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Extraction and determination of trace amounts of chlorpromazine in biological fluids using hollow fiber liquid phase microextraction followed by high-performance liquid chromatography

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Abstract

In the present work, hollow fiber liquid phase microextraction (HF-LPME) in conjunction with reversed-phase HPLC/UV was developed for extraction and determination of trace amounts of chlorpromazine in biological fluids. The drug was extracted from an 11 ml aqueous sample (source phase; SP) into an organic phase impregnated in the pores of the hollow fiber (membrane phase; MP) followed by the back-extraction into a second aqueous solution (receiving phase; RP) located in the lumen of the hollow fiber. The effects of several factors such as the nature of organic solvent, compositions of SP and RP solutions, extraction time, ionic strength and stirring rate on the extraction efficiency of the drug were examined and optimized. Under the optimal conditions, enrichment factor of 250, dynamic linear range of 1–500 $\mu g\,l^{-1}$, and limit of detection of 0.5 $\mu g\,l^{-1}$ were obtained for the drug. The percent relative intra-day and inter-day standard deviation (R.S.D.%) based on three replicate determinations were 6.7 and 10.3%, respectively. The method was applied to drug level monitoring in the biological fluids and satisfactory results were obtained.

Keywords: HF-LPME; Hollow fiber membranes; Chlorpromazine; Reversed phase HPLC

1. Introduction

Chlorpromazine (CPZ) is a phenothiazine drug with an aliphatic side chain, used in the management of psychotic condition [1]. It controls excitement, agitation and other psychomotor disturbances in schizophrenic patients and reduces the manic phase of manic-depressive conditions. It is used to control hyperkinetic states and aggression and is sometimes given in other psychiatric conditions for the control of anxiety and tension. CPZ is also used in palliative care to act as an anti-emetic drug. Spectrophotometric [2–15] and spectrofluorimetric [16–19] methods which are performed in the presence of several oxidant reagents such as V(V) [2,3], Cr(VI) [4], Fe(III) [5,6] and Ce(IV) [7–9,16] have been reported for the quantitative determination of CPZ in pure solutions and/or in pharmaceutical preparations. High-performance liquid chromatography (HPLC) [20–26], voltammetric [27–30] and polarographic [31] procedures have been developed as well.

Hollow-fiber-based liquid phase microextraction (HF-LPME) is a relatively new isolation technique introduced by Pedersen-Bjergaard and Rasmussen [32,33]. HF-LPME is based on traditional liquid–liquid extraction but only microliters of the extracting solvent are used and the analytes are concentrated without additional solvent evaporation steps. In this method, a porous hollow polypropylene fiber is used to protect the extracting solvent. The fiber is placed directly into the sample solution and serves as the interface between the sample and the extracting solvent (receiving phase, RP). The RP solution may be the same organic solvent as immobilized in the pores, resulting in the extraction of the analyte into a two-phase system. The RP solution in this mode is directly compatible with GC, whereas, evaporation of the solvent and reconstitution in an aqueous medium is required for HPLC or capillary electrophoresis (CE) analysis. Alternatively, the RP solution may be another aqueous phase providing a three-phase system, in which the analytes are extracted from an aqueous sample (source phase, SP), into

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a thin film of the organic solvent, and back extracted into the RP solution. This extraction mode is limited to basic or acidic analytes with ionisable functionalities. For extraction of basic compounds, pH of the sample has to be adjusted at alkaline region to suppress analyte solubility, whereas, pH in the RP solution should be low to promote analyte solubility. In this manner, the basic compounds may be easily extracted into the organic phase and finally into the acceptor phase. In contrast, for acidic analytes, pH of the sample should be low and an alkaline RP solution should be utilized within the lumen of the fiber. Following the extraction, the RP solution is directly compatible with HPLC and CE.

Due to the small volume of the extracting solvent, the extracted samples do not require further concentration prior to analysis and thus total analysis time considerably decreases in comparison to traditional liquid–liquid extraction procedure. Additional advantages of LPME also make the technique attractive. Since, LPME tolerates a wide pH range; it can be used in applications that would not be suitable for solid phase extraction (SPE) or solid-phase microextraction (SPME). Sample carry-over can be avoided because the hollow fibers are inexpensive enough to be single-used and disposable. In cases, where large numbers of samples are prepared by SPE, an equivalent LPME preparation procedure could also be more economical. It has been proven that HF-LPME is very useful for extraction of drugs and metabolites from biological matrices and pollutants from environmental samples with simultaneous clean-up of the extracts [32,34–52]. In the present study, HF-LPME in combination with HPLC/UV was applied for extraction and preconcentration of CPZ in aqueous samples. The enrichment factor (EF) was studied as a function of the nature of the immobilized organic phase, compositions of source phase (SP) and receiving phase (RP), ionic strength, extraction time and stirring rate. These parameters were optimized and the system was finally applied to extract CPZ drug from different aqueous and biological samples.

2. Experimental

2.1. Chemicals

All the reagents were of analytical grade. Chlorpromazine hydrochloride was kindly donated by the Department of Chemistry, Tehran University (Tehran, Iran). HPLC-grade methanol, *n*-dodecane, ethyl acetate, diethyl ketone, *n*-dodecanol, HCl, NaCl, and NaOH were purchased from Merck (Darmstadt, Germany). Phosphate and acetate buffers were prepared from phosphoric and glacial acetic acid and their salts, respectively (Merck). The reagent water used was purified with a Milli-Q system from Millipore (Bedford, MA, USA).

2.2. HPLC system

The HPLC system consisted of a Shimadzu (Tokyo, Japan) LC-10AV pump, a Rheodyne 7725 injector equipped with 20 μl sample loop combined with a SPD-10AV UV–Vis detector. A Shim-Pack CLC-C8 (250 mm × 4.6 mm) column was applied to separate the drug under isocratic elution conditions. The mobile phase was a mixture of methanol–sodium acetate (pH 4.1; 0.1 M) (80/20, v/v) with a flow rate of 1.0 ml min^{-1}. UV detection at 254 nm was used for quantification.

2.3. Extraction procedure

All the HF-LPME experiments were performed using Accurel Q3/2 polypropylene hollow fiber membrane (600 μm I.D., 200 μm wall thickness, 0.2 μm pore size) from Membrana (Wuppertal, Germany). The whole fiber was cut into small segments with the length of 8.8 cm. One end of each resulting hollow fiber was heat-sealed using a soldering iron. A 25 μl syringe model 702 NR from Hamilton (Bonaduz, Switzerland) was employed to introduce the RP solution into the lumen of the hollow fiber, to suspend the hollow fiber and also to inject the extracted analyte at the end of the extraction into the HPLC loop.

The outer diameter of the needle was 800 μm and thus had to be inserted into the hollow fiber by applying some force. Extraction and injection processes were performed in the following steps: (1) 11 ml of the aqueous sample solution was transferred into a 12 ml glass vial containing a 10 mm × 4 mm magnetic stirring bar; (2) the vials were placed on a magnetic stirrer model ZMS 74 from ZAG Chimi Company (Tehran, Iran); (3) a carefully measured portion of 20 μl of the receiving phase was injected into the hollow fiber; (4) the fiber was submerged in the organic solution for 5 s and then into the reagent water for 5 s for washing the extra organic solution from the surface of the fiber; (5) the fiber was bent into a U-shape and together with a small part of the supporting syringe needle was submerged in the sample solution; (6) the vial was covered with Para Film and stirred for a prescribed time period; (7) at the end of the extraction time, the hollow fiber was removed from the sample solution, and its closed end was cut and the receiving phase was withdrawn into the syringe; (8) finally 10 μl of the receiving phase was injected into the HPLC. In initial experiments, the volumes of SP and RP solutions were 11 ml and 20 μl, respectively. Also to obtain suitable signals in the optimization experiments, relatively high concentration of aqueous solution of CPZ (200 μg l^{-1}) was used. All the experiments were done at room temperature and the SP was stirred at a rate of 1000 rpm for 20 min.

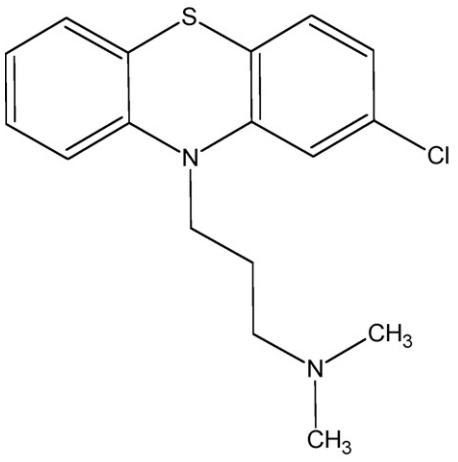
2.4. Calculations

The enrichment factor (EF) and percent extraction of the drug were calculated by the following equations:

$$\mathrm{EF} = \frac{C_{\mathrm{RP,final}}}{C_{\mathrm{SP,initial}}} \quad (1)$$

$$\mathrm{Extraction}\,(\%) = \mathrm{EF} \times \frac{V_{\mathrm{RP}}}{V_{\mathrm{SP}}} \times 100 \quad (2)$$

where $C_{\mathrm{RP,final}}$ and $C_{\mathrm{SP,initial}}$ are the final and initial concentrations of the drug in the receiving and the source phases, respectively. $C_{\mathrm{RP,final}}$ of the extracted drug was calculated from the calibration curve. V_{SP} and V_{RP} are the volumes of the source and receiving phases, respectively.



$pK_{a\,=}$ 9.3 (20 °C), $\log K_{octanol/buffer\ (pH\,=\,7.4)} = 3.4$

Fig. 1. Chemical structure and pK_a and log K_{ow} values of chlorpromazine.

The chemical structure, log K_{ow} and pK_a values of the drug [53] are shown in Fig. 1.

2.5. Standard solutions and real samples

Stock standard solution of CPZ (100 μg ml^{-1}) was prepared by dissolving its hydrochloride salt in methanol. All the standard solutions were stored at 4 °C. The working solutions were prepared by proper dilution of the standard solution in the reagent water. The concentration of the drug in preliminary experiments was 200 μg l^{-1}. Tap water sample was collected freshly from our laboratory (Tehran University) and a human urine sample was obtained from a healthy male. Iranian Blood Transfusion Organization (Tehran, Iran) was the supplier of the serum sample as well. These samples were filtered through a 0.45 μm pore-size cellulose acetate membrane filters prior to extraction.

3. Results and discussion

3.1. Basic principle of extraction

In three phases LPME, the analyte is extracted from the aqueous sample solution (SP) into the organic phase immobilized within the pores of the hollow fiber known as membrane phase (MP) and then it is back-extracted into the aqueous receiving phase (RP) located inside the hollow fiber. For an analyte such as *A*, the extraction process can be written as:

$$A_{SP} \leftrightarrow A_{MP} \leftrightarrow A_{RP} \quad (3)$$

The initial amount of analyte, *n*, is equal to the sum of individual amounts of analyte present in all the phases during the whole extraction process:

$$n_i = n_{SP} + n_{MP} + n_{RP} \quad (4)$$

where n_{SP} is the amount of analyte in the SP solution, n_{MP} the amount of analyte in the MP solution and n_{RP} is the amount of analyte in the RP solution. At the equilibrium condition, Eq. (3) can be written as:

$$C_i V_{SP} = C_{eq.SP} V_{SP} + C_{eq.MP} V_{MP} + C_{eq.RP} V_{RP} \quad (5)$$

where C_i is the initial concentration of analyte, $C_{eq.SP}$, $C_{eq.MP}$ and $C_{eq.RP}$ are analyte concentrations in the SP, MP and RP solutions at equilibrium condition, respectively. V_{SP}, V_{MP} and V_{RP} are the volumes of the source, membrane and receiving phases, respectively.

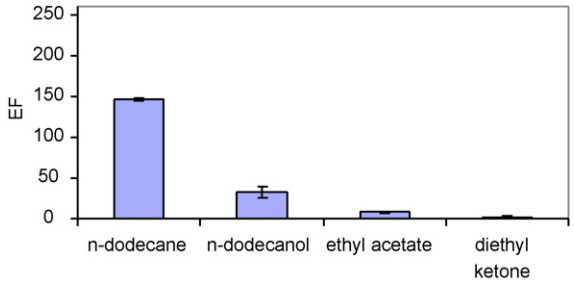


Fig. 2. Effect of impregnation solvent on EF of chlorpromazine. Conditions: SP, 11 ml of 0.01 M NaOH (pH 11.80); C_{cpz}, 200 μg l^{-1}; RP, 20 μl of 0.01 M phosphate buffer (pH 2.0); stirring rate, 1000 rpm; time, 20 min.

3.2. Organic solvent selection

Selection of the solvent should be based on comparison of selectivity, extraction efficiency and the level of toxicity. In addition, the polarity of the organic phase should be similar to that of the polypropylene fiber so that it can be easily immobilized within the pores of the fiber. This function greatly affects the performance of HF-LPME, since extraction occurs on the surface of the immobilized solvent [39,40]. Four different organic solvents (i.e. *n*-dodecane, *n*-dodecanol, ethyl acetate, and diethyl ketone) were used in the present work as organic membrane solvents. As can be seen in Fig. 2, the best solvent seems to be *n*-dodecane. Thus *n*-dodecane was chosen as membrane solvent in the subsequent studies.

3.3. Effect of compositions of SP and RP solutions

The effect of the concentration of NaOH in the SP solution on EF at the range of 0.0–0.1 M was studied. EF had its maximum value in the presence of 10^{-2} M NaOH (pH 11.8). In subsequent experiments, pH of SP solution was adjusted at 11.80 using 5 M of NaOH solution. At this pH, CPZ presents mostly in its free form. The dependence of the EF of CPZ to HCl concentration in the RP solution at the concentration range of 0.0–0.1 M was also investigated. It proved that EF had its maximum value in the presence of 10^{-2} M HCl (pH 2.0). It is worthy to note that degradation of C8 column can be accelerated in the presence of Cl^- ions, thus in further experiments, pH of the RP solution was adjusted at 2.0 using phosphate buffer. At this pH, CPZ is mostly ionized. Thus, in the present study, gradient of the pH between the SP and the RP solutions is a driving force for the drug transport which was in accordance with the already expectations.

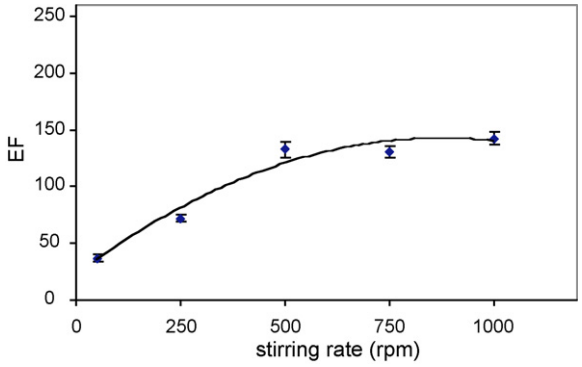


Fig. 3. Effect of stirring rate on the EF of the chlorpromazine. Conditions: SP, 11 ml of 0.01 M NaOH (pH 11.80); C_{cpz}, 200 μg l^{-1}; RP, 20 μl of 0.01 M phosphate buffer (pH 2.0); time, 20 min.

3.4. Agitation speed

Like other microextraction techniques, the extraction in HF-LPME can be enhanced by agitation of the sample solution, thereby, reducing the "time" required to attain thermodynamic equilibrium especially for the higher molecular mass analytes [41,42]. In HF-LPME, the organic solvent is sealed and protected by the hydrophobic hollow fiber membrane, so it is easier to handle and it can tolerate higher stirring speeds. In our experiments, partitioning of the analytes into the organic solvent was enhanced by increasing the stirring speed from 50 to 1000 rpm (Fig. 3). So, the stirring speed with the maximum value (1000 rpm) was chosen for the rest of the experiments.

3.5. Salt effect

The effect of salt addition on EF was examined by adding sodium chloride to aqueous samples at the concentration levels of 0, 0.5, 1, 1.5 and 2 M (Fig. 4). The EF of CPZ was decreased by increasing the salt concentration. This effect may be due to increased interactions between the analyte and salt in solution with increasing salt concentration. Such interactions would tend to restrict movement of the analyte from the SP to the membrane solvent. So, all the subsequent experiments were performed in the absence of salt. It is worthy to note that in the biological samples due to existence of salts, lower extractions in comparison with the aqueous sample may be expected.

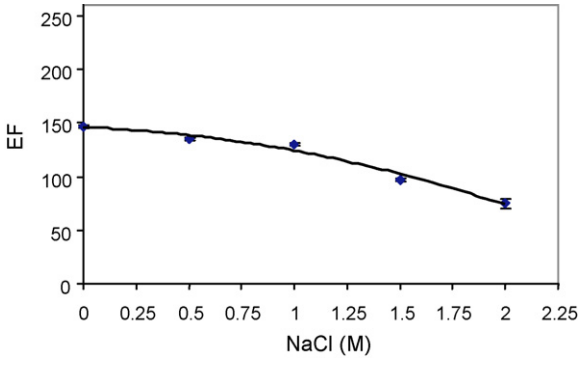


Fig. 4. Effect of salt addition on the EF of chlorpromazine. Conditions: SP, 11 ml of 0.01 M NaOH (pH 11.80); C_{cpz}, 200 μg l^{-1}; RP, 20 μl of 0.01 M phosphate buffer (pH 2.0); stirring rate, 1000 rpm; time, 20 min.

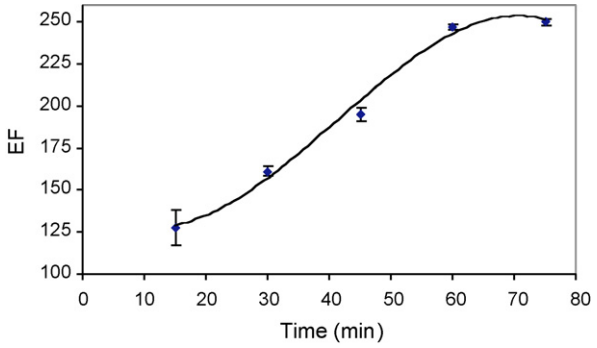


Fig. 5. Effect of time on the EF of chlorpromazine. Conditions: SP, 11 ml of 0.01 M NaOH (pH 11.80); C_{cpz}, 200 μg l^{-1}; RP, 20 μl of 0.01 M phosphate buffer (pH 2.0); stirring rate, 1000 rpm.

Table 1
Limit of detection, regression equation, correlation coefficient, dynamic linear range, enrichment factor and extraction percent for HF-LPME of chlorpromazine

Analyte	Chlorpromazine
LOD (μg l^{-1})	0.5
R^2	0.9992
Regression equation	$A = 11.968C$ (μg l^{-1}) − 16.406
DLR (μg l^{-1})	1–500
EF	250 (±2)[a]
Extraction (%)	45

[a] Standard deviation for three replicate measurements.

3.6. Extraction time

LPME is not an exhaustive extraction technique, thus maximum sensitivity is attained at equilibrium condition. On the other hand, complete equilibrium need not be attained for accurate and precise analysis. However, choosing an exact extraction time is essential to obtain good precision [40,43]. Therefore, extraction time is one of the most important factors influencing the extraction efficiency. In this study, EF of the drug was investigated as a function of time in the range of 15–75 min. Then, EF of the drug was increased by increasing the extraction time. As shown in Fig. 5, the optimal extraction time was 60 min. Thus, 60 min was chosen as the extraction time in the subsequent experiments. It is noteworthy that the optimum extraction time is dependent on sample composition and may be re-evaluated for real samples to obtain suitable EFs.

Table 2
Determination of chlorpromazine in different spiked samples

Sample	Chlorpromazine			
	C_{added} (μg l^{-1})	C_{found} (μg l^{-1})	R.S.D. (%) ($n = 3$)	E[a] (%)
Tap water	10.0	9.8	3.9	−2
Urine	100.0	111.0	6.7	11
Serum	50.0	55.0	5.0[b]	10

[a] Relative error (%).
[b] Inter-day serum R.S.D. (%) was 10.3 (for 3 consecutive days).

Table 3
Comparison of the proposed method with other developed methods to determine chlorpromazine in aqueous solutions

Ref.	Instrumentation	LOD ($\mu g\,l^{-1}$)	DLR ($\mu g\,l^{-1}$)	R.S.D. (%) (intra-day)	R.S.D. (%) (inter-day)
Present work	HPLC/UV	0.5	1–500	<6.7 ($n=3$)	<10.3 ($n=3$)
[51]	HPLC/UV	5	10–300	<10.2 ($n=6$)	<10.2 ($n=6$)
[52]	Chemiluminescence	6	50–10,000	<2.6 ($n=11$)	<6 ($n=11$)
[54]	Chemiluminescence	6.5	0–10,000	<4.1 ($n=11$)	–
[55]	CE-electro chemiluminescence	1.5	5–800	3.6 ($n=5$)	–

3.7. Evaluation of the method performance

The calibration curve of CPZ was plotted in the concentration range of 1–500 $\mu g\,l^{-1}$ in aqueous solutions. For each level, three replicate extractions were performed under optimal conditions. The corresponding regression equation, correlation coefficient (R^2), dynamic linear range (DLR), the limit of detection (LOD), EF and percent extraction of CPZ were calculated and are summarized in Table 1. The LOD (0.5 $\mu g\,l^{-1}$ for CPZ) was calculated at a signal-to-noise ratio of 3.

3.8. Application of HF-LPME for real samples

It is apparent that porous hollow fiber functions as a filter in dirty samples, since particles and also large molecules, which can also be soluble in the organic solvent, will not be extracted. In this way, the present newly developed microextraction technique can be potentially used to extract complex matrices, while preventing co-extraction of other extractable components. In order to assess the applicability of the newly developed extraction system to the analysis of the drug in real samples with complex matrices, the spiked tap water, urine and serum samples were extracted and analyzed using the proposed method under optimum conditions. Since the drug was not detected, thus $\mu g\,l^{-1}$ amounts of CPZ were added into the real samples and extraction and determination procedure was repeated again. Table 2 shows that the results of three replicate analyses of each real sample obtained by the proposed method are in satisfactory agreement with the spiking amounts. Fig. 6 depicts chromatograms of the spiked (at the concentration level of 25.0 $\mu g\,l^{-1}$) and non-spiked serum samples with chlorpromazine under optimum conditions.

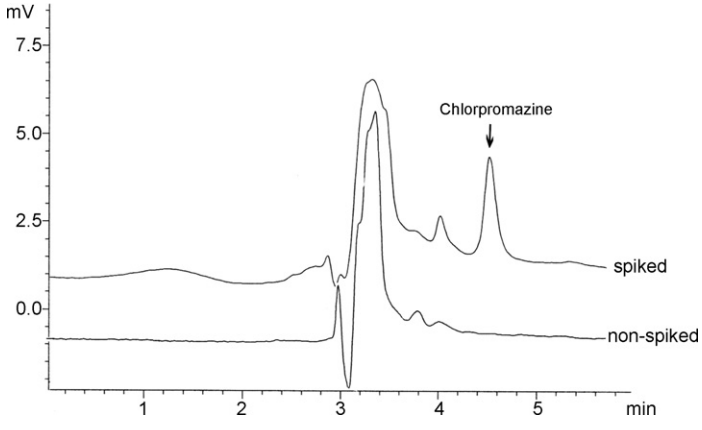


Fig. 6. The chromatograms of the spiked (at the concentration level of 25.0 $\mu g\,l^{-1}$) and non-spiked serum samples with chlorpromazine.

Moreover, the proposed method displayed good reproducibility to determine the drug in the serum sample with intra-day R.S.D.% values in the range of 3.9–6.7 and inter-day serum R.S.D.% value of 10.3 (for 3 consecutive days).

3.9. Comparison of the applied method with other reported methods

The present method was compared with the other methods in terms of validation and precision (Table 3). As can be deducted, the method is quite comparable to those mentioned in Table 3.

4. Conclusion

The new HF-LPME method was successfully developed for the extraction and analysis of trace amounts of chlorpromazine in biological fluids. The results showed that the developed method is precise, linear and accurate over the investigated concentration range. The LPME technique demonstrated several advantages over the other extraction methods: firstly, high clean-up in cases of dirty and also complex samples like biological fluids; secondly, only microliter amounts of the extraction solvent were needed. As a result, no further concentration of the extract was required before final analysis.

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