showed the maximum extraction recovery (Fig. 2).

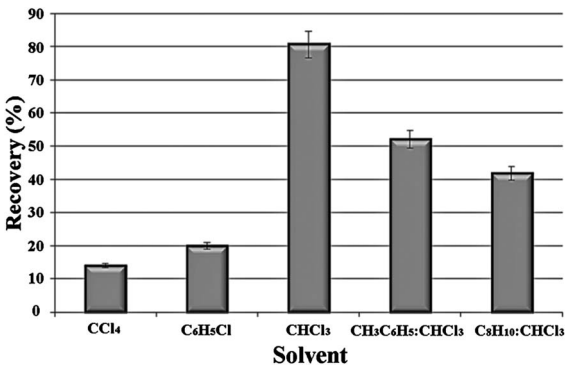

Fig. 1 Effect of various extraction solvents on the extraction recovery.

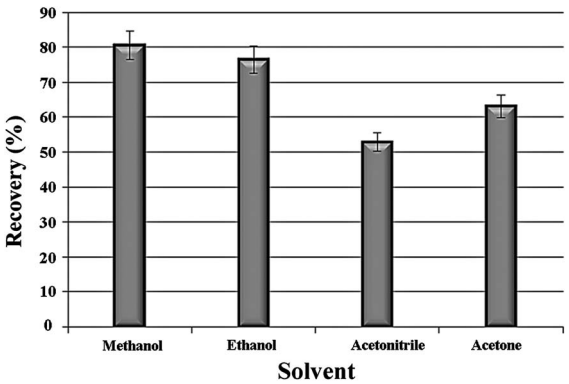

Fig. 2 Effect of various disperser solvents on the extraction recovery.

Response surface methodology optimization

In order to obtain the best extraction conditions, the method was optimized using a rotatable and orthogonal central composite design (RO-CCD). In this design the variance of the predicted response at any point depends only upon the distance from the center of design (rotatability), and each factor can be evaluated independently (orthogonality).[19] The design is a combination of two-level, half-fraction factorial points ($N_f = 2^{f-1}$) (f is the number of factors), star points ($N_a = 2f$), and a set of center points (N_0). The center point is usually repeated to get a good estimate of the experimental error. According to a literature survey and the preliminary experiments, the volume of extraction solvent, pH, and salt concentration were recognized as the main parameters of the DLLME. Therefore, f is equal to three. The parameters (factors), their symbols and levels including axial points ($\pm\alpha$), factorial points (±1) and, central points (0) are given in Table 1. The axial points are located at $+\alpha$ and $-\alpha$ from the center of the experimental domain. The value of α, needed to ensure the rotatability, was equal to ±1.414 from eqn (1):

$$\alpha = \sqrt[4]{2^{f-1}} \quad (1)$$

To obtain an estimate of the pure error, N_0 was calculated equal to 7. The total number of the experiments (N) needed to perform CCD was calculated as equal to 16.

In order to ensure the reproducibility of the results, each run was repeated twice. Furthermore, to minimize the effect of uncontrolled factors, the sequence of experiments was randomized. The absorbance of the analyte at 335 nm was recorded and considered as the "experimental response". The experimental design matrix and the related responses (absorbance) are shown in Table 2.

A quadratic (second order) polynomial response surface model with the most reasonable statistics and low standard error to fit the experimental data in terms of the coding of the significant effects is shown in eqn (2). It consists of three main effects (P, S, and E), two two-factor interaction effects (PS and SE), and two curvature effects (S^2, and E^2) as follows:

$$A = b_0 + b_1P + b_2S + b_3E + b_4PS + b_5SE + b_6S^2 + b_7E^2$$
$$b_0 = 0.46;\ b_1 = 0.07;\ b_2 = -0.06;\ b_3 = -0.15;\ b_4 = -0.07;\ b_5 = 0.03;\ b_6 = 0.03;\ b_7 = 0.04. \quad (2)$$

where Y is the response (absorbance), b_0 is the intercept and b_1 to b_7 are the regression coefficients. The sign of each coefficient defines the direction of the relationship between the related effect and the response. The positive sign indicates that as the value of one effect changes, the value of the response changes in the same direction, whereas for the negative sign the response operates in the opposite direction. The absolute value of the coefficients measures the strength of the relationship. P (pH), S (salt concentration), and E (extractor volume) are the linear terms, PS is the interaction term, and S^2 and E^2 are the quadratic terms of the model. An interaction between two factors occurs when the effect of one factor on the response depends on the level of the second factor. The quadratic terms affect the response in a non-linear or curved way. The effects of the quadratic effects E^2 and S^2 on the response are similar to the curves shown in Fig. 3a and 3c, respectively.

Table 1 Factors, their symbols and levels for the CCD

		Level				
Factor	Symbol	$-\alpha$	-1	0	1	$+\alpha$
pH	P	8.00	8.32	9.10	9.88	10.20
Salt concentration (w/v%)	S	0.0	2.2	7.5	12.8	15.0
Volume of extraction solvent/μL	E	150	160	180	200	210

Table 2 Design matrix and responses for the CCD

Run	P	S (w/v%)	E/μL	Absorbance	Run	P	S (w/v%)	E/μL	Absorbance
1	9.10	7.5	210	0.23	17	8.32	2.2	160	0.51
2	9.10	7.5	150	0.65	18	8.00	7.5	180	0.27
3	9.10	7.5	180	0.36	19	9.10	7.5	180	0.40
4	9.88	2.2	200	0.51	20	9.10	7.5	180	0.34
5	9.10	15.0	180	0.31	21	10.20	7.5	180	0.50
6	9.10	0.0	180	0.51	22	9.10	7.5	210	0.25
7	9.10	7.5	180	0.34	23	9.10	7.5	180	0.36
8	9.10	7.5	180	0.34	24	9.10	7.5	150	0.67
9	8.32	12.8	200	0.24	25	8.32	12.8	200	0.26
10	9.10	15.0	180	0.36	26	9.10	7.5	180	0.32
11	8.32	2.2	160	0.52	27	9.10	7.5	180	0.35
12	9.10	7.5	180	0.38	28	9.10	0.0	180	0.52
13	9.10	7.5	180	0.31	29	9.10	7.5	180	0.36
14	9.88	2.2	200	0.47	30	8.00	7.5	180	0.23
15	9.10	7.5	180	0.43	31	10.20	7.5	180	0.47
16	9.10	7.5	180	0.36	32	9.10	7.5	180	0.35

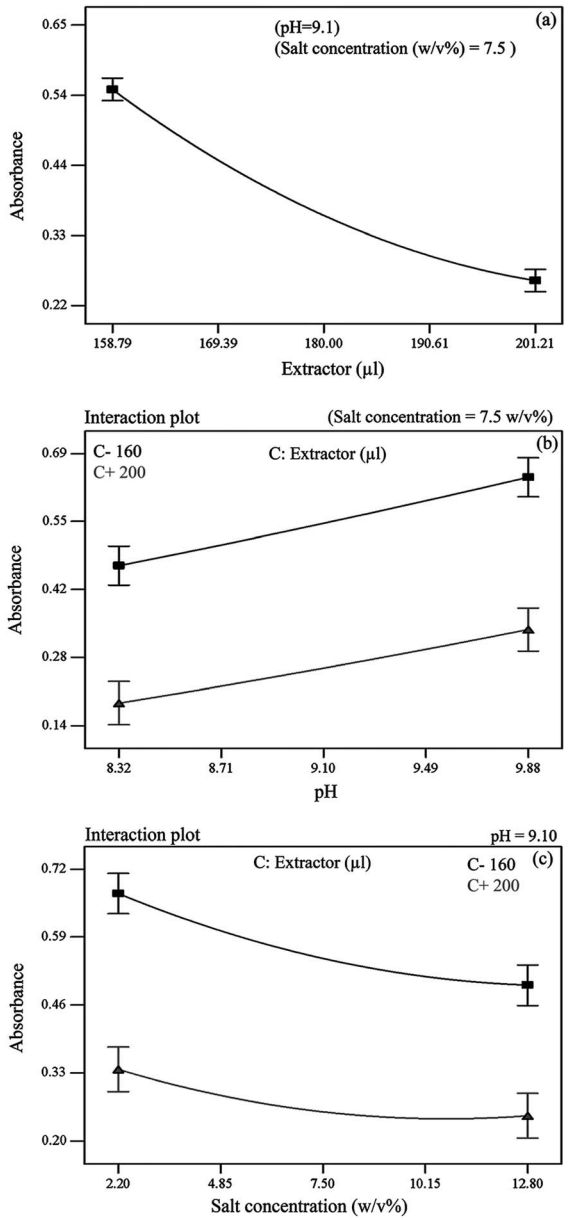

Fig. 3 (a) Effect of volume of extraction solvent on the absorbance. Two-factor interactions and their effects on the efficiency: (b) extractor-pH; and (c) extractor-salt concentration.

The analysis of variance (ANOVA) (Table 3) was carried out to evaluate the precision, fitness and significance of the model, and the effect of individual factors and their interactions on the response. The *F*-value which is the test for comparing the variance associated with a term with the residual variance, implies that the model is significant. The *lack of fit* which is the weighted sum of squared deviations between the mean response at each factor level and the corresponding fitted value, with the *F*-value of 0.38 and *p*-value (probability of error value) of 0.92 is not significant for the model. The model terms with *p*-values of less than 0.05 are significant for 95% confidence intervals and values greater than 0.1000 indicate that the model terms are not significant. Therefore, *P*, *S*, *E*, *PS*, S^2 and E^2 were the significant model terms. The quality of the polynomial model was expressed by the coefficient of determination R^2 and adjusted-R^2, which were obtained as being equal to 0.96 and 0.95, respectively. The elimination of the insignificant terms such as *PE* and P^2 improved the regression model and simplified the equation. Nevertheless, in this case removing the *SE* term resulted in a reduced predicted R^2 and the model precision, and thus cannot be removed.

According to the model and ANOVA table, the volume of extraction solvent (*E*) (Fig. 3a) is considered as the most important parameter, whereas its interactions with the other factors are not important (Fig. 3b and 3c). Obviously, when the volume of the extraction solvent (chloroform) increases from 150 to 210 µL, the volume of sedimented phase will also increase. Therefore, according to the Beer–Lambert law, the related absorbance decreases.

Fig. 4 depicts response surface and contour plots of the effects of the two variables, namely pH (*P*) and salt concentration (*S*) on the absorbance of the sedimented phase. These plots represent the relationship between the response and levels of the two factors simultaneously, while the other factor (volume of extraction solvent) is fixed at its central point (180 µL).[20] The plots suggest that at high levels of salt concentration, the pH drifts do not change the response significantly. However, by decreasing the concentration of salt in the sample the pH effect becomes more significant and at a low concentration of salt, the pH shows a nearly linear effect on the response. This interaction can be explained by the effect of increasing the salt concentration on the pH of aqueous solutions. In plain words, by raising the ionic strength of an aqueous solution, based on the Debye–Hückel equation, the activity of the hydroxide ion decreases. And in other words, by adding salt to an aqueous solution with a high or low pH due to increasing the ionic strength, the pH drifts towards the center of the pH spectrum (pH = 7).

Finally, the optimal conditions were calculated based on the fitted model and the desirability function. Desirability is a multiple response method that makes use of an objective function, *D*(*X*), called the desirability function.[21] It reflects the desirable ranges for each response (d_i). The desirable ranges are from zero to one (least to most desirable respectively), and the goal for optimization is one. The simultaneous objective function is a geometric mean of all the transformed responses:

$$D = (d_1 \times d_2 \times \ldots \times d_n)^{\frac{1}{n}} = \left(\Pi_{i=1}^{n} d_i\right)^{\frac{1}{n}} \quad (3)$$

where *n* is the number of responses in the measure. The numerical optimization finds a point that maximizes the desirability function. The characteristics of a goal may be altered by adjusting their weight or importance. For several responses and factors, all goals become combined into one desirability function. If any of the responses or factors fall outside their desirability range, the overall function becomes zero. Therefore, the optimum set points of the method were 160 µL for the volume of extraction solvent, 2.2 (w/v%) the for salt concentration and 9.88 for the pH.

Analytical figures of merit

Under the optimal conditions (extraction solvent (chloroform), 160 µL; disperser solvent (methanol), 1 mL; salt concentration,

Table 3 Analysis of variance (ANOVA) for the small CCD

Source	Sum of squares	df [a]	Mean square	*F*-value[b]	*p*-value prob > *F* [c]	
Model	0.370003	9	0.041111	59.84	<0.0001	Significant
P	0.053449	1	0.053449	77.79	<0.0001	Significant
S	0.032399	1	0.032399	47.16	<0.0001	Significant
E	0.171529	1	0.171529	249.65	<0.0001	Significant
PS	0.008317	1	0.008317	12.10	0.0025	Significant
PE	0.000079	1	0.000079	0.11	0.7383	Not significant
SE	0.000675	1	0.000675	0.98	0.3341	Not significant
P^2	0.000172	1	0.000172	0.25	0.6229	Not significant
S^2	0.015796	1	0.015796	22.99	0.0001	Significant
E^2	0.022058	1	0.022058	32.10	<0.0001	Significant
Residual	0.013054	19	0.000687			
Lack of fit	0.003318	9	0.000369	0.38	0.9202	Not significant
Pure error	0.009736	10	0.000974			
Corr. total[d]	0.398815	31				

[a] Degrees of freedom. [b] Test for comparing model variance with residual (error) variance. [c] Probability of seeing the observed *F*-value if the null hypothesis is true. [d] Totals of all information corrected for the mean.

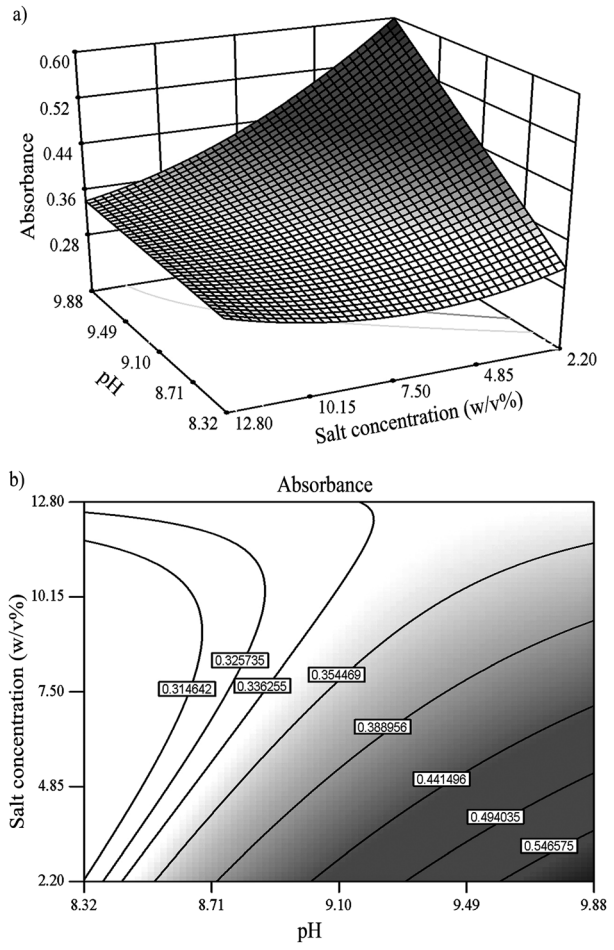

Fig. 4 Response surface and contour plots for value of pH and salt concentration (w/v%). *Condition*: volume of extraction solvent, 180 μL.

2.2% (w/v); and pH, 9.88) the basic analytical characteristics of the method including the linear dynamic range (LDR), determination coefficients (R^2), limit of detection (LOD), and relative standard deviations (RSDs) were determined and are represented in Table 4. The calibration curve was constructed with ten concentration levels in the range of 25–700 μg L^{-1} and was characterized with high determination coefficients (R^2), slope and intercept, which were equal to 0.994, 0.0017 and 0.0717, respectively.

The limit of detection (LOD) based on $3S_d/m$, (where S_d and m are standard deviation of the blank and slope of calibration graph, respectively) was 14.71 μg L^{-1}. The enrichment factor (EF) which was considered as the ratio of the analyte concentration in the sedimented phase (C_{sed}) to its initial concentration (C_0) within the sample (EF = C_{sed}/C_0), was obtained as equal to 103. The precision of the method based on the relative standard deviation (RSD, $n = 6$, $C = 300$ μg L^{-1}) was 1.13%.

Comparison with other methods

The results of a literature review for the determination of QN in different types of samples were summarized in Table 4. A good RSD value, better limit of detection and comparable linear dynamic range are the advantages of the proposed method.

Analysis of real samples

In order to evaluate the applicability of the validated method, determination of QN in quinine medicine and shampoo quinine (Klorane, Paris, France) was investigated using the optimized procedure. For this purpose, 5 mg of the medicine (purchased from a local herbal medicine shop) was placed into a test tube and 1.5 mL methanol was added to it. The resulting mixture was vortexed at 2000 rpm for 3 min and was then centrifuged at 4000 rpm for 5 min. Finally, 1 mL of the resulting methanol-phase was placed in a conical test tube, and after adjusting the pH and salt concentration the resulting solution was diluted to 10 mL.

For the determination of QN in shampoo, 50 mg of the sample was placed in a 25 mL beaker, then 20 mL distilled water that was adjusted to pH 3 and containing 1% (w/v) salt was added to the beaker. In order to reduce the matrix effects, the mixture was gently stirred with 1 mL of carbon tetrachloride for

Table 4 Comparison of the proposed method with the other methods for determination of QN in different real samples

Sample type	Extraction	Analysis	LOD[a]/μg L^{-1}	LOQ[b]/μg L^{-1}	LDR[c]/μg L^{-1}	R^2	RSD%[d]	EF[e]	Ref.
Plasma whole blood	SPE	RP-HPLC/UV	—	100	10^2 to 5×10^3	0.998 0.997	5.6–8.4, 6.5–12	—	5
Beverages		RP-IP HPLC/UV	20	—	10^2 to 2×10^4	0.9996	1.27	—	7
Plasma	SPE	GC-MS	12.2	40.6	Up to 10^4	0.9977	1.9–4.3	—	8
Pharmaceutical	Flow injection	Chemiluminescence	33	—	10^2 to 10^5	0.9994	<5	—	10
Deionized water	DDSME	MS	48.66	—	100–7000	—	7	14	12
Urine			58.39		1200–7000		8.5		
Plasma			77.86		490–10 000		10.2		
Tonic		AAS[f]	2000	—	5×10^3 to 1.1×10^5	—	2.1	—	13
Urine	SDME	MS	97.32	—	—	—	8.5	40	16
Drug and shampoo	DLLME	UV spectrophotometer	14.7	49	25–700	0.994	1.13	103.11	This work

[a] Limit of detection. [b] Limit of quantification. [c] Linear dynamic range. [d] Relative standard deviation (in this work $n = 6$). [e] Enrichment factor. [f] Atomic absorption spectrometry.

Table 5 Determination of QN in different real samples

Sample	QN
Mixed powder ± S.D.[a]/μg g^{-1}	805.00 ± 24.77
Added/μg g^{-1}	400
Found ± S.D./μg g^{-1}	1225.44 ± 43.14
Relative recovery (%)	108.02
Shampoo ± S.D.[b]/μg g^{-1}	578.60 ± 66.18
Added/μg g^{-1}	800
Found ± S.D./μg g^{-1}	1390.67 ± 59.42
Relative recovery (%)	101.51

[a] Standard deviation (n = 5) [b] Standard deviation (n = 3)

15 min. Then, the mixture was centrifuged at 4000 rpm for 5 min. After that, 1 mL of the upper phase was transferred to a conical test tube and after adjusting the pH value to 9.88 and salt concentration, the solution was diluted to 10 mL. Details of the results are given in Table 5.

Conclusions

In the present work, DLLME combined with sensitive UV-Vis spectrophotometry was used for the extraction/preconcentration and determination of QN. The response surface methodology was used for optimization of the effective parameters of the method. A simple and fast procedure, good RSD value, satisfactory enrichment factor, high relative recoveries (108.02% and 101.51%), low detection limit and wide linear dynamic range are the advantages of the proposed method. In addition, the method is environmentally friendly because it consumes low volumes of organic solvents (1 mL methanol and 160 μL chloroform).

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