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Hollow Fiber-Based Liquid Phase Microextraction Combined With High-Performance Liquid Chromatography for Extraction and Determination of Loratadine in Human Plasma

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ABSTRACT

The applicability of hollow fiber-based liquid phase microextraction (HF-LPME) was evaluated for the extraction and preconcentration of Loratadine prior to determination by HPLC. In order to obtain high extraction recovery, the parameters affecting the HF-LPME including type of organic phase, pH of the source and receiving phases, stirring rate, extraction time and salt addition were studied and optimized. Under the optimized conditions, enrichment factor of 308 with relative standard deviation (R.S.D.%) equel 3.8% were achieved. The calibration curve was linear in the range of 0.3–600 ng/ml with good linearity (R^2 = 0.9991). The limit of detection (LOD) was 0.1 ng/ml (based on S/N = 3). Finally, determination of Loratadine in human plasma was used by HF-LPME-HPLC and indicated that this method had an excellent clean-up and high recovery factor (84%) for Loratadine.

KEYWORDS: Hollow Fiber Liquid Phase Microextraction; Loratadine; HPLC; Human Plasma Sample.

1. INTRODUCTION

Allergic rhinitis (AR) is a global health problem of increasing prevalence, affecting between 10% and 40% of the world's population [1-2]. In some countries it is now approaching epidemic proportions and is becoming a significant public health concern [3]. The cumulative symptoms of allergic rhinitis can be troubling [4] and may impair daily activities and sleep patterns, resulting in a significant effect on patients health-related quality of life (HRQoL) [5-7], learning and psychomotor performance[8] and thereby in an economic effect on society in terms of both direct and indirect costs [9]. Rhinitis is also associated with other conditions such as asthma, sinusitis and otitis media [10-14].

First- and second-generation oral antihistamines are generally viewed as being more effective in controlling the nasal itching, sneezing and rhinorrhea associated with allergic rhinitis than in relieving nasal congestion [15-18]. Some recent evidence suggests that the newer second-generation agents such as Loratadine, Fexofenadine and Levocetirizine have anti inflammatory effects that may relieve nasal congestion [19-20].

Loratadine, a member of the second generation H_1-antagonist antihistamines, is a potent, long-acting, nonsedating, peripherally acting H_1 antagonist that has been used successfully in treating allergic rhinitis, chronic idiopathic urticaria and allergic skin diseases. Loratadine is a long-acting tricyclic antihistamine with selective peripheral histamine H_1-receptor antagonistic activity. This compound is a white powder not soluble in water, but very soluble in organic solvents. It's chemical name is ethyl 4-(8-chloro-5,6-dihydro-11 H-benzo {5,6} cyclohepta {1,2-b} pyridin-11-ylidene) -1-piperidine carboxylate.

Biological sample analysis without sample preparation at low analyte concentrations, complex sample matrices and limited sample volumes available for the determinations, is very difficult. Therefore, sample isolation as well as pre-concentration technique is necessary. Liquid-liquid extraction (LLE) and solid-phase extraction (SPE) are the most commonly used techniques for preconcentration and clean-up of samples prior to high-performance liquid chromatographic (HPLC) and capillary electrophoretic (CE) analysis [21-25]. After extraction in LLE or elution in SPE, the common practice is to evaporate the solvent to dryness and to reconstitute the dry residue in a suitable solvent for HPLC or CE. These steps are tedious and also prone to less of analytes by evaporation and adsorption. For trace enrichment, a large volume of sample is often required because the initial-to-final sample volume ratio determines the enrichment factor. However, handling a large volume of sample can be extremely time-consuming [26]. To eliminate the need for solvent evaporation and other tedious manual manipulations, SPE has been performed on-line using a short precolumn [27-28]. In

this way, analytes in the whole sample can be transferred to the HPLC or CE system, resulting in a larger enrichment factor. Solid-phase microextraction (SPME) is another SPE technique which does not require solvent evaporation and makes possible high preconcentration from a small volume of sample [29-31]. When SPME is coupled to HPLC or CE, a solvent desportion step is required [32] and sometimes a lengthy process is needed to recover all sorbed analytes and to avoid carry-over [33-34]. Because the coating available so far are nonpolar or slightly polar, the current applications of SPME are limited to nonpolar compounds or compounds of medium polarity [35]. To overcome or reduce these problems, alternative sample preparation methods for drug analysis such as hollow fiber liquid phase microextraction (HF-LPME) have been developed. This technique was introduced by Pedersen-Bjergaard and Rasmussen in 1999 [36]. There are two modes of HF-LPME: two-and three-phase HF-LPME. In two-phase the analytes are extracted from an aqueous sample matrix into an organic receiving phase and in three-phase mode, three liquid phases participate in analyte extraction: (1) the sample solution (donor phase), with a pH that is adjusted to keep analytes neutrally charged, (2) the water immiscible organic extractor phase, which is immobilized in the wall pores of the hollow fiber and (3) the aqueous acceptor phase, with a pH that is adjusted to ionize the analytes. Compounds in their non-ionized form are extracted from the sample into the organic solvent and are subsequently extracted into the acceptor phase. This extraction mode is used for basic or acidic analytes with ionizable functionalities. The major advantages of HF-LPME are simplicity, negligible volume of solvents used, high enrichment, low cost and excellent sample clean-up ability. Sample carry-over can be avoided because the hollow fibers are inexpensive enough to be single-used and disposable. In addition, HF-LPME tolerates a wide pH range, a feature which could not be done using solid phase extraction (SPE) and solid phse microextraction (SPME). The aim of this study was to use a sensitive and reliable method for analysis of Loratadine in human plasma which is capable of complementing existing clinical methods. For this purpose, three-phase HF-LPME followed by HPLC–UV was applied for extraction and determination of theis drug in the human plasma sample. Various parameters which affect the recoveris of Loratadine including nature of organic extraction solvent, pH of donor and acceptor phases, stirring rate, extraction time and salt addition to the sample solution were studied and optimized in aqueous solutions of Loratadine. Finally, the optimized conditions were applied to determine this drug in plasma sample from a patient under Loratadine treatment.

2. EXPERIMENTAL

2.1. Chemicals and stock solutions

Loratadine (≥98%) purchased from cipla (Cipla Ltd, India). The chemical structure of this drug is shown in Fig.1. HPLC grade methanol and acetonitrile, sodium hydroxide, hydrochloric acid, phosphoric acid, formic acid, sodium chloride, 1-octanol and toluene were obtained from Merck (Darmstadt, Germany). Benzyl alcohol and n-dodecane were from Fluka (Buchs, Switzerland). Water used was double distilled deionized. The Accurel Q3/2 polypropylene hollow fiber (200 µm wall thickness, 600 µm internal diameter and 0.2 µm average pore size), purchased from Membrana GmbH (Wuppertal, Germany), was used for all HF-LPME experiments.

Stock solution of loratadine (1000.0 µg/ml) was prepared in methanol and stored in the dark at 4˚C and was diluted with deionized water to obtain working standard solution with a concentration of 0.1µg/ml.

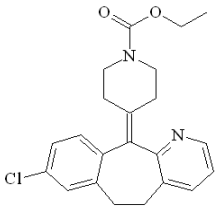

Fig.1. Chemical structure of loratadine.

2.2. Instrumentation

Chromatographic measurements were carried out using a HPLC system equipped with a series 10-LC pump, UV detector model LC-95 set at 220 nm and model 7725i manual injector with a 20 µl sample loop (Perkin-Elmer, Norwalk, CT, USA). Column used was C_{18} (250 × 4.6 mm, 10 µm particle size) from Dr. Maisch GmbH (Ammerbuch-Entringen, Germany). Mobile phase was deionized water-acetonitrile-0.5 M KH_2PO_4 and concentrated H_3PO_4 (48:44:8:0.1, v/v) at a flow rate of 1.5 ml/min at room temperature. The pH of solutions were measuerd by a 3030 Jenway pH meter (Leeds, UK).

2.3. Hollow fiber liquid phase microextraction (HF-LPME) procedure

The method of HF-LPME was used for preconcentration and clean-up of Loratadine in plasma sample. The hollow fibers were cut into 8.8 cm pieces and each was used once to prevent memory effects. A 100 µl syringe (Hamilton, Bonaduz, Switzerland) was applied to introduce the 30µl of acceptor phase (NaOH) into the lumen of the hollow fiber and also as a support to which the hollow fiber was attached during the extraction period. The hollow fiber, attached to the syringe, was immersed into organic solvent (Toluene) for 10 second and then acceptor phase was introduced into the lumen of the hollow fiber with slow pushing of the microsyringe plunger and the end of the hollow fiber was sealed by a piece of aluminum foil. Then the fiber was bent (U shape) and was immersed into the sample solution (11mL). A stirrer was used for stirring the samples during extraction. At the end of the extraction time (15 min), the hollow fiber was removed from the sample solution, the closed end was opened, the acceptor phase was withdrawn into the syringe and

injected into the HPLC for analysis.

2.4. Calculation of recovery and enrichment factors

Extraction recovery % (ER%) and enrichment factor (EF) were calculated according to the following equations for the analyte [37–39].

$$ER\% = \frac{n_{a,final}}{n_{s,initial}} \times 100 = \frac{C_{a,final}V_a}{C_{s,initial}V_s} \times 100 \quad (1)$$

$$EF = \frac{C_{a,final}}{C_{s,initial}} = \frac{V_s}{V_a} \times \frac{R}{100} \quad (2)$$

where $n_{s,initial}$ and $n_{a,final}$ are the number of moles of analyte present in the initial sample and analyte finally collected in the acceptor phase, respectively. V_s ,V_a , $C_{s,initial}$ and $C_{a,final}$ are the volume of sample, volume of the acceptor phase, initial analyte concentration within the sample and final concentration of analyte in the acceptor phase, respectively.

3. RESULTS AND DISCUSSION

3.1. Optimization of HF-LPME

In order to obtain the highest recovery for Loratadine from sample solution, experimental parameters affecting the recovery such as type of organic phase, pH of the source and receiving phases, stirring rate, extraction time and salt addition were investigated and optimized as the following.

3.1.1. Effect of the organic extraction solvent

Solvent selection is one of the main steps in solvent microextraction techniques. For this critical stage, several factors have to be taken into consideration. First, the analyte in the sample solution should have high solubility in the organic solvent in the pores of the hollow fiber. Second, the water solubility extraction solvent should be as low as possible, with high boiling point to avoid evaporation during the experiment. This solvent system should be also compatible with polypropylene hollow fiber. In this work, organic solvents such as 1-octanol, n-hexane, toluene, undocanol and dodecane were examined Fig. 2 and toluene showed higher analyte recovery than the other solvents.

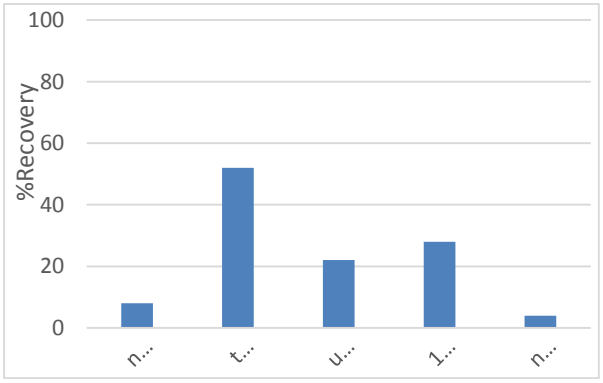

Fig. 2. Effect of organic solvent type on the extraction recovery of Loratadine. Extraction conditions: donor phase, 11 mL of aqueous solution containing 0.1 µg/mL of loratadine (pH = 3.0 adjusted with 2 M HCl); extraction time = 30 min; stirring speed = 250 rpm ; acceptor phase, 30 µl of 0.1 mM NaOH.

3.1.2. Optimization of donor phase pH

Loratadine is an acidic drug (pK_a = 5.0). To obtain high extraction recovery for acidic compounds, the donor phase should be acidified to deionize the analyte and consequently increase their transfer from the donor phase into the organic phase. For this purpose, three different acids including hydrochloric, phosphoric and formic acid (2 M) were tested to adjust the solution at pH = 3.0. The highest Loratadine recovery was obtained using formic acid. Therefore, formic acid was used to adjust acidity (pH = 1.0–4.0). Results in Fig. 3 show that the highest extraction recovery was obtained at pH = 3.5. In a more acidic solution, a decrease in the extraction recovery was observed. This can be attributed to protonation of the carbonyl groups of loratadine. Therefore, pH = 3.5 was used for subsequent experiments.

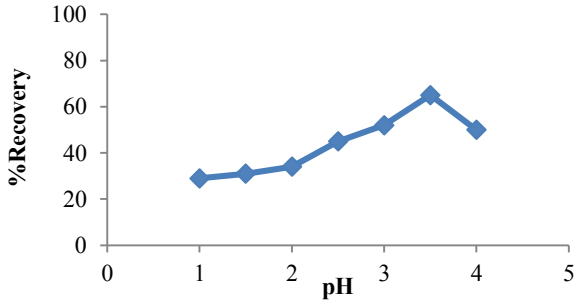

Fig. 3. Effect of donor phase pH on the extraction recovery of loratadine. Extraction conditions: toluene as organic extraction solvent. Other conditions as Fig. 2.

3.1.3. Optimization of acceptor phase pH and type of base

The acceptor solution should be basic to provide high solubility for the acidic analytes and ionize the analytes to prevent them re-entering the organic phase. In general, the pH of the acceptor phase was required at least 3.0 pH units higher than the pK_a of acidic analytes. To select the composition of acceptor phase, sodium hydroxide and ammonium hydroxide were tested at pH=10.0 based on recovery. Higher recovery was obtained with sodium hydroxide. Therefore, sodium hydroxide was used to adjust the pH of acceptor phase in the range of 7.0–12.0. Results showed that, the highest recovery for Loratadine was obtained at pH=11 Fig. 4. Therefore, this pH was selected as the optimum pH value for further study.

3.1.4. Effect of stirring rate

Stirring rate affects the kinetics of the extraction. In fact it improves mass transfer in the source phase and induces convection in the membrane phase. Sample agitation enhances the extraction rate and reduces extraction time because the equilibrium can be achieved more rapidly. It also enhances the diffusion of the analyte from the source phase into the receiving phase. The effect of stirring rate in the range of 100–1000 rpm was evaluated. Extraction recovery of the analyte improved as the agitation rate increased from 100 to 500 rpm Fig.5. However, when stirring rate

exceeded 500 rpm, the peak area decreased. This phenomenon can be accounted for the fact that although agitation could accelerate distribution equilibrium by facilitating mass transfer, high stirring rate would generate air bubbles adhering on the surface of hollow fiber and promote solvent loss. Therefore, 500 rpm of stirring rate was selected for subsequent experiments.

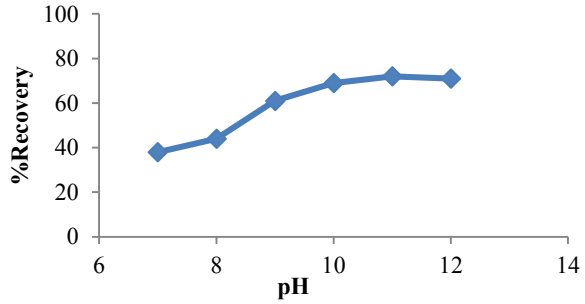

Fig. 4. Effect of pH of the acceptor phase on the extraction recovery of loratadine. Extraction conditions: pH $_{donor}$ = 3.5. (adjusted with 2 M formic acid) Other conditions as Fig. 3.

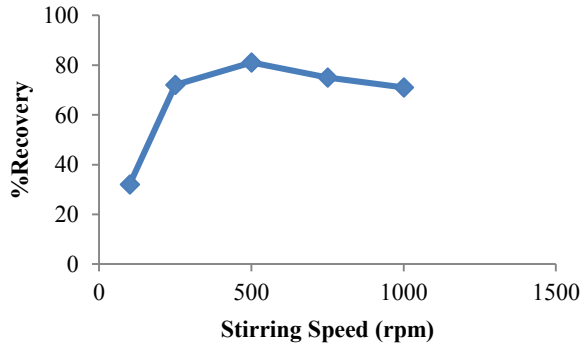

Fig. 5. Effect of stirring rate on the extraction recovery of loratadine. Extraction conditions: pH $_{acceptor}$ = 11.0 (adjusted with 1 M NaOH). Other conditions as Fig. 4.

3.1.5. Effect of extraction time

The extraction time is an important parameter in HF-LPME procedure because it influences the partition of the target analyte between the donor phase and organic phase and subsequently, between the organic phase and acceptor phase. To study the effect of extraction time on the extraction recovery, a solution of Loratadine was extracted at various extraction times at the range of 10–120 min. Results show that the ER decreases rapidly by the increasing of the extraction time higher than 15.0 min, marked decrease in the extraction recovery is due to extraction solvent dissolution. Based on these observations, 15 min period was selected as the optimum extraction time for the next experiments.

3.1.6. Effect of salt concentration

Some researchers have reported that the addition of salt to the sample solution has been beneficial for the recovery in microextraction procedures [40-41]. So, in this study, the effect of salt addition on the extraction recovery was examined by adding different amounts of NaCl into the sample solution of Loratadine in the range of 0.0 to 2.5 M. Recovery of analyte was decreased by addition of salt as was also found in other studies [42]. Most likely, the presence of salt may changes the physical properties of the diffusion film and reduces the rate of diffusion of analyte into the organic phase [43]. Hence, no salt was added in the subsequent experiments.

3.2. Method validation

Table 1 presents an overview of the quantitative results, including linearity, limit of detection, RF and EF for loratadine. The calibration curve was linear from 0.3 to 600 ng/ml (R^2 = 0.9991). Limit of detection (LOD) was 0.1 ng/ml and defined as a signal to noise ratio (S/N) of 3. EF and RF for loratadine were 308 and 84%, respectively at optimized extraction condition.

Table1. Figures of merit for extraction and determination of Loratadine using HF-LPME and HPLC.

LOD (ng/ml)	0.1
Linear range (ng/ml)	0.3-600
R^2	0.9991
EF	308
ER%	84
RSD% (intra-day, *n* = 5)	3.8
RSD% (inter-day, *n* =5)	9.7

3.3. Plasma sample preapration

Blank plasma sample was provided by a healthy student volunteer. Real plasma sample was obtained from a patient (26 years old woman) after administration of an oral dose of Loratadine after 60 min. In order to eliminate the protein binding of the drug in plasma (greater than 99%), the pretreatment was performed as outlined in the work of Tahmasebi et al. [44-45]. In order to eliminate protein binding of Loratadine, 3 mL of methanol was added to 2 mL of the plasma and the resulting mixture was strongly vortexed for 10 min. The mixture was placed for 10 min in an ice bath, followed by 10 min at ambient temperature and then centrifuged at 3500 rpm for 10 min. The supernatant was transferred into a 10 mL volumetric flask and diluted to the mark with deionized double distilled water. pH of the final solution was adjusted to 3.5 using 2 M formic acid solution and the extraction procedure was done under the optimized condition

3.4. Application of HF-LPME for analysis of Loratadine in plasma sample

Due to the importance analysis of Loratadine in plasma sample, the optimized method (toluene as organic solvent, pH of donor = 3.5, pH of acceptor = 11.0, stirring speed of 500 rpm, extraction time of 15 min, with no salt addition) was applied to determine the concentration of this drug in the plasma sample from a patient under Loratadine treatment. The concentration of Loratadine in plasma was 212 ng/ml. The chromatograms of HF-LPME extracts from blank plasma sample, patient plasma sample and spiked

patient plasma sample by standard addition method are shown in Fig. 6 (a–c).

Table 2. Figures of merit comporison of the present method (HF-LPME-HPLC-UV) and those of other methods reported in literature for analysis of Loratadine

Method	LOD	Linear range	RSD (%) (intra-day)	RSD (%) (inter-day)	sample	Reference
LLE-HPLC-FL[a]	0.2 ng/ml	0.62-20 ng/ml	<9.7	<9.7	Plasma	[46]
MHLLE-HPLC-PDA[b]	0.2 µg/ml	1-1000 µg/ml	-	<8	Plasma and urine	[47]
APCI-LC-MS[A]	0.07 ng/ml	0.5-20 ng/ml	-	-	Serum	[48]
HF-LPME-HPLC-UV	0.1 ng/ml	0.3-600 ng/ml	3.8	9.7	Plasma	this work

[a]Liquid-liquid extraction-high performance liquid chromatography-fluorescence detection.
[b]Miniaturized homogenous liquid-liquid extraction- high performance liquid chromatography-photo diode array detection detection.
[c]atmospheric pressure chemical ionization -liquid chromatography-mass spectrometry.

The chromatogram of blank plasma dose not show any interfering peak at the retention time of Loratadine. This indicates that Loratadine can be determined without any interferences in the sample.

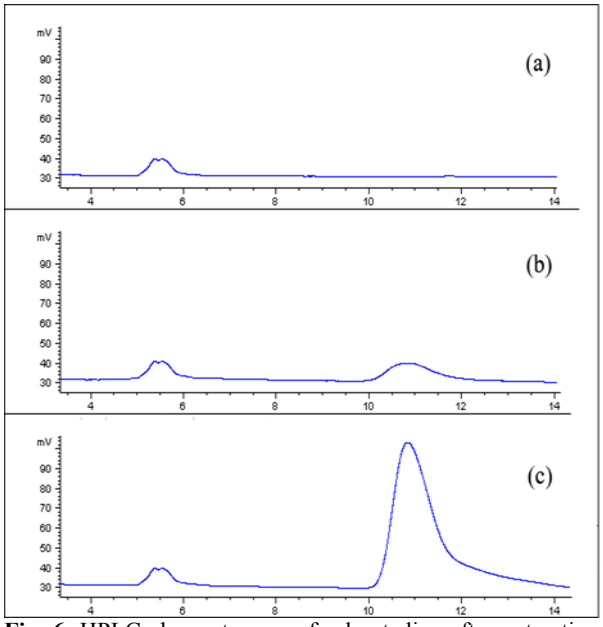

Fig. 6. HPLC chromatograms for loratadine after extraction at optimum conditions. (a) blank plasma sample (b) patient plasma sample and (c) 400 ng/mL spiked patient plasma sample. Mobile phase: deionized water-acetonitrile-0.5 M KH_2PO_4 and concentrated H_3PO_4 (48:44:8:0.1, v/v); flow rate: 1.5 mL/min; column: C_{18} (250 × 4.6 mm, 10µm); λ =220 nm at room tempreture.

3.5. Comparison of the applied method with other reported methods for extraction and determination of Loratadine

Table 2 show LOD, linear range and RSD of the present method (HF-LPME-HPLC-UV) and those of other methods reported in literature for analysis of Loratadine. In most cases the present method as Compared with other reported methods exhibits adequately low LOD, broad linear ranges and low quantities of the solvent consumption.

4. CONCLUSION

Hollow-fibre LPME coupled to HPLC-UV was successfully applied for the analysis of Loratadine in human plasma sample. This method presented a high recovery and good sensitivity, with efficient sample clean-up. Due to the simplicity and low cost of the the hollow fiber, it can be discarded after each extraction to avoid carry over and cross contamination. This serves to maintain high reproducibility and repeatability. Accordingly, it is concluded that HF-LPME is an effective method to extract Loratadine from the biological sample prior to HPLC analysis.

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