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Optimization of carrier-mediated three-phase hollow fiber microextraction combined with HPLC-UV for determination of propylthiouracil in biological samples

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ABSTRACT

Carrier-mediated three-phase hollow fiber microextraction combined with high-performance liquid chromatography-ultra violet detection (HPLC-UV) was applied for the extraction and determination of propylthiouracil in biological samples. Propylthiouracil (PTU) was extracted from 7.5 mL of the basic solution (the source phase) with pH 12 into an organic phase (*n*-octanol containing 6% (w/v) of Aliquat 336 as the carrier) impregnated in the pores of a hollow fiber, and finally was back extracted into 24 μL of the acidic solution located inside the lumen of the hollow fiber (the receiving phase). The extraction was performed through the gradient of counter ion from the source to the receiving phase. The effects of different variables on the extraction efficiency were studied simultaneously using an experimental design. A half-fractional factorial design was employed for screening to determine the variables significantly affecting the extraction efficiency. Then, the factors with significant effect were optimized using a central composite design (CCD) and the response surface equations were developed. The optimal experimental conditions obtained from this statistical evaluation included: source phase, pH 12; temperature, 25 °C; extraction time, 40 min; counter ion concentration, 2 mol L^{-1} of $NaClO_4$; organic solvent 6% of Aliquat in octanol and without salt addition in the source phase. Under the optimized conditions, the preconcentration factors were between 125 and 198 and also the limit of detections (LODs) ranged from 0.1 μg L^{-1} to 0.4 μg L^{-1} in different biological samples. The calibration curve was linear ($r^2 = 0.998$) in the concentration range of 0.5–1000 μg L^{-1}. Finally, the feasibility of the proposed method was successfully confirmed by extraction and determination of PTU in human plasma and urine as well as the bovine milk and meat samples in microgram per liter, and suitable results were obtained (RSDs < 6.3%).

1. Introduction

Propylthiouracil (PTU), 6-propyl-2-sulfanylidene-1H-pyrimidin-4-one (Fig. 1), is a white or pale cream-colored crystal or crystalline powder with a pK_a of 8.3. Propylthiouracil is an antithyroid drug, which inhibits the synthesis of thyroid hormones, and thus is effective in the treatment of hyperthyroidism. It is rapidly and almost completely absorbed after oral administration. Within 24 h, approximately 35% of the drug is excreted in the urine in intact and conjugated forms. The peak plasma concentrations of 3.50 mg L^{-1} about 2 h after a conventional-release tablet and 0.50–1.25 mg L^{-1} about 3 h after sustained-release tablets were obtained after oral administration of 300 mg [1]. On the other hand, PTU has been illegally applied to animals to obtain a weight gain due to higher water retention in the edible tissues and the gastro-intestinal tracts. Although PTU has been used in treatment of hyperthyroidism, the uncontrolled introduction of it into the human food chain could have serious health implications. Therefore, specific legislation has been promulgated within the European Union prohibiting the use of thyreostats in animal production [2]. Therefore, the analysis of residues in milk and meat can provide the indexes of exposure to this compound.

Determination of PTU in a variety of biological matrices is generally performed by gas chromatography or high performance liquid chromatography coupled to a sample pre-treatment step such as the traditionally used liquid–liquid extraction (LLE) [3], solid-phase extraction (SPE) [4,5], and matrix solid-phase dispersion (MSPD) [6]. Application of conventional LLE and SPE methods was limited with respect to the disadvantages such as solvent losses, large secondary wastes, a long procedure, and complex equipment. The solvent microextraction technique effectively overcomes these problems by reducing the amount of organic solvent. Further, extraction, preconcentration, and sample introduction are done in

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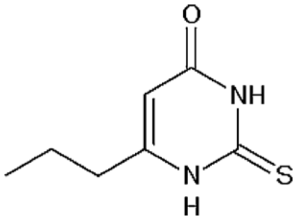

Fig. 1. Chemical structure of PTU.

one step [7]. Recently, a novel liquid phase microextraction technique combined with a hollow fiber membrane (HF-LPME) was developed [8,9]. HF-LPME can be performed either in the two- or three-phase mode. In two-phase HF-LPME, the solubility of analytes in the organic solvent should be higher than that in the aqueous sample solution. The analytes are transferred by diffusion from the sample into the organic solvent [10]. Three-phase HF-LPME includes extraction of the analytes from an aqueous sample into the organic membrane and a following back extraction from the organic membrane into the aqueous acceptor solution. However, this extraction mode is limited to basic or acid analytes with ionizable functional groups [11]. The above-mentioned two- and three-phase LPME systems are both based on passive diffusion, where extraction requires high partition coefficients from the sample into the acceptor phase. However, for highly polar analytes, partition coefficients into water immiscible organic solvents are low, and consequently their extractability in two- and three-phase LPME is very poor. In these situations, hollow fiber-based LPME may be accomplished in a carrier-mediated mode, where a carrier is dissolved in the impregnation solvent in the pores of hollow fiber. Ionic carriers are associated with counter-ions to maintain electro neutrality in the apolar membrane phase. The transport mechanism is counter-coupled transport, in which the driving force of mass transport over the membrane is created by the gradient of counter ion from the source to the receiving phase [12]. Carrier-mediated three-phase hollow fiber microextraction is one of the effective solvent microextraction techniques that has been discussed in several papers [13–15]. In this study, carrier-mediated three-phase hollow fiber microextraction combined with high performance liquid chromatography-ultra violet (HPLC-UV) was applied for extraction and determination of PTU in biological samples.

2. Experimental

2.1. Chemicals and reagents

PTU (>99.5%) was purchased from Sigma–Aldrich (St. Louis, MO, USA). Methyltrioctylammonium chloride (Aliquat-336), sodium perchlorate, sodium hydroxide, and ammonium acetate were obtained from Fluka (Buchs, Switzerland). HPLC grade methanol was purchased from Caledon (Georgetown, Ont., Canada). Moreover, *n*-octanol, benzyl alcohol, ethyl acetate, isoamyl alcohol, cyclo hexanone, and *n*-octane were purchased from Merck (Darmstadt, Germany). Ultrapure water was prepared using a Milli-Q system from Millipore (Bedford, MA, USA). Plasma and urine samples were obtained from the Clinic of Taleghani Hospital (Tehran, Iran) and the milk and meat samples were purchased from the market (Tehran, Iran).

2.2. Preparation of standard solutions and real samples

Stock standard solution of PTU (1000 μg mL^{-1}) was prepared in methanol and stored in a fridge at 4 °C and brought to ambient temperature just prior to use. The working solutions were prepared daily by diluting the standard solutions prior to use.

The sample preparation procedure before main extraction consists of the following steps:

For plasma samples: (1) 2 mL spiked plasma sample is mixed with 3 mL acetonitrile in order to precipitate proteins, (2) the obtained solution was vortexed and centrifuged for 5 min at 3000 rpm, (3) the supernatant was removed and diluted at the ratio of 1:3 with ultrapure water. For urine samples: 4 mL spiked urine was diluted at the ratio of 1:1. For milk samples: (1) 2 mL of milk samples is mixed with 85 μL of concentrated HCl, (2) the obtained solution was exposed to centrifugation at 3000 rpm for 10 min, (3) the supernatant was removed and diluted at the ratio of 1:3 with ultrapure water. For meat samples: (1) 1 g of meat was sliced into very thin pieces, (2) 5 mL of methanol was added to the samples to obtain homogeneous sample, (3) the mixture was placed in an ultrasonic bath for 30 min, (4) after centrifugation at 3000 rpm for 5 min the supernatant was removed and evaporated to almost dry under vacuum and the remainder was dissolved in 8 mL ultrapure water.

2.3. HPLC instrument

Separation and determination of the analyte were performed on the Wellchrom HPLC system from Knauer Company (Berlin, Germany). The HPLC instrument consisted of an online K-5020 degasser, a K-501 pump, a 6-port/3-channel injection valve equipped with a 20-μL loop, and a K-2501 UV detector. Eurochrom 2000 was used for the acquisition and processing of the data. Chromatographic separations were carried out using a Capital HPLC column (Scotland, UK) ODS-H C_{18} (250 mm × 4.6 mm I.D., 5 μm). A mixture of 10 mmol L^{-1} of ammonium acetate (pH 5.3) and methanol (50:50) with a flow rate of 1.0 mL min^{-1} was used as a mobile phase in isocratic elution mode. The detection was performed at the wavelength of 275 nm.

2.4. HF-LPME procedure

The Accurel Q3/2 polypropylene hollow fiber membrane (200 μm wall thickness, 600 μm I.D. and 0.2 μm pore size) was purchased from Membrana Company (Wuppertal, Germany) and used for all experiments. The membrane unit was ultrasonically cleaned in acetone for several minutes. Each dried fiber was cut manually into 8.8 cm segments, which may approximately accommodate 24 μL of the receiving phase. Then, 7.5 mL of the sample solution with the pH 12 (NaOH, 2 mol L^{-1}) containing 100 μg L^{-1} of PTU was placed in a 9 mL vial with a 4 mm × 14 mm magnetic stir bar. The sample vial was placed on a Heidolph MR 3001K magnetic stirrer (Schwa Bach, Germany) and a 25 μL Hamilton microsyringe (Bonaduz, Switzerland) was used to introduce the receiving phase into the hollow fiber. Then, 25 μL of the acidic receiving phase ($NaClO_4$; 2 mol L^{-1}) was withdrawn into the microsyringe and its needle was inserted into the lumen of the hollow fiber. The fiber was inserted in the organic phase (6% (w/v) of Aliquat-336 in *n*-octanol) for 30 s and the excess of organic phase was carefully removed by washing the outside of the hollow fiber with ultrapure water. Subsequently, 24 μL of the receiving phase was injected into the lumen of hollow fiber and the end of the hollow fiber was sealed by a piece of aluminum. The U-shape hollow fiber was immersed into the sample solution. The extraction was performed at room temperature and the sample was stirred at 1250 rpm during the extraction (40 min). After extraction, the fiber was removed from the sample vial, the end of the hollow fiber was opened, and the RP was retracted into the microsyringe. Finally, 20 μL of receiving phase was injected into the HPLC system for subsequent analysis.

Table 1
Experimental variables and levels of the half fractional factorial design.

Variable	Key	Level	
		Low	High
Source phase pH	A	8	12
Extraction temperature (°C)	B	25	45
Extraction time (min)	C	10	40
$NaClO_4$ ($mol\,L^{-1}$)	D	0.5	3
Aliquat 336 (%, w/v)	E	1	15
Ionic strength ($mol\,L^{-1}$)	F	0	2

2.5. Optimization strategy

There are several factors, such as source phase pH, receiving phase composition, salt effect, Aliquat 336 concentration, extraction temperature, and time that affect the extraction process. In order to obtain optimal conditions of HF-LPME for extraction of PTU from the biological samples, a half-fractional factorial design was used for screening the variables. After determining the variables that significantly affect the extraction process, and in order to investigate the interaction among these variables, a central composite design (CCD) was employed to develop the corresponding response surface equation. The experimental design matrix and data analysis were carried out by the StatGraphics Plus Package, version 5.1.

3. Results and discussion

In this study, carrier-mediated HF-LPME combined with HPLC-UV was developed for the extraction and determination of PTU in biological samples.

3.1. Screening design

Half-fractional factorial design is the most popular first order design owing to its simplicity and relatively low cost. It is very useful for preliminary studies or in initial optimization steps. Moreover, it is almost mandatory to use this method when the problem involves a large number of factors [16]. Based on the preliminary experiments, at least six factors might have affected the experimental response in the present work. Therefore, six factors (source phase pH, receiving phase composition, salt effect, Aliquat 336 concentration, extraction temperature, and time) at two levels were selected and a 2^{6-1} half-factorial design in two blocks was investigated to optimize the analytical conditions that affect the analyte response signals. The upper and lower values attributed to each factor were selected from the experience gathered in preliminary experiments (Table 1).

The ANOVA results were evaluated for determining the main effects. The normalized results of the experimental design were evaluated at the 5% level of significance, and were analyzed by standardized Pareto chart (Fig. 2). The standard effect was estimated for computing the *t* statistic for each effect. The vertical line on the plot judges statistically significant effects. The bar extracting beyond the line corresponds to the effects that are statistically significant at 95% level of confidence [17]. Furthermore, the positive or negative sign (corresponding to a colored or colorless response) can be enhanced or reduced, respectively, when passing from the lowest to the highest level set for the specific factor. According to Fig. 2, extraction time was the most significant factor having a positive effect on the extraction efficiency in this study. Also, as shown in Fig. 2, source phase pH is the next significant factor, which has a positive effect on the extraction efficiency.

Aliquat 336 concentration, extraction temperature, and receiving phase composition showed a positive but non-significant effect on the extraction efficiency. Fig. 2 also reveals that sodium chloride appeared to have a negative effect on the extraction efficiency. This observation can be explained by the fact that in the presence of salt, interaction may take place between the analyte and the salt. Such interactions would tend to restrict the movement of analyte from the source phase to the membrane solvent. Therefore, all the subsequent studies were performed in the absence of salt. Extraction temperature has a positive effect on the extraction efficiency. In fact, by increasing the source phase temperature, diffusion coefficients of analyte increased and the time required to reach equilibrium decreased. Fig. 3 shows response surface plots for the peak areas of the factors. To continue the optimization process, one variable was fixed at appropriate value (extraction temperature: 45 °C, without addition of salt), considering the results of the first screening study.

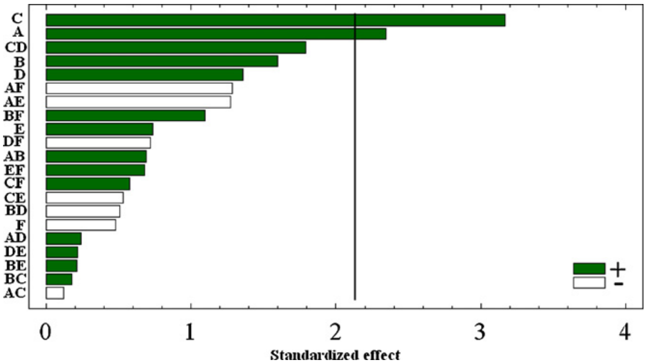

Fig. 2. Pareto charts of the main effects obtained from the half-fractional factorial design for PTU.

3.2. Optimization design

In the next step, a central composite design was applied to optimize the four factors (source phase pH, receiving phase composition, Aliquat 336 concentration, and extraction time). The factors

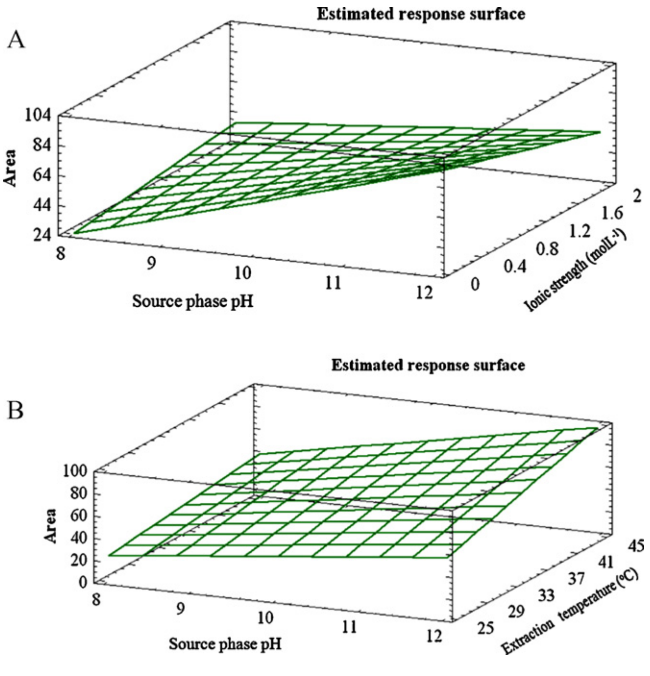

Fig. 3. Response surface for PTU using the half-fractional factorial design obtained by plotting of (A) source phase pH *vs.* ionic strength and (B) source phase pH *vs.* the extraction temperature.

Table 2
Experimental variables, levels and star points of the central composite design (CCD).

Variable	Key	Level			Star points ($\alpha = 2$)	
		Lower	Central	Upper	$-\alpha$	$+\alpha$
Source phase pH	A	9	10.5	12	7.5	13.5
Extraction time (min)	C	20	35	50	5	65
$NaClO_4$ ($mol\,L^{-1}$)	D	2	2.5	3	1.5	3.5
Aliquat 336 (%, w/v)	E	4	6	8	2	10

Table 3
Results of analysis of variance.

Source	Sum of squares	Df	Mean square	*F*-ratio	*p*-Value
A	15,259.1	1	15,259.1	50.79	0
C	51,836.4	1	51,836.4	172.55	0
D	299.874	1	299.874	1	0.336
E	0.595035	1	0.595035	0	0.9652
AA	26,741	1	26,741	89.01	0
AC	1373.09	1	1373.09	4.57	0.0521
AD	1177.54	1	1177.54	3.92	0.0693
AE	0.244778	1	0.244778	0	0.9777
CC	13,899.8	1	13,899.8	46.27	0
CD	2113.22	1	2113.22	7.03	0.0199
CE	901.215	1	901.215	3	0.1069
DD	3015.67	1	3015.67	10.04	0.0074
DE	129.51	1	129.51	0.43	0.5229
EE	11,463.9	1	11,463.9	38.16	0
Blocks	12,132.4	2	6066.18	20.19	0.0001
Total error	3905.38	13	300.414		
Total (corr.)	130,498	29			

R^2 = 97.0073%, R^2 (adjusted for degree of freedom (Df)) = 94.2141%, standard error of est. = 17.3324, mean absolute error = 9.23071.

were chosen from the first screening design. According to the number of experiment equation: $N = (2^f + 2f + C)$, f and C were set at 4 and 6, respectively, which means that 30 experiments had to be done. The examined levels of the factors are given in Table 2. The experimental data showed a good accordance with the second-order polynomial equations. The coefficients of determination, R^2, were higher than 0.97 for the areas, which were statistically acceptable at $p < 0.05$ levels. The data obtained were evaluated by the ANOVA test (Table 3) and the effects are shown using Pareto Chart in Fig. 4.

Based on the central composite design, extraction time and source phase pH had the highest significantly positive effect. However, receiving phase composition and Aliquat 336 concentration were not significant factors.

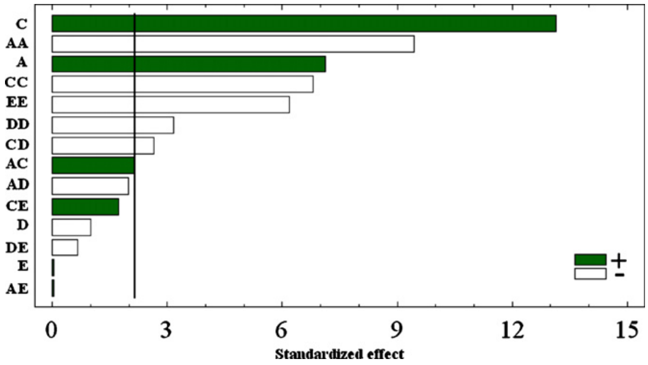

Fig. 4. Pareto charts of the main effects in the central composite design for PTU. AA, CC, DD, and EE are the quadratic effects of the source phase pH, extraction time, $NaClO_4$ concentrations, and Aliquat 336 concentration, respectively. CD, AC, AD, CE, DE, and AE are the interaction effects between extraction time and $NaClO_4$ concentration; source phase pH and extraction time; source phase pH and $NaClO_4$ concentration; extraction time and Aliquat 336 concentration; $NaClO_4$ concentration and Aliquat 336 concentration; and source phase pH and Aliquat 336 concentration, respectively.

In fact, as other microextraction techniques, carrier-mediated HF-LPME is a type of equilibrium extraction [18,19]. The analyte is partitioned between the source and receiving phases until the equilibrium is established [20]. Hence, the positive effect of extraction time is corresponding to the equilibrium, which is established at longer time. Since PTU is a weak basic compound ($pK_a = 8.3$),

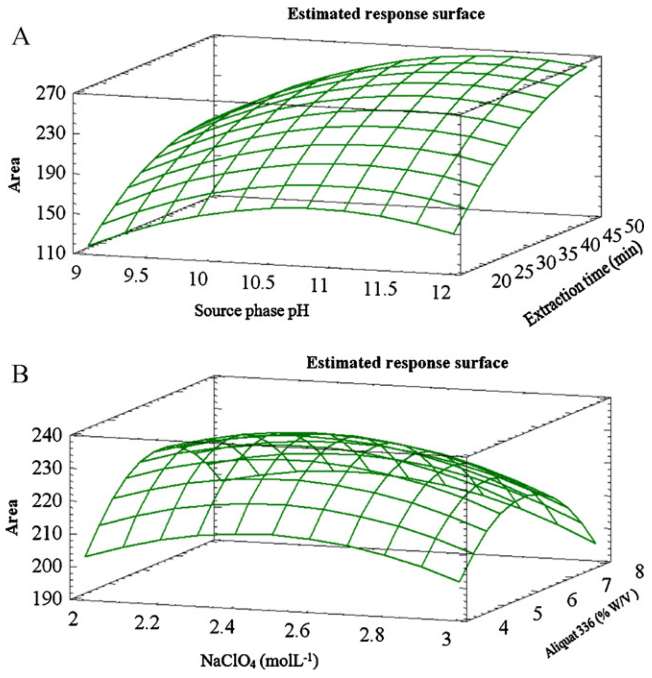

Fig. 5. Response surfaces for PTU using the central composite design obtained by plotting of (A) source phase pH *vs.* extraction time and (B) $NaClO_4$ concentration *vs.* Aliquat 336 concentration.

Table 4
Figures of merit of the proposed method.

Sample	Regression equation	r^2	DLR ($\mu g L^{-1}$)	LOD ($\mu g L^{-1}$)	Preconcentration factor[a]	RSD (%)[c]
Water	$Y = 39{,}432C^b + 38{,}186$	0.998	0.5–1000	0.1	198	6.2
Urine	$Y = 26{,}828C + 25{,}723$	0.988	2–700	0.4	137	5.7
Plasma	$Y = 25{,}963C + 24{,}321$	0.986	2–700	0.4	130	6.3
Bovine milk	$Y = 25{,}605C + 24{,}697$	0.992	2–700	0.4	128	6.2
Bovine meat	$Y = 25{,}956C + 23{,}956$	0.990	2–700	0.4	125	5.8

[a] PF and extraction recovery were obtained at 60 $\mu g L^{-1}$ level of the analyte.
[b] Concentration in $\mu g L^{-1}$.
[c] Relative standard deviation ($n = 5$).

Table 5
Determination of PTU in biological samples.

Sample	C_{added} ($\mu g L^{-1}$)	C_{found} ($\mu g L^{-1}$)	RSD (%) ($n = 3$)	Error (%)
Urine	–	–	–	–
	20	19.0 ± 0.07	5.7	–5
Plasma	–	–	–	–
	40	38.9 ± 0.05	6.3	–2.8
Bovine milk	–	–	–	–
	40	38.3 ± 0.10	6.2	–4.2
Bovine meat	–	–	–	–
	40.0[a]	39.1 ± 0.10	5.8	–2.2

[a] ($\mu g kg^{-1}$).

the source phase should be sufficiently basic to keep the analyte in its neutral form and reduce its solubility in the source phase. On the other hand, PTU is a hydrophilic compound with high solubility in aqueous media ($\log P = 1.0$). Hence, the direct passive transport of PTU from the source phase to the receiving phase using organic impregnated solvents is difficult. PTU has nonbonding pairs of electrons in its structure. Therefore, by utilizing a cationic carrier in membrane solvent, it is possible to actively transport PTU via ion-pair formation. Consequently, the positive effects of source phase pH and Aliquat 336 concentration confirm the results. The experiments showed that presence of an anion such as ClO_4^- as a competitor ion in the receiving phases can promote the back extraction of PTU into the receiving phase. In the sample solution–membrane interface, PTU form a neutral ion-pair with Aliquat-336, while releasing a Cl^- anion. Due to concentration gradient, the ion-pair diffuses across the membrane. At the receiving phase–membrane interface, PTU is released from the organic phase, while ClO_4^- is given back to the carrier. In this process, the driving force for transport of PTU is the gradient of pH and concentration of anion between the source phase and receiving phase. Fig. 5 shows response surface plots for the peak areas. Accordingly, the plots given in Fig. 5 were used for interpreting the variation of areas as a function of each pair of the independent variables graphically. The source phase pH *vs.* extraction time is shown in Fig. 5A. It indicates that longer extraction time and higher source phase pH values are optimal for the extraction process. In Fig. 5B, the interaction between $NaClO_4$ and Aliquat-336 concentrations can be observed, suggesting that $NaClO_4$ and Aliquat-336 concentrations are effective for the extraction process.

According to the overall results of the optimization study, the following experimental conditions were chosen: source phase pH, 12; $NaClO_4$ concentration, 2 mol L^{-1}; Aliquat 336 concentration, 6% (w/v); and extraction time, 40 min.

3.3. Method performance

Under optimum conditions, limit of detection (LOD), regression equation, correlation of determination (r^2), dynamic linear range (DLR), preconcentration factor (PF), and extraction recovery (R%) were obtained. LOD was calculated at the signal to noise ratio of 3. Also, PF at a given time was defined as the ratio of the analyte concentration in the receiving phase to its initial concentration in the source phase. The preconcentration factor was calculated by the following equation:

$$\mathrm{PF} = \frac{C_{\mathrm{RP,final}}}{C_{\mathrm{SP,initial}}}$$

where, C_{RP} and C_{SP} are the final concentration and initial concentration of analyte in the receiving phase and source phase, respectively. The analytical performance of the proposed method is summarized in Table 4.

3.4. Determination of PTU in the bovine meat and milk, and human plasma and urine samples

The bovine meat and milk, and human urine and plasma samples were used to evaluate the feasibility of the carrier-mediated HF-LPME procedure. Fig. 6 represents chromatograms of the bovine meat and milk and also human plasma samples spiked at 40 $\mu g L^{-1}$ of PTU.

Table 5 shows that the results of the three replicate analyses of each real sample obtained by the proposed method are in good

Table 6
Comparison of the figures of merit of the proposed method with those of the other methods applied for the extraction and determination of PTU.

Analytical technique	DLR ($\mu g L^{-1}$)	LOD ($\mu g L^{-1}$)	RSD (%)	Preconcentration factor	Reference
HF-LPME-HPLC-UV	0.5–1000	0.1	<6.3	198	Proposed method
LLE-HPLC-UV	–	3.5	<14.8	–	[2]
SPE-HPLC–MS	–	0.9	–	–	[5]
MSPD[a]-GC–MS	–	10[b]	<4.5	–	[21]

[a] Matrix solid-phase dispersion.
[b] ($\mu g kg^{-1}$).

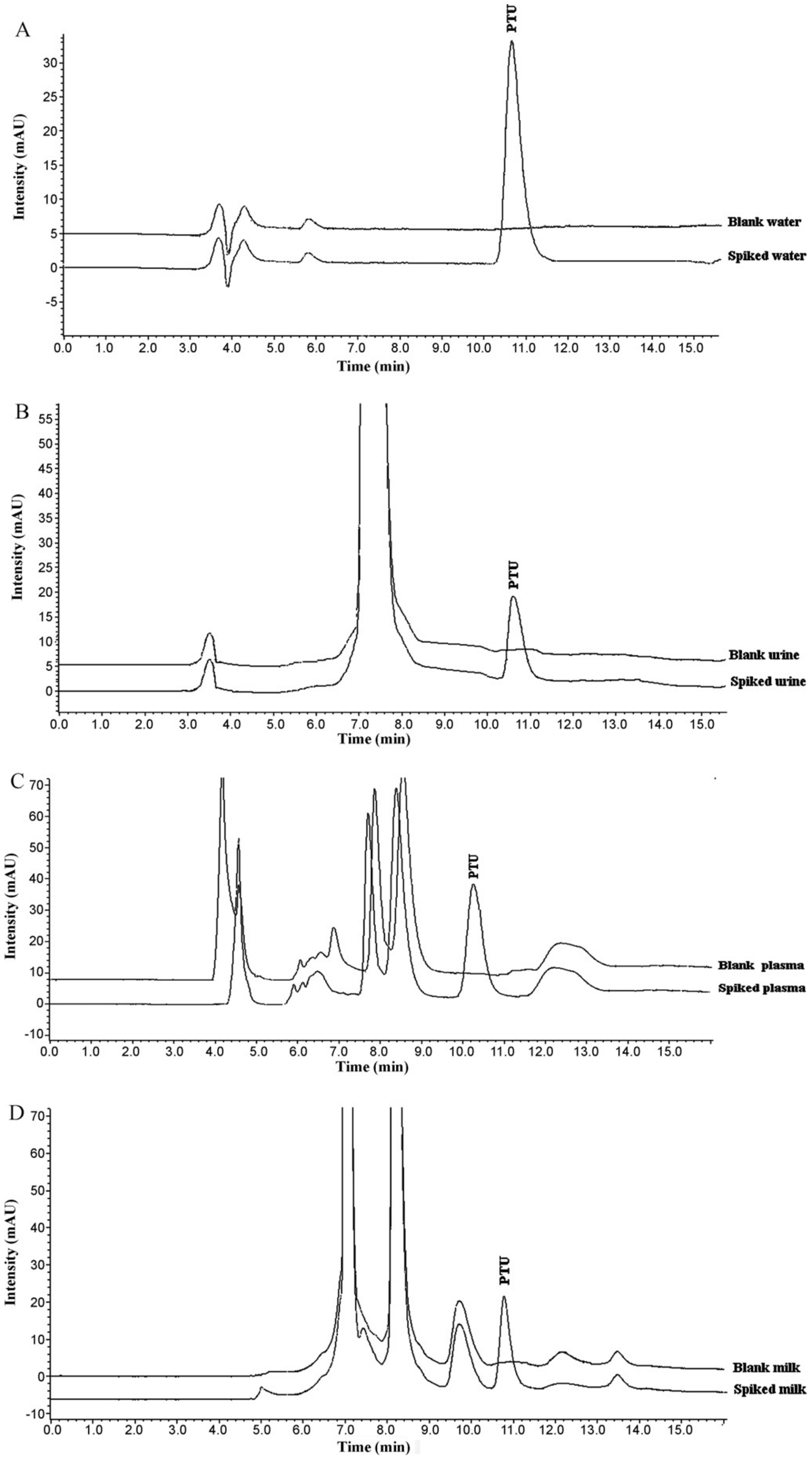

Fig. 6. Chromatograms of the (A) water, (B) human urine, (C) human plasma, (D) bovine milk and (E) bovine meat samples spiked at 30, 20, 40, 20, and 40 $\mu g\,L^{-1}$ of PTU, respectively, after HF-LPME under optimal conditions.

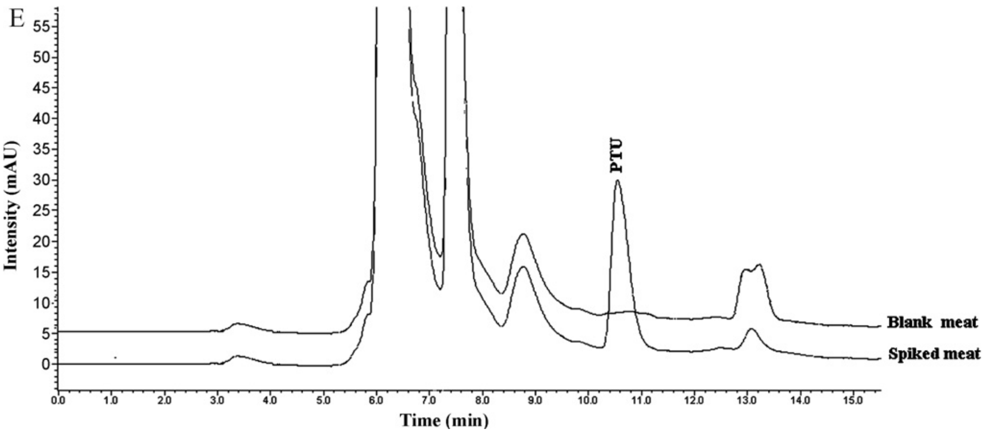

Fig. 6. (*Continued*)

agreement with the spiking amounts. Table 6 compares the figures of merit of the proposed method and the alternative methods for the extraction of PTU from biological samples. The comparison results showed that the proposed method is more sensitive (lower LOD) and also has higher PF as compared with other reported methods. The table clearly shows that RSD of HF-LPME method is similar to those obtained from other methods.

4. Conclusion

In the present study, carrier-mediated HF-LPME combined with HPLC-UV was applied for the extraction and determination of PTU in aqueous and biological samples. This method exhibits a very low LOD with high PF. The proposed method is simple, inexpensive, and fast, and can be successfully applied for separation, preconcentration, and determination of PTU in different biological samples.

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