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Simultaneous determination of chloropheniramine maleate and dextromethorphan hydrobromide in plasma sample by hollow fiber liquid phase microextraction and high performance liquid chromatography with the aid of chemometrics

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ABSTRACT

A simple and high sensitive technique based on three phase hollow fiber liquid phase microextraction (HF-LPME), optimized by using a four-variable experimental design and response surface methodology was performed to evaluate dextromethorphan hydrobromide (DEX) and chloropheniramine maleate (CLP) simultaneously in human plasma. The influence of source phase pH, HCl concentration of acceptor phase, time and salt addition were investigated. Under the optimized conditions analytes were extracted in their neutral form, pH 12.5 and salt concentration 2% (w/v), through a supported liquid membrane (SLM) of hexadecane into the HCl 0.0005 mol L^{-1} located inside the lumen of hollow fiber to be back extracted. The mass transfer of the analytes from the donor phase through the SLM into acceptor phase was driven by the pH gradient. Determination was accomplished by UV-high performance liquid chromatography with recoveries 92% and 84% for CLP and DEX, respectively. Linearity was obtained in the range of 0.01–1000 μg L^{-1} ($R^2 > 0.994$). The obtained enrichment factors (EFs) were 233–276 for DEX and CLP respectively and limits of detection were 0.003 μg L^{-1} with RSDs below 6%. The method proposed acceptable values to determine CLP and DEX in plasma samples sensitively and accurately.

1. Introduction

Generally most cold remedies are a combination of active ingredients such as paracetamol (PARA), chlorpheniramine maleate (CLP), diphenhydramine hydrochloride (DPH), tripolidine hydrochloride (TPL), phenylpropanolamine hydrochloride (PPA), dextromethorphan hydrobromide (DEX), loratadine (LOR), aspirin (ASA) and caffeine (CAF), or contain just one of the above compounds [1]. Binary combinations of antihistamine and antitussive pharmaceutical preparations are widely used for cough and cold treatments. Herein a combination drug, composed of chlorpheniramine and dextromethorphan is in a point of view (Fig. 1).

Chlorpheniramine (2-pyridinepropanamine, γ(4-chlorophenyl)-N,N-dimethyl,(Z)-2 butenedioate, CPM) is one of the most potent commonly used antihistamines, marketed in its salt form as chlorpheniramine maleate. It is a first-generation alkylamine antihistamine that is generally used in pharmaceutical preparations for symptomatic relief of common cold, allergic disease [2] and antitussive symtoms [3] and causes a moderate degree of sedation as well [4].

Dextromethorphan hydrobromide ((+)-3-methoxy-17-methyl-(9α,13α,14α)-morphinan, DEX) is the isomer of levorphanol, a codeine analog [5]. It is an over-the-counter, highly effective antitussive drug that is widely prescribed for temporary relief of cough caused by minor throat and bronchial irritation (such as flue and common cold) [6] which it mainly acts on cough center in the medulla to treat mentioned respiratory disorders [7]. Dextromethorphan is utilyzed in at least 125 products as an antitussive agent of cough and cold medications [5]. Its antitussive effect is similar to codeine but has no analgesic or addictive activity [7]. Ready accessibility of dextromethorphan, has caused increasing recreational abuse in recent years [8]. Indeed, at therapeutic dose, DEX is not an addictive drug and is safe to take. But at higher dose, it has psychoactive properties similar to those of phencyclidine, hence it is abused in addicted people [9]. It is assumed that therapeutic activity of DEX is due to its combination with its active metabolite, dextrophan (DOR). DEX is metabolized by a first-pass metabolic effect, resulting a low concentration level, 1–20 ng mL^{-1}, in plasma [9].

There have been numerous publications describing quantification methods of these compounds individually and in combination

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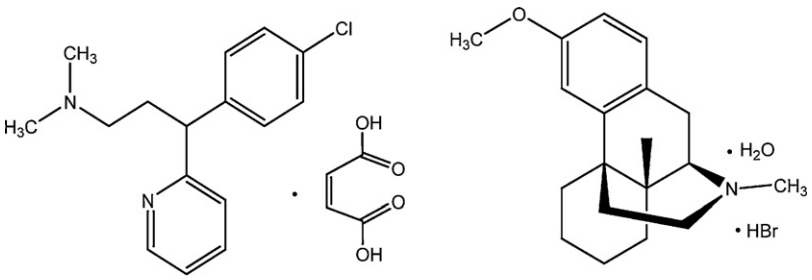

Chlorpheniramine
pKa = 4.91; 9.42
Log p = 3.50

Dextromethorphan
pKa = 8.85
Log p = 3.35

Fig. 1. The chemical structure and properties of DEX and CLP.

with other drugs such as HPLC, GC–MS, LC–MS, LC–MS/MS [10–16] potentiometric sensor [17], spectrophotometry [18], capillary electrophoresis [19] and fluorimetry [20]. However these reported methods required laborious extraction procedures, relatively large sample volume and also showed low sensitivity that were not sufficient for pharmacokinetic and bioequivalence studies [21]. Anyway, all of the aforementioned listed procedures have been successfully validated and applied for routine analysis but none of them afford simultaneous quantification of binary compounds in one step. Before chromatographic separation of a biological sample such as plasma, sample preparation step is required to clean up the matrix [6]. Therefore usually sample pretreatment is done in order to extract, isolate or concentrate the analyte from complicated matrix to make sample compatible for instrumental analysis [22]. Conventional liquid–liquid extraction (LLE), is the common method that despite its high reproducibility and high sample capacity is not preferable since it requires large amounts of expensive and toxic solvents resulting hazardous laboratory waste [23,24]. This method has the tendency to form emulsion and also is a time and labor consuming procedure [25]. To overcome these difficulties by reducing the amount of organic solvent and accomplishing sample extraction and preconcentration in a single step, microextraction methods have been developed that are faster and simpler than conventional methods [26–29]. Hollow fiber liquid phase microextraction (HF-LPME) is a simple and inexpensive technique that makes extraction and preconcentration the analytes of interest from complex matrixes possible [30]. In the two phase LPME sampling mode extraction is done to extract the analyte from an aqueous sample to a water immiscible extractant immobilized in the pores and lumen of the hollow fiber and in the three phase sampling mode (HF-LLLME), limited to ionizable analytes, the analytes are extracted from an aqueous sample through the water immiscible extractant immobilized in the pores of the hollow fiber and finally into an acceptor aqueous phase inside the lumen of the hollow fiber [31]. Three phase mode is limited to basic or acidic analytes with ionizable moieties. So extraction of basic compounds is possible when pH of the sample solution is adjusted in the alkaline region to suppress solubility of analytes whereas pH in the acceptor solution is low enough to promote analyte diffusion from organic phase to acceptor phase that is controlled by partition coefficient [32].

To the best of our knowledge, there has been no report on the use of any microextraction techniques for preconcentration and separation of DEX and CLP. In this paper HF-LLLME coupled with HPLC-UV was proposed for quantitative analysis of DEX and CLP in plasma samples and an experimental design was used for investigating the affective parameters on the extraction efficiency. Moreover, compared with other techniques, HF-LPME with HPLC-UV provides advantage of utilizing a microextraction method to achieve a much less expensive method to preconcentrate the analytes more sensitively and reproducibly.

2. Experimental

2.1. Chemicals, reagents and materials

CLP and DEX were from Sigma–Aldrich (St. Louis, MO, USA). Hydrochloric acid, octanol, dihexylether, cyclohexanol, 1-undecanol, hexadecane, sodium hydroxide, sodium chloride, and sodium dihydrogenphosphate were from Merck (Darmstadt, Germany) and Fluka (Buchs, Switzerland). Deionized water was prepared using a Milli-Q system from Millipore (Bedford, MA, USA). HPLC grade acetonitrile (ACN) and methanol (MeOH) was purchased from Caledon (Georgetown, Ont., Canada). Plasma sample was obtained from the Clinic of Taleghani Hospital (Tehran, Iran).

The Accurel Q3/2 polypropylene hollow fiber membrane (20 μm wall thickness, 600 μm I.D. and 0.2 μm pore size) was purchased from Membrana Company (Wuppertal, Germany). A 25 μL Hamilton HPLC microsyringe (with a needle of 800 μm outer diameter and 25 mm length) for single use, obtained from (Bonaduz, Switzerland) was used to fill the acceptor solution into the lumen of the hollow fiber for extraction and to flush out the acceptor phase.

2.2. Standard solutions and real sample

Individual standard stock solutions of each drug were prepared by dissolving 50 mg standard in 100 mL of methanol. Working solutions were prepared by appropriate dilution of the stock solutions at the required concentration levels with water.

For plasma samples, 2 mL spiked plasma sample is mixed with 3 mL acetonitrile in order to precipitate proteins. The obtained solution was vortexed and centrifuged for 3 min at 3200 rpm, then the supernatant was removed and diluted at the ratio of 1:3 with ultrapure water. All the solutions were stored at 4 °C in refrigerator, but thawed to room temperature before use.

2.3. Apparatus

HPLC analysis of the samples was conducted using a Wellchrom HPLC system from Knauer Company (Berlin, Germany). The instrument consisting online K-5020 degasser, a K-501 pump, a 6-port/3-channel injection valve equipped with a high pressure manual injection valve (20 μL loop), and a UV/vis detector (model K-2501). The detector was operated at 220 nm. Eurochrom 2000 was the software used for the data acquirement and processing. Chromatographic separations were performed by a Capital HPLC column (Scotland, UK) ODS-H C_{18} (250 mm × 4.6 mm I.D., 5 μm). Isocratic elution was carried out by a mobile phase consisted of

KH_2PO_4 (pH = 2.5, 0.01 M); acetonitrile: methanol; 60: 24: 16 at flow rate = 1 mL min^{-1}.

An ultrasonic water bath (frequency 35 kHz, 320 W, Super RK 510, Sonorex, Bandelin, Germany) was used to clean fibers with Ultrasonic irradiation prior to use.

Centrifugation was done with Hettich centrifuge model EBA 20 (Oxford, England).

2.4. LPME procedure

The extraction and preconcentration procedure was as follows: First, the hollow fibers were cut into 8.8 cm pieces. Before using, the fiber segments were sonicated in acetone to remove any possible contaminates and dried in air till evaporation was complete. 25 μL of the aqueous solution (HCl; 0.0005 mol L^{-1}), acceptor phase, was withdrawn into the microsyringe, then the hollow fiber was attached to its needle and subsequently it was submerged in the organic solvent for a few seconds to impregnate with organic phase. In order to remove extra amount of organic solvent from the surface of the fiber, it was inserted to the water for 30 s. Then 24 μL of the acceptor phase was flushed carefully with slow pushing of the microsyringe plunger into the fiber. At last, the end of the hollow fiber was sealed by a piece of aluminum foil and folded by metal wire binding. The prepared extraction device was introduced into 7.5 mL of the aqueous sample (100 μg L^{-1}, pH = 12.5, Salt% = 2) containing DEX and CLP that was poured into 8 mL sample vial having a 4 mm × 14 mm magnetic stirring bar, at a U-shape configuration and top of the vial was sealed with a piece of parafilm. After performing extraction at 1250 rpm for 60 min, the microsyringe containing the hollow fiber was removed from the sample vial and the sealed end of the hollow fiber was opened and the receiving phase was withdrawn into the microsyringe. Ultimately receiving phase was injected into the 20 μL HPLC loop for subsequent analysis.

2.5. Data modeling

Optimization of the different parameters that significantly affect on the extraction procedure and also investigating the interaction between these parameters was performed by central composite design (CCD), through applying the StatGraphics Plus Package, version 5.1. Salt effect, extraction time, pH of donor phase and acceptor phase are four independent variables that were studied.

3. Results and discussion

3.1. Preliminary investigations

Before confining any specific limits for carrying out central composite design, some pilot experiments should be carried out to evaluate the approximate domains for each factor. It has been revealed that several factors such as the pH of donor phase, the pH of acceptor phase, time, stirring rate and salt concentrations are effective factors. Out of these five factors stirring rate was fixed at 1250 rpm, since observations showed that by increasing stirring rate up to 1250 rpm, the extraction of analytes was increased as well. The volume and shape of the vial was suitable enough, so no air bubble was formed at such a high speed and extraction kinetics would be promoted.

3.1.1. Selection of membrane solvent

Compatibility with the lipophilic polypropylene membrane, low water solubility to prevent dissolution into the aqueous phase, affinity for target analytes, reasonable higher solubility of analytes in the organic phase than in the aqueous phase and low volatility which will restrict solvent evaporation during extraction, are several important selection criteria for organic solvents as the liquid membrane to achieve the highest enrichment factor [33,34].

Based on the required characteristic, it was observed (Fig. 2) that hexadecane was more appropriate not only for longer extraction time but also with less risk of solvent loss.

3.2. Response surface method

A fundamental motivative interest for developing a new method to separate and quantify the analyte is reducing the required time and number of trials that ends in overall required costs. Thus in order to optimize the preconcentration of the analytes of interest by HF-LPME a circumscribed central composite design was employed. For an experimental design with four factors, the model including linear, quadratic and cross terms can be expressed by CCD.

Through the statistical processes, the response surface plots were obtained that is based on the design and modeled CCD data. The exact optimum point can be attained by the aid of response surface methodologies that illustrate relationships between parameters and responses graphically [35–38].

This design is composed of a two level factorial design ($N_f = 2^f$) (f is number of factors) with additional star points ($N_a = 2f$) and center points that are located at the center of the experimental region (N_0). Actually, this experimental strategy is combination of a factorial

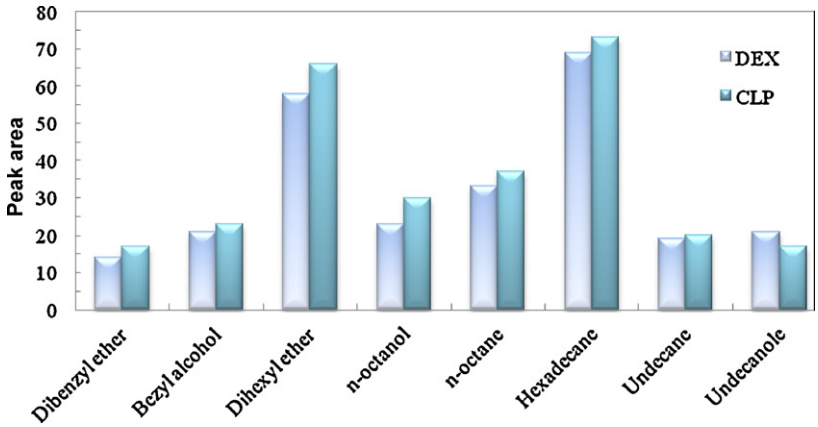

Fig. 2. Effect of organic solvent on peak area. Conditions: sample volume: 7.5 mL; without salt addition; stirring rate: 1250 rpm; extraction time: 60 min; concentration of analytes: 1 ppm; pH of donor phase: 12; concentration of HCl in acceptor phase: 0.1 mol L^{-1}.

Table 1
Experimental factors and their notations together with their levels.

Factor	Key	Level	
		Low	High
Source phase pH	A	8	11
Ionic strength (%, w/v)	D	1	3
HCl (mol L^{-1})	C	0.5	1.5
Extraction time (min)	B	25	50

design and additional design (star design) in which their centers coincide. Generally center points are repeated to get a good estimation of experimental error and the star points are located at $\pm\alpha$ from the center of experimental region and establish new extremes for the low and high settings of factors [39]. The value of α is calculated from Eq. (1) and insures orthogonality and rotatibility of design. In the present work there had been four factors, so at $\alpha = \pm 2$ by choosing six center points (C) the total number of experiments was equal to 30 according to Eq. (2).

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

$$N = 2^f + 2f + C \quad (2)$$

The general empirical model is a second order polynominal, that the response Y is related to the variables x to quantify and interpret the relationships between responses and each factor's effects, Eq. (3).

$$Y = b_0 + \sum_{i=1}^{k} b_i x_i + \sum_{1 \le i \le j}^{k} b_{ij} x_i x_j + \sum_{i=1}^{k} b_{ii} x_i^2 \quad (3)$$

where k is the number of variables, b_0 the intercept parameter and b_i, b_{ij}, b_{ii} are the regression parameters for linear, interaction and quadratic factor effects, respectively. The goals of CCD strategy in this work were: (i) to maximize the peak area, (ii) to determine the variables that have a higher impact on the peak area, (iii) to show the robustness of the method close the optimum conditions and (iv) showing the involving interactions between variables.

3.2.1. Optimization by the central composite design

In the next step, a central composite design was applied to optimize effective factors of HFLLME. From the preliminary experiments factors, their levels and symbols were selected as they are depicted at Table 1.

Model validation is ensured by, the most powerful numerical method, the application of analysis of variance (ANOVA). A p-value less than 0.05 in the ANOVA table indicates the statistical significance of an effect at 95% confidence level. So the effects <0.05 in the p-value column are statistically significant. The F-ratio is the ratio of the mean squares error to the pure error obtained from replicating experiment at the center of the design. Fig. 3 shows the Pareto chart of DXM and CLP based on the results illustrated in Table 2.

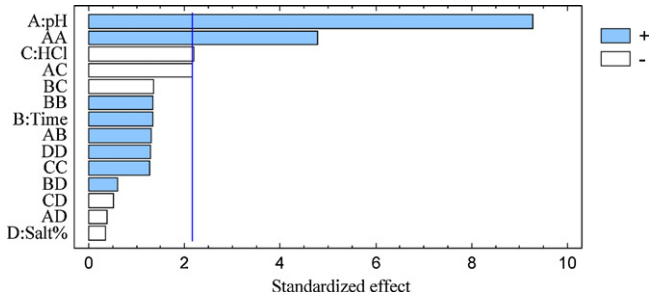

Fig. 3. Pareto charts of the main effects and interaction effects in the central composite design for DEX and CLP.

Table 2
Analysis of variance (ANOVA) study.

Source	Sum of squares	D.f.[a]	Mean square	F-ratio	p-Value
A: pH	4738.15	1	4738.15	85.88	0.0000
B: Time	97.3989	1	97.3989	1.77	0.2068
C: HCl	260.754	1	260.754	4.73	0.0488
D: Salt%	5.9222	1	5.9222	0.11	0.7484
AA	1250.68	1	1250.68	22.67	0.0004
AB	91.2878	1	91.2878	1.65	0.2208
AC	256.133	1	256.133	4.64	0.0505
AD	7.69501	1	7.69501	0.14	0.7148
BB	98.1015	1	98.1015	1.78	0.2053
BC	100.465	1	100.465	1.82	0.2002
BD	19.5091	1	19.5091	0.35	0.5623
CC	87.8226	1	87.8226	1.59	0.2292
CD	14.0292	1	14.0292	0.25	0.6225
DD	89.1323	1	89.1323	1.62	0.2260
Blocks	475.242	2	237.621	4.31	0.0367
Total error	717.199	13	55.1692		
Total (corr.)	8084.72	29			

[a]Degrees of freedom.

It can be seen that source phase pH (A) and source phase pH square effect (AA) have a positive effect on the peak area while HCl concentration of acceptor phase shows negative effect. As it is shown, the most significant parameter is the pH of the donor phase. Since the ionic or molecular form of the analytes largely influences the affinity of compounds to transfer from one medium to another, controlling the pH of the extraction medium is of a great importance. The higher the source phase pH, the higher was the peak area. Increasing the pH pushes the system beyond the equilibrium state, hence the analytes are transferred more easily. This is due to the fact that DEX and CLP are basic ionizable compounds and in alkaline region they are in their neutral form, thus can both be transported from the donor to the acceptor phase by the gradient of pH. Acceptor phase pH should be lower than pK_a value of the analytes in order to prevent the ionized analytes from being back extracted to the organic solvent. It was observed that by increasing HCl concentration, the response decreases. This may be attributed to the increase of the ionic strength of acceptor solution by increasing the HCl concentration [40]. It is shown that extraction time and salt% of the source phase are non-significant effects. As HF-LLLME is an equilibrium technique, prolonged extraction time is beneficial and thus extraction improves with time. Salt addition to the sample solution increases the ionic strength of solution and changes the physical properties of the Nernst diffusion film, so diffusion rate into the organic phase is reduced [41]. Some of the response surface plots are depicted at Fig. 4 and their curvatures indicate the interaction between the factors. The optimum extraction conditions are shown in Table 3 and also in estimated response surface (Fig. 4(a) and (b)).

By using CCD, experimental results were fitted to a second order polynomial model relating average peak area of DEX and CLP to the

Table 3
Optimized and applied values of factors affecting the extraction.

Factor	Optimum	Applied
Source phase pH	12.499	12.5
Ionic strength (%, w/v)	2.20297	2
HCl (mol L^{-1})	0.000586248	0.0005
Extraction time (min)	62.5	60

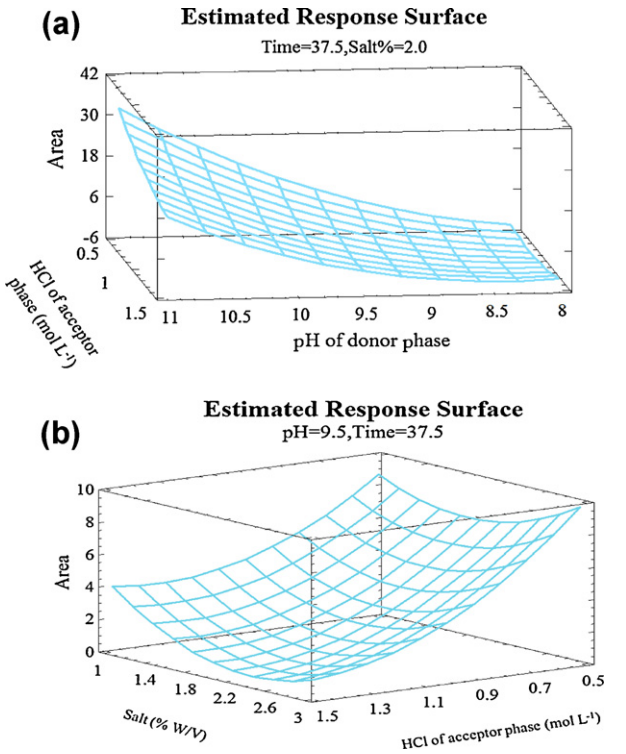

Fig. 4. Response surfaces for DEX and CLP using the central composite design obtained by plotting of (a) HCl concentration of acceptor phase *vs* source phase pH (b) Salt% *vs* HCl concentration of acceptor phase.

factors. The proposed model was described as follows:

$$Y = 190.918 - 46.1728 \times \mathrm{pH} - 1.73259 \times \mathrm{Time} + 48.5529 \times \mathrm{HCl} - 4.75518 \times \mathrm{Salt\%} + 3.00116 \times \mathrm{pH}^2 + 0.127393 \times \mathrm{pH} \times \mathrm{Time} - 5.33472 \times \mathrm{pH} \times \mathrm{HCl} - 0.462331 \times \mathrm{pH} \times \mathrm{Salt\%} + 0.0121036 \times \mathrm{Time}^2 - 0.400928 \times \mathrm{Time} \times \mathrm{HCl} + 0.0883383 \times \mathrm{Time} \times \mathrm{Salt\%} + 7.1575 \times \mathrm{HCl}^2 - 1.87278 \times \mathrm{HCl} \times \mathrm{Salt\%} + 1.80267 \times \mathrm{Salt\%}^2$$

3.3. Analytical performances

Table 4 summarizes the data related with the performance of the proposed method, in terms of corresponding correlation equation, correlation of determination (R^2), dynamic linear ranges (DLR), the limits of detection (LODs) obtained from Eq. (6), preconcentration factor (PF) obtained from Eq. (4) and extraction recovery (R%) obtained from Eq. (5) under the optimized conditions. LOD was calculated as the three times of the average signal of blank solution over the calibration curve's slope. It was found that under optimal conditions, extraction recoveries were obtained in the range of 92–84% for CLP and DEX.

$$\mathrm{PF} = \frac{C_a}{C_i} \tag{4}$$

$$R\% = \frac{C_a \times V_a}{C_i \times V_i} = \mathrm{PF} \times \frac{V_a}{V_i} \tag{5}$$

$$\mathrm{LOD} = \frac{3S_b}{m} \tag{6}$$

where, C_a and C_i are the final concentration and initial concentration of analyte in the receiving phase and source phase, respectively. V_a and V_i are the acceptor phase volume and source phase volume, respectively.

Comparison of the proposed methods with other existing methods in terms of some of their figures of merit is provided in Table 5. As can be seen the proposed HF-LPME has some advantageous properties such as wide DLRs, low LODs and RSDs.

3.4. Real sample analysis

Plasma samples were analyzed to assess the applicability of the method. Table 6 shows the extraction recovery after spiking plasma samples at three concentrations levels. Observations showed that extraction procedure was not affected so much due to the sample matrix, thus the proposed method can be a suitable sample preparation method for the determination of DEX and CLP in a complex matrix such as plasma. The chromatogram of blank and spiked plasma sample at 100 μg L^{-1} is shown in (Fig. 5).

Table 4
Figures of merit of the proposed method.

Compounds	DLR (μg L^{-1})	Correlation equation	R^2	PF[a]	LOD (μg L^{-1})
CLP	0.01–1000	$Y = 0.136\,C^{b} + 2.743$	0.996	276	0.003
DEX	0.01–1000	$Y = 0.090C + 1.231$	0.994	233	0.003

[a] Preconcentration factors were calculated at 50 μg L^{-1}.
[b] Concentration in μg L^{-1}.

Table 5
Comparison of the figures of merit of the proposed method with those of the other methods applied for the extraction and determination of GBP.

Extraction method	Analyte	DLR (ng mL^{-1})	LOD (ng mL^{-1})	RSD%	Reference
HF-LPME-HPLC-UV	DEX	0.01–1000	0.003	5.7	The current method
	CLP	0.01–1000	0.003	6.3	
Second order calibration – excitation–emission matrix fluorescence	DEX	–	18.45	–	[42]
Molecularly imprinted polymer cartridges coupled on-line with HPLC	DEX	–	0.12	3.35	[43]
UPLC–tandem triple-quadrupole mass spectrometry	DEX	0.136–27	0.136	–	[44]
Potentiometric method	DEX	271–271.4 × 10^4	271.4	–	[45]
First-derivative spectrophotometry	DEX	–	33	–	[46]
LLE-LC–MS/MS	CLP	50–0.2	0.2	–	[47]
Solvent Extraction-GC	CLP	–	0.4	–	[48]
LLE-LC–MS/MS	CLP	0.05–20	–	11.3≥	[49]
Normal-phase LC method	DEX	75 × 10^3–225 × 10^3	–	–	[50]
	CLP	10^4–3 × 10^4			

Table 6
Analyte concentration (C_{addad}, C_{found} in μg L^{-1}) and spike recovery (R = mean, %, n = 5) in samples by the proposed method.

CLP					DEX			
C_{added} (μg L^{-1})	C_{found} (μg L^{-1})	R%	RSD%[a]	RSD%[b]	C_{found} (μg L^{-1})	R%	RSD%[a]	RSD%[b]
10	8	80	4.2	3.8	7.5	75	4.7	4.3
50	42	84	3.1	2.6	41	82	3.9	3.8
100	76	76	2.9	3.3	74	74	3.5	3.8

[a] Relative standard deviation, interday (n = 5).
[b] Relative standard deviation, intraday (n = 5).

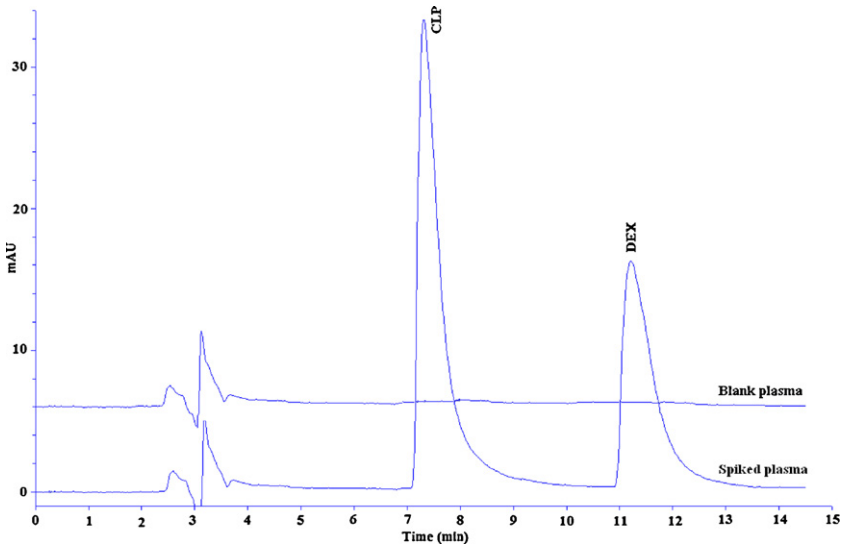

Fig. 5. Chromatogram of blank plasma and spiked plasma at 100 μg L^{-1} of DEX and CLP.

4. Conclusion

The current work presented application of three phase hollow fiber microextraction combined with HPLC-UV for extraction and determination of trace amounts of DEX and CLP in plasma sample. The method provided good precision, wide dynamic linear range, high preconcentration factor and a very low limit of detection comparing to the common methods. Regard to few microliters of organic solvent consumption, the extraction procedure can be considered as an environmentally friendly technique. Utilizing fresh acceptor phase and discarding the hollow fiber after each extraction has led to high reproducibility and repeatability of the method, thus the method can be successfully applied for analyzing the drugs in plasma.

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