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Urine sample preparation of tricyclic antidepressants by means of a supported liquid membrane technique for high-performance liquid chromatographic analysis

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Abstract

Supported liquid membrane (SLM) technique for sample work-up and enrichment was used for determination of tricyclic antidepressant drugs in urine by high-performance liquid chromatography (HPLC) with UV detection. The studied antidepressant drugs were amitriptyline, opipramol, noxiptyline and additionally diethazine was used as possible internal standard. Alkaline phosphoric buffer with urine sample, as the donor solution, was passed over the liquid membrane into which investigated substances were extracted. On the other side of the membrane, analyzed compounds were trapped due to creating non-extractable form in acidic acceptor solution. Enriched and cleaned up drugs were then injected into a HPLC system with ultraviolet detection to analyze of their concentration in acceptor solution. Optimum extraction efficiency was determined by changing acceptor and donor solutions pH, application of different flow rates of donor solution and by using different solvents in the membrane. Also, donor solution volume, extraction time and concentration of analytes were varied to check the linearity of extraction process. The highest extraction efficiency: 43% for opipramol, 56% for noxiptyline, 43% for amitriptyline and 42% for diethazine (R.S.D. values were <6% and $n = 3$) was achieved when 0.05 M phosphate buffer pH 4.0 and 9.5 were used as donor and acceptor solutions, respectively, *n*-undecane with 5% tri-*n*-octylphosphine oxide (TOPO) was used as liquid membrane. Limit of quantification (LOQ) for tricyclic antidepressants after enrichment of 100 ml of urine sample was about 1 ng/ml.

Keywords: Amitriptyline; Opipramol; Noxiptyline; Diethazine

1. Introduction

For many years tricyclic antidepressants are commonly used in psychiatry for treatment of depressive illness. These drugs are also frequently encountered in emergency toxicology screening, drug abuse testing and forensic medical examinations.

Common methods that have been used for routine analysis of tricyclic drugs were chromatographic and immunoassay techniques. In all these methods, the problem of sample pretreatment has attracted much attention in recent years, because it is the most limiting and crucial step in analyses of biological fluids.

Tricyclic antidepressants were determined in human and animal urine by micellar electrokinetic capillary chromatography using a bile salt [1]. This method used simple liquid–liquid extraction and achieved the detection limit about 4 ng/ml, what is similar to results obtained by Chen et al. [2]. Forensic analysis of 11 tricyclic antidepressants in human biological samples was described by Tanaka et al. [3]. After extraction with mixture of hexane and isoamyl alcohol, evaporation of solvents under stream of nitrogen, the dissolved residue in mobile phase was analyzed by HPLC. They were able to determine 50 ng/ml of antidepressants in spiked samples of serum, urine, brain and liver. Imaizumi et al. [4] introduced polymer-coated fibrous material as the extraction medium for a miniaturized sample preparation method, which was coupled with microcolumn liquid chromatography. Another sensitive and specific method [5] with direct-injection HPLC atmospheric pressure chemical ionization tandem mass-spectrometry (HPLC–APCI-MS–MS) has been developed for analysis of seven tricyclic antidepressants in human plasma. This method omitted time-consuming sample preparation but required expensive instruments.

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Solid-phase microextraction (SPME) is solvent-free sample preparation technique, where a thin coating is attached to the surface of fused silica-fiber as extraction medium. Recently an on-line interface between the fiber-in-tube SPME and capillary electrophoresis has been developed [6] for the preconcentration and separation of amitriptyline, imipramine, nortriptyline and desipramine from human urine. Another on-line capillary electrophoresis method coupled with electrospray ionization-mass spectrometry [7] has been used to determine the tricyclic antidepressant drugs as well as the beta-adrenergic blocker drugs. Capillary electrophoresis is very modern technique but limit of quantification is rather poor because of very small volume of injected sample.

Also headspace solid-phase microextraction [8] were used for urine sample preparation to analyze tricyclic antidepressants. In this method limit of quantification with flame-ionization detector was 24–38 ng/ml. Fast liquid chromatographic-mass spectrometric analyses [9] of multicomponent mixture containing flavones, sulfonamides, benzodiazepines and tricyclic amines were applied to biological samples. Recently, mixed-mode silica- and resin-based sorbents [10] have also been used for modern solid-phase extraction of tricyclic antidepressants from clinical samples, yielding ultra clean extracts. Another modification of sample preparation using solvent extraction was adding diethylamine to the extract before evaporation [11] eliminate the adsorption losses of tricyclic antidepressants during the solvent evaporation step.

This work introduces another way of preparation for tricyclic antidepressant samples in order to increase detectability of analyte. Recently, the supported liquid membrane technique has been applied for the extraction of variety of environmental and biological samples, e.g. for the determination of metoxy-*s*-triazines in river water [12], amino acids [13–15], volatile organic acids in confined animal buildings [16], thiophanate-methyl and its metabolites in spiked water [17], cationic surfactant in waste water [18] and ropivacaine metabolites in urine [19], amphetamines in water and urine samples [20], amperozide by ASTED automated system [21], propazine and simazine in surface water [22] and diprivan in urine [23].

In this experiment, supported liquid membrane technique was used for extraction and enrichment of tricyclic antidepressants from water and urine samples. A basic solution of opipramol, noxiptyline, amitriptyline and diethazine (as possible internal standard) was passed over the membrane and after enrichment the acceptor solution was analyzed by reversed-phase high-performance liquid chromatography with UV detector. The acceptor and donor pH, flow-rate and volume of donor, concentration of analytes and different membrane solvents were varied to optimize the extraction efficiency. In our studies, limit of quantification for 100 ml of a spiked water and urine sample was 1 ng/ml of tricyclic antidepressants.

2. Experimental

2.1. Chemicals

Opipramol, noxiptyline, amitriptyline and diethazine (Fig. 1) were obtained from Sigma (St. Louis, MO, USA). A stock solution of tricyclic antidepressants were prepared in methanol (Chemical Factory Odczynniki, Lublin, Poland) at concentration of 0.5 mg/ml. Working solutions (300 μg/ml to 3 μg/ml) for HPLC–UV calibration were obtained by diluting the stock solution with 0.001 M hydrochloric acid (POCh, Gliwice, Poland) and for membrane extraction (10 ng/ml to 10 μg/ml) diluted with adequate pH of 0.02 M sodium phosphate (POCh, Gliwice, Poland) buffer. Acetonitrile (Merck, Darmstadt, Germany), dimethylamine (Fluka AG, Buchs SG, Germany), sodium dihydrogenphosphate (POCh, Gliwice, Poland), ortho-phosphoric acid (Chemical Factory, Oswiecim, Poland) were used for the preparation of mobile phase. All chemicals were “pure for analysis” grade and water was double-distilled.

n-Undecane (Reachim, Russia) and di-*n*-hexyl ether (Sigma, St. Louis, MO, USA) were the organic solvents used for impregnation of the membrane. Tri-*n*-octylphosphine oxide (TOPO) used as chemical carrier dissolved in the membrane liquid came from Fluka, Buchs (Germany).

2.2. Apparatus and chromatographic conditions

The LC apparatus consisted of a HPP 4001 syringe pump (Laboratorni Pristroje Prague, Czech Republic), Reodyne valve injector (Berkeley, CA, USA) equipped with a 20 μl

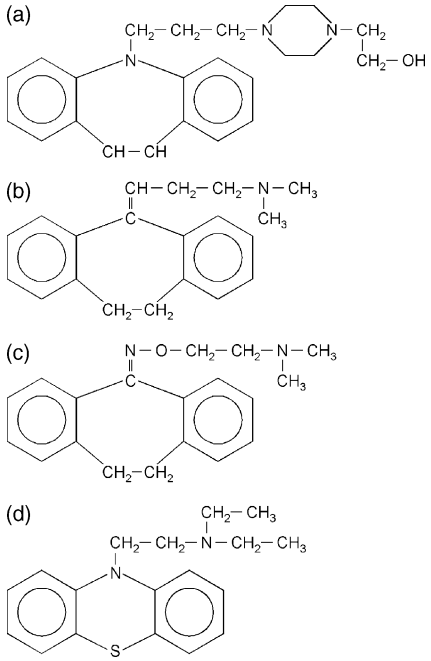

Fig. 1. Structural formulae of tricyclic antidepressants: (a) opipramol, (b) amitriptyline, (c) noxiptyline, (d) diethazine.

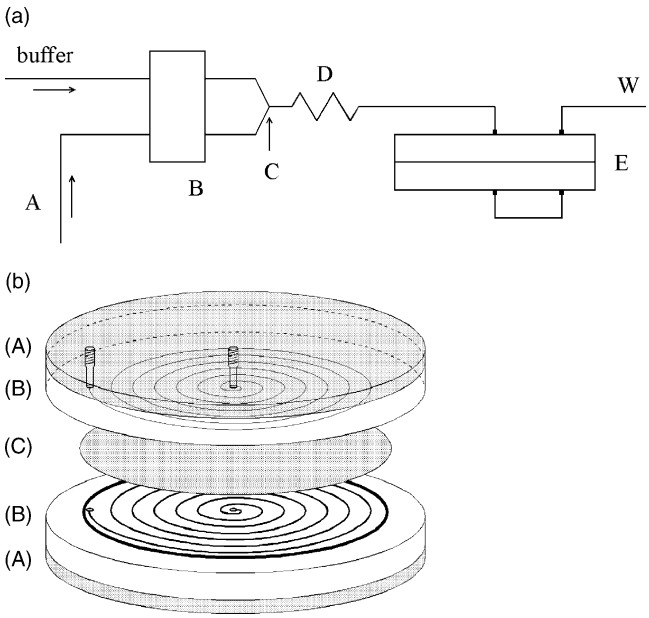

Fig. 2. (a) Set-up for membrane enrichment of tricyclic antidepressants in water samples: (A) sample; (B) peristaltic pump; (C) confluence point of sample and phosphate buffer solution; (D) mixing coil; (E) membrane separator with stagnant acceptor solution; (W) waste. (b) The membrane separator: (A) aluminum back-up; (B) PTFE block with grooves like Archimedes' spiral; (C) impregnated liquid membrane.

loop and UV 254 nm detector LCD 2563 (Laboratorni Pristroje Praha, Czech). The chromatographic analysis was carried out on Shiseido 5 μm RP-18, 250 mm × 4.6 mm ID column (gift from Prof. Hideharu Shintani, National Institute of Health Sciences, Ministry of Health and Welfare of Japan). Mixture of 0.01 M sodium phosphate buffer pH 3.2–methanol–acetonitrile–dimethylamine in ratio 37:55.4:7.4:0.2 (v/v) was used as mobile phase, which was filtered (17 G5 glass filter) and degassed with water vacuum pump during 2 min to prevent bubble formation in detector. Flow rate of mobile phase was 0.8 ml/min. In this chromatographic conditions complete separation of investigated tricyclic antidepressants and diethazine as internal standard was achieved within 12 min.

2.3. Extraction procedure

Sodium phosphate buffer pH 9.0 and sample solution containing 1 μg/ml of tricyclic antidepressants were pumped with peristaltic pump into a mixing coil that consisted about 1 m × 0.5 mm I.D. PTFE tubing coiled with diameter about 20 mm (Fig. 2a). Mixed solutions were passed with flow rate 0.8 ml/min over the liquid membrane in membrane separator (Fig. 2b) which was made of two PTFE blocks (diameter: 120 mm and thickness: 8 mm) with machined spiral grooves facing each other (depth: 0.25 mm, width: 1.5 mm, length: 250 cm and total volume: ∼0.80 ml).

Aluminum discs with 6 mm thickness were used to rigid the Teflon construction. A porous PTFE membrane with polyethylene backing, was Millipore (Bedford, MA, USA), with 90 mm of diameter and pore size: 0.2 μm, porosity: 0.70, total thickness: 175 μm, of which 115 μm is polyethylene net. After impregnation by soaking for 15 min in *n*-undecane the membrane was placed between two PTFE grooved discs and the whole separator was assembled and forced together with eight screws. Excess of solvent on the surface of the liquid membrane was removed by pressing about 50 ml of water through both channels. In the extractor the membrane separated two channels: the donor channel for extraction of opipramol, noxiptyline, amitriptyline and diethazine as internal standard from alkaline solution into the membrane solvent and the acceptor channel with acidic solution for reextraction of analytes from the membrane solvent. After 40 min of extraction procedure, 20 μl of acceptor solution directly or after neutralization (for pH lower than 2.0 and higher than 8.0) was injected into the HPLC column.

3. Results and discussion

3.1. Optimization of membrane extraction

To optimize the membrane process extraction efficiency was plotted as a function of donor solution pH and acceptor solution pH. Extraction efficiency E is expressed in percent of analyte extracted from the donor solution to the acceptor solution and was calculated from equation:

$$E(\%) = \frac{V_a\, h_a}{f_d t_e h_d} \times 100 \quad (1)$$

where V_a, volume of acceptor solution (ml); h_a, peak height of analyte in acceptor solution determined by HPLC after enrichment, f_d, flow-rate of donor solution (ml/min), t_e, time of the extraction procedure (min) and h_d, peak height of analyte in donor solution (determined by HPLC).

3.2. Influence of donor solution pH

Donor solution pH was changed from 4.5 to 12.5 by adding adequate amounts of 1 M sodium hydroxide to 0.01 sodium phosphate solution with 1 μg/ml of opipramol, noxiptyline, amitriptyline and diethazine. Acceptor solution was 0.05 M phosphate buffer pH 4.0 and *n*-undecane was as organic phase in the membrane. After extraction of 30 ml of donor solution with flow rate 0.8 ml/min the acceptor channel was washed with 3 ml of 0.05 M phosphate buffer pH 4.0 and 10 μl of this solution was injected to HPLC-UV and the extraction efficiency was calculated according to equation mentioned above (Section 3.1).

Fig. 3 shows the influence of donor solution pH on extraction efficiency. We observed very significant changes in passing of tricyclic antidepressants through the liquid membrane. At pH 4.5, extraction efficiency was about 4 times lower than at pH 9.5 because more investigated substances were protonated at low pH. The maximum extraction efficiency was

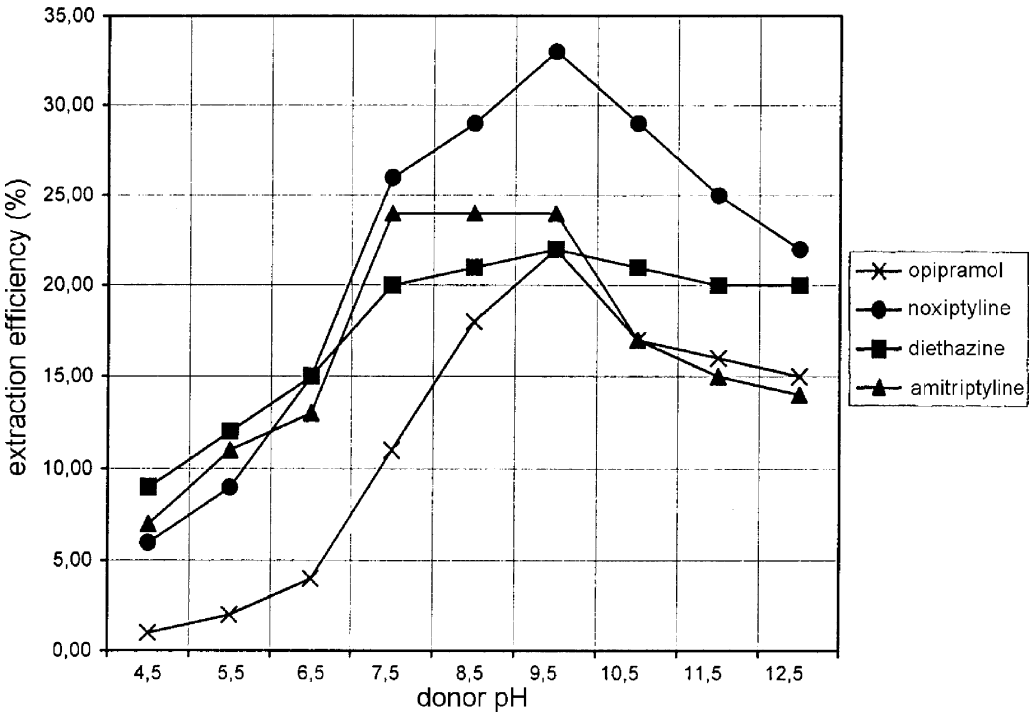

Fig. 3. Extraction efficiency for: noxiptyline (●), opipramol (×), diethazine (■) and amitriptyline (▲) vs. donor solution pH. Donor solution was 30 ml of 0.01 M phosphate buffer with different pH (4.5–12.5) containing 1 μg/ml of tricyclic antidepressants, $F_d = 0.8$ ml/min. Acceptor solution was 0.05 M phosphate buffer pH 4.0. Liquid membrane impregnated with *n*-undecane.

obtained for donor solution at pH 9.5: 22, 33, 22 and 24% for opipramol, noxiptyline, diethazine and amitriptyline, respectively. Lowering of tricyclic antidepressants enrichment at pH 13.0 was probably due to diffusion or adsorption problems of investigated substances in very basic donor solution.

The optimum pH of extraction was higher than pK_a values of all antidepressants. Opipramol as a divalent amine has two pK_a values: 7.80 ± 0.7 and 4.16 ± 0.7 but the rest of the compounds have 9.07 ± 0.28, 9.81 ± 0.26 and 9.24 ± 0.28, for noxiptyline, diethazine and amitriptyline, respectively.

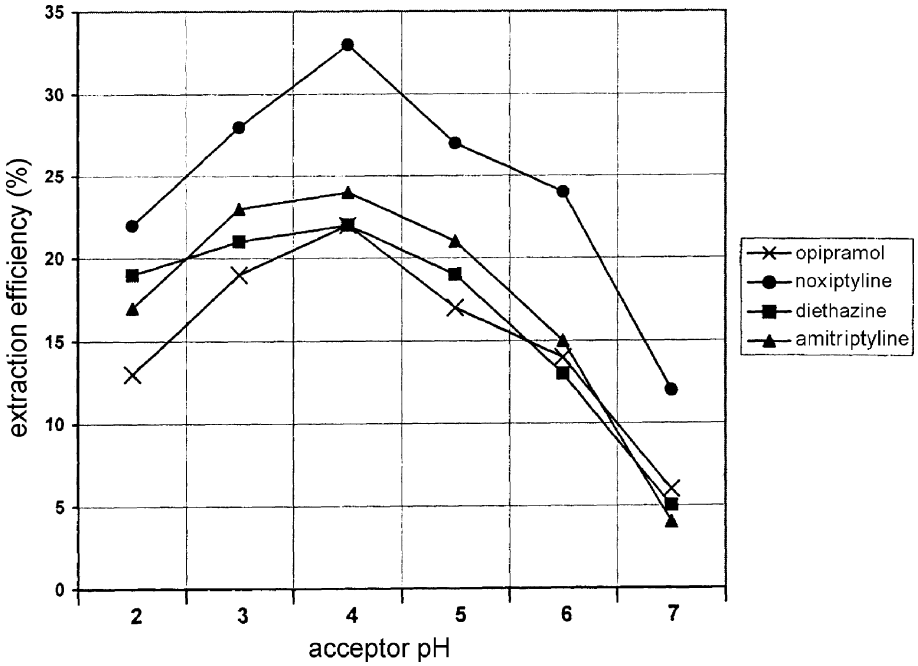

Fig. 4. Extraction efficiency for: noxiptyline (●), opipramol (×), diethazine (■) and amitriptyline (▲) vs. acceptor solution pH. Acceptor solution: 0.05 M phosphate buffer pH 2.0–7.0. Donor solution: 30 ml of 0.01 M phosphate buffer pH 9.5 containing 1 μg/ml of tricyclic antidepressants, $F_d = 0.8$ ml/min. Membrane impregnated with *n*-undecane.

The pK_a values were calculated by Jonsson [24] from a commercial program (ACD/pK_a DB 3.0, Advanced Chemical Development, Toronto). In this pH of donor, the tricyclic antidepressants were deprotonized and extracted into non-polar *n*-undecane liquid membrane.

3.3. Influence of acceptor solution pH

The 0.05 M sodium phosphate buffers pH 2.0–7.0 were prepared to investigate the influence of acceptor solution pH on the extraction efficiency of tricyclic antidepressants. Thirty milliliter of 0.01 M phosphate buffer pH 9.5 containing 1 μg/ml of investigated substances was passed with flow rate 0.8 ml/min over the *n*-undecane liquid membrane. After the extraction with different pH of acceptor solution and HPLC analysis, the extraction efficiencies were calculated.

Fig. 4 shows influence of acceptor solution pH on extraction efficiency of opipramol, noxiptyline, amitriptyline and diethazine as internal standard. As we can see the extraction of antidepressants was increased when pH was increased from 2.0 to 4.0 and next decreased almost four times with increasing pH from 4.0 to 7.0. This result is in agreement with Jonsson et al. [25], who has found that acceptor pH has to be 3.3 units lower than pK_a values in order to prevent basic compounds from re-entering the membrane liquid.

3.4. Influence of donor solution flow rate

The influence of donor solution flow-rate on extraction efficiency of opipramol, noxiptyline, amitriptyline and diethazine was also investigated. In this experiment, 0.01 M sodium phosphate buffer pH 9.5 with 0.1 μg/ml of antidepressants as donor solution and 0.05 M phosphate buffer pH 4.0 as acceptor solution were used. Different flow-rates: 0.10, 0.15, 0.2, 0.3, 0.4, 0.8 and 1.2 ml/min were used for pumping the same volume (30 ml) of donor solution. After each extraction procedure 20 μl of acceptor solution was injected into HPLC column and peak heights were compared with these obtained for 20 μl of donor solution and extraction efficiency was calculated according to equation shown in Section 3.1. From Fig. 5, we can observe lowering from 80 to 35% of extraction efficiency with increasing of donor solution flow rate. This is probably connected with shorter time of diffusion of analytes from the donor solution and their extraction to the membrane liquid. To obtain higher concentration of tricyclic antidepressants in acceptor solution rather lower flow rates are more suitable for small and limited volume of samples. In all experiments for optimization of extraction efficiency, the donor solution flow rate 0.8 ml/min was chosen, because the amount of extracted antidepressants/1 min of extraction was almost two times higher compared with donor solution flow rate 0.2 ml/min.

3.5. Influence of analyte concentration in donor solution

The influence of opipramol, noxiptyline, amitriptyline and diethazine concentrations in donor solution on the amount (or simply peak heights obtained from acceptor solution) of extracted tricyclic antidepressants was also investigated. In this purpose different concentrations of investigated substances (0.01, 0.05, 0.1, 0.2, 0.5, and 1 μg/ml) were prepared and 30 ml of each solution were pumped with flow rate 0.8 ml/min over the liquid membrane with *n*-undecane. The pH of acceptor and donor solution was 4.0 and 9.5, respectively. For all investigated substances the linear increase of their amounts in acceptor solution, in relation to the concentrations in donor solution, was observed.

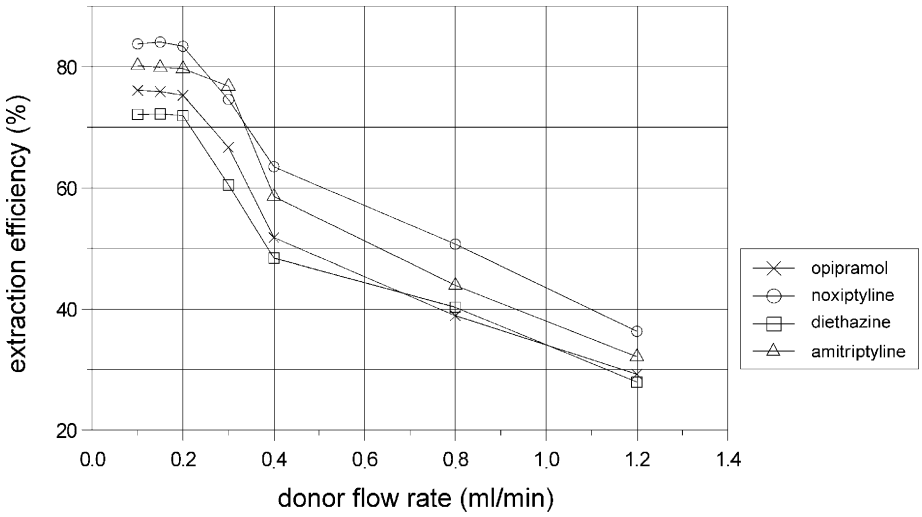

Fig. 5. Influence of donor solution flow rate on extraction efficiency. *n*-Undecane + 5% (w/w) trioctylphosphine oxide (TOPO) as a membrane solvent and 0.05 M phosphate buffer pH 4.0 as acceptor solution were used. The 30 ml of 0.01 M phosphate buffer pH 9.5 with 0.1 μg/ml of tricyclic antidepressants was pumped with different flow-rate.

3.6. Influence of extraction time

The influence of extraction time on peak height of extracted tricyclic antidepressants in acceptor solution was also investigated. Different extraction times (20, 40, 60 min, 1.5, and 2 h) for 0.1 μg/ml of opipramol, noxiptyline, amitriptyline and diethazine in donor solution at pH 9.5 and flow-rate 0.8 ml/min were applied. Acceptor solution was phosphate buffer pH 4.0. Increasing of extraction time of antidepressants has given the linear increase of their amounts in acceptor solution.

3.7. Influence of membrane solvent

As extraction efficiency of opipramol, noxiptyline, amitriptyline and diethazine was not higher than 35% for membrane impregnated with *n*-undecane, additionally various solvents were chosen to improve the SLM extraction procedure. For this purpose di-*n*-hexyl ether, 1:1 mixture of *n*-undecane with di-*n*-hexyl ether and *n*-undecane as pure solvents and with addition of 5% (w/w) tri-*n*-octylphosphine oxide (TOPO) were used. In this experiment, 30 ml of donor solution pH 9.5 with 0.1 μg/ml of tricyclic antidepressants were passed with flow-rate 0.8 ml/min over each type of liquid membrane. After HPLC analysis of acceptor solution (0.05 M phosphate buffer pH 4.0) extraction efficiencies were calculated. In Table 1 the extraction efficiencies of tricyclic antidepressants for various membrane solvents are shown.

After changing the organic solvent in membrane for di-*n*-hexyl ether lower extraction efficiency was observed in comparison with *n*-undecane. Probably tricyclic compounds are quite hydrophobic at pH 9.5 of the donor solution. Also, the mixture of di-*n*-hexyl ether with undecane (1:1 (v/v)) did not significantly improve the extraction process. For all types of organic solvents (di-*n*-hexyl ether, *n*-undecane and mixture of di-*n*-hexyl ether with *n*-undecane 1:1 (v/v)) mixed with 5% of tri-*n*-octylphoshine oxide (TOPO) higher extraction efficiencies were obtained, what is in agreement with data for another extracted substances using SLM method [19,21]. The greatest improvements for extraction was observed for *n*-undecane with 5% of TOPO: 43, 56, 43 and 42% for opipramol, noxiptyline, amitriptyline and diethazine, respectively. We also have to consider the influence of logarithm of the octanol–water partition coefficient ($\log P$) on extraction efficiency of investigated substances. Values of $\log P$ calculated by Jonsson [24] for opipramol, amitriptyline, noxiptyline and diethazine were 3.6 ± 0.5, 6.1 ± 0.3, 5.1 ± 0.6 and 5.40 ± 0.26, respectively. According to publication by Chimuka et al. [26], if $\log P$ of investigated compounds is higher than 4, supported liquid membrane extraction becomes harder because these compounds have incomplete stripping into the acceptor solution. This is another explanation for rather low extraction efficiency of investigated substances.

3.8. Chromatograms

After optimization of SLM extraction procedure, this technique was used for enrichment of tricyclic antidepressants from natural samples. For this purpose, 100 ml of urine, spiked with 50 ng/ml of opipramol, noxiptyline, amitriptyline and diethazine was passed with flow-rate 0.8 ml/min over the liquid membrane with undecane and 5% TOPO. After extraction, 20 μl of acceptor solution was injected into HPLC column. Fig. 6A shows chromatogram obtained (see details of chromatographic conditions in Section 2.2 or in legend of Fig. 6) after enrichment 100 ml of urine spiked with 50 ng/ml of tricyclic antidepressants. Complete separation of: opipramol (1), noxiptyline (2), diethazine (3) and amitriptyline (4) was achieved in 12 min. Fig. 6B shows chromatogram after direct injection of 20 μl of urine containing 50 ng/ml of investigated substances. Obtained signals from investigated substances were very small and only 2–3 times higher than the noise level. From both figures, we can conclude that the concentration of analyzed substances after SLM extraction of urine increased about 50 times in acceptor solution to compare with concentration in donor solution. Direct injection of urine sample have given very wide matrix peak and many other unknown peaks which have been disappeared after SLM extraction due to the clean-up effect of this technique.

The presented method permits analysis of tricyclic antidepressants in biological fluids at very low (ng/ml) range

Table 1
Extraction efficiencies (%) for tricyclic antidepressants and internal standard with different membrane solvents (R.S.D. values were <6% and $n = 3$)

Solvent	Compound			
	Opipramol	Noxiptyline	Amitriptyline	Diethazine
Di-*n*-hexyl ether	16	23	15	10
Di-*n*-hexyl ether + 5% TOPO	22	29	22	18
Di-*n*-hexyl ether + undecane (1:1)	21	29	22	18
Di-*n*-hexyl ether + undecane (1:1) plus 5% TOPO	26	35	28	26
n-Undecane	22	30	24	22
n-Undecane + 5% TOPO	43	56	43	42

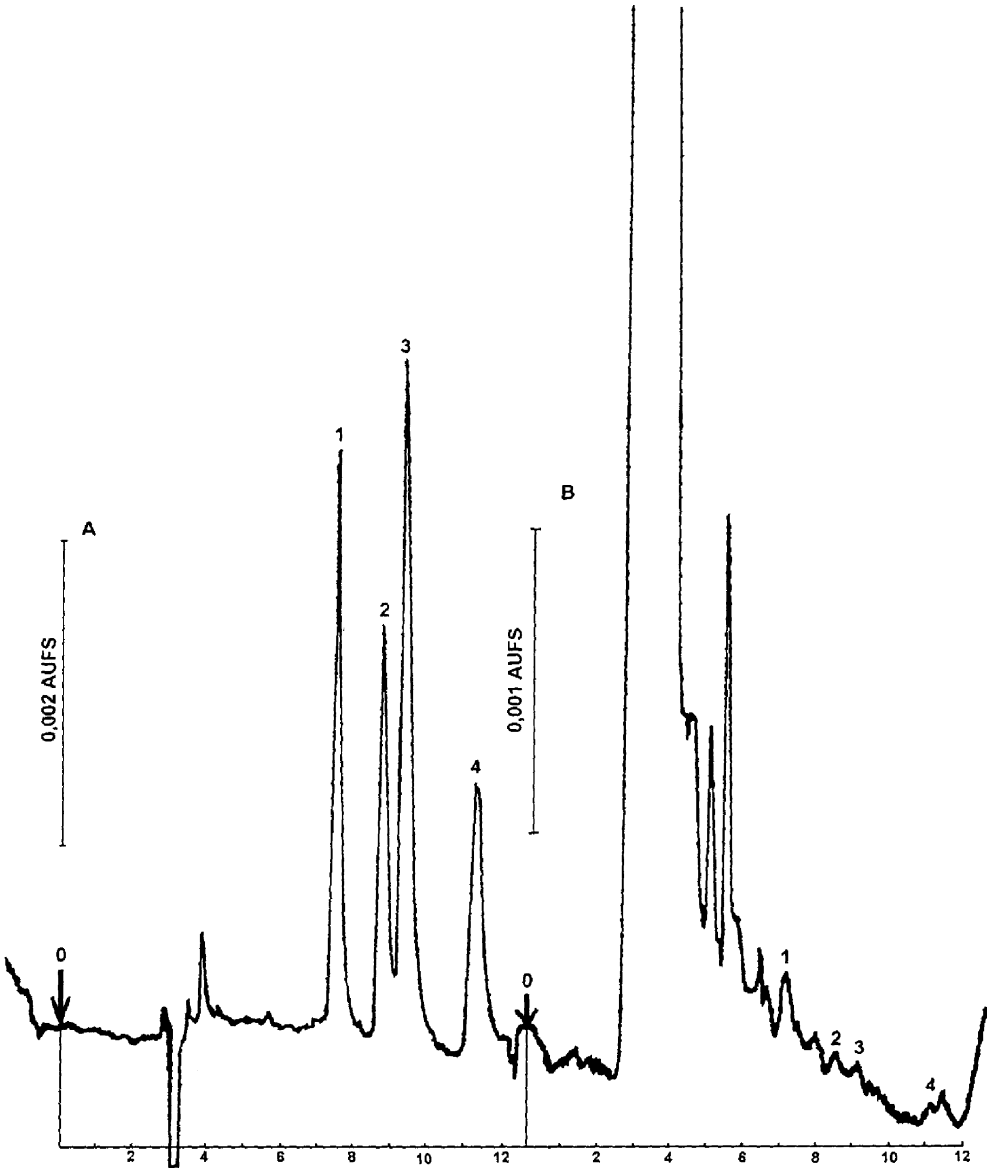

Fig. 6. Chromatograms of: (A) acceptor solution after extraction of 100 ml urine sample spiked with 50 ng/ml of tricyclic antidepressants: (1) opipramol, (2) noxiptyline, (3) diethazine (internal standard) and (4) amitriptyline; (B) direct analysis of urine sample containing 50 ng/ml of investigated substances. SLM extraction with *n*-undecane + 5% TOPO as membrane solution was done with donor solution at pH 9.5, flow-rate 0.8 ml/min, acceptor solution was 0.05 M phosphate buffer pH 4.0. HPLC with UV 254 nm detector, column 250 mm × 4.6 mm I.D. Shiseido 5 μm RP-18, 0.01 M phosphate buffer pH 3.2, methanol, acetonitrile and dimethylamine (37:55.4:7.4:0.2 (v/v)) was used as mobile phase with flow rate 0.8 ml/min. Injection volume of analyzed solution was 20 μl.

without additional derivatization procedures or applying complicated procedures [2,3] or expensive instrumentation [5].

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