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Short communication

Multi-syringe chromatography (MSC) system for the on-line solid-phase extraction and determination of hydrochlorothiazide and losartan potassium in superficial water, groundwater and wastewater outlet samples

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ABSTRACT

In this paper, a combination of multi-syringe chromatography analysis technique with extraction disks sorbents for the pre-concentration and determination of hydrochlorothiazide and losartan potassium in superficial water, groundwater and wastewater outlet samples has been developed. The system developed was proved for the determination of hydrochlorothiazide and losartan potassium in spiked water samples with recoveries ranging from 95 to 118%. The method involves the on-line enrichment of the targeted analytes from spiked water samples onto a Cation-SR sorbent material. The analytes are subsequently eluted and transported to the monolithic column, Chromolith Flash RP-18e column (25 mm × 4.6 mm i.d.). The mobile phase used was 10 mM potassium dihydrogen phosphate (pH 3.0):acetonitrile:methanol (60:30:10 v/v/v), flow-rate 0.8 mL min^{-1}. UV detection is carried out at 226 nm. Under the optimized chemical and physical variables, the detection limit for hydrochlorothiazide and losartan potassium calculated as 3*Syx/b* was 0.07 and 0.09 mg L^{-1}, respectively, for a sample loading volume of 1.0 mL.

1. Introduction

In recent years, pharmaceuticals residues in the environment have become a subject of public and scientific concern. Pharmaceuticals comprise a large class of predominantly organic compounds; thousands of different active molecules are currently used in the world to treat or to prevent diseases. These compounds can enter the aquatic environment following manufacture, use or ingestion/excretion. Once administered, pharmaceuticals can be excreted unchanged or as active metabolite in high percentages, and continuously discharged into domestic wastewaters. Besides improper disposal of expired medications and manufacturing facilities are other important local point sources. Several pharmaceuticals can, therefore, reach sewage treatment plant in substantial amounts; depending on chemical and physical properties including aqueous solubility, volatility and lipophilicity, pharmaceutical residues may be physically removed in varying degrees from the bulk sewage during primary treatment. In the biologically oxidative environment of secondary sewage treatment, organic compounds differ widely in their susceptibility to microbial degradation. Some compound will be ultimately degradable, while others may persist, which flow into surface waters and drinking waters reservoirs [1–5]. In the last 10 years several analytical methods have been published to measure pharmaceuticals in sewage treatment plants, rivers, the sea and groundwater. Some methods intended for the detection of specific therapeutic categories while others measured wide ranges of compounds, over 40 pharmaceuticals drugs and metabolites have been identified in environmental samples, primarily in Europe and the USA. Reported compounds include analgesic, anti-inflammatory, diuretic, cardiovascular, antiepileptic, antineoplastic, antibiotic drugs and others [1,2,5–10]. The analytical methods used for the determination of pharmaceutical residues in water samples include high-pressure liquid chromatography (HPLC) [1–3,7–13], gas chromatography (GC) [3,7,8,10], coupled with fluorometric [12], mass spectrometric [8,9] and tandem mass spectrometric detection [1–3,8–13]. Generally, all these methods include an isolation procedure prior to the chromatographic step. The most frequently used procedure is off-line solid-phase extraction cartridges [1,2,7–9,11,13] or disks [10,12] with sorbents of different nature.

In contrast to conventional HPLC Columns, monolithic silica columns are packed with a single piece of silica gel into a straight rod of highly porous silica with a bimodal pore structure referred to as macroporous and mesoporous. The small pores ensure sufficient surface area for separation efficiency, while the large macropores

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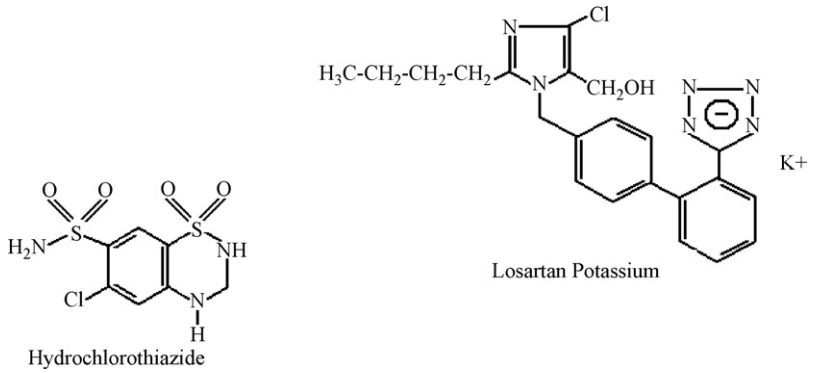

Fig. 1. Chemicals structures of hydrochlorothiazide and losartan potassium.

are responsible for a low resistance and for that reason allow the application of high eluent flow-rate; the resulting column back-pressure is, therefore, much lower [14]. The advantages of the combination of chromatographic techniques with flow techniques are noteworthy. Thus, flow analysis equipments are not extremely expensive, but these methods do not allow the separation of several analytes in a mixture. On the other hand, HPLC has been widely used in pharmaceutical analysis and analytical research due to its selectivity. However, it requires very expensive instrumentation with regard to flow techniques.

Šatínský et al. [15] developed a sequential injection chromatography (SIC) method for the determination of drug in pharmaceuticals using a short monolithic column coupled to a sequential injection system. These systems have been used for the determination of triamcinolone acetonide, salicylic acid, sodium diclofenac, paracetamol, caffeine, acetylsalicylic acid, ambroxol hydrochloride, betamethasone, chloramphenicol and other compounds in different pharmaceutical preparations [15–20]. Multi-syringe flow injection analysis (MSFIA) was introduced by Cerdà et al. in 1999 as a robust alternative to its predecessor techniques [21], combining the multi-channel operation of FIA with the possibility of selecting only the exact volume of the sample and reagent required for analysis, as presented in SIA. Among its most important advantages are the great versatility of manifold configuration and the feasibility to use organic solvents [21,22]. The operational versatility of MSFIA methodology can be increased even more by coupling it to others techniques or modules [22]. The on-line coupling of the MSFIA technique with chromatographic monolithic column provides an excellent tool to solve the separation problems without using HPLC instrumentation, with low cost per analysis and low consumption of organic solvents [23]. Multi-syringe chromatography (MSC) was used to separate β-lactamic and vitamins [24,25]. The coupling of chromatographic separation to flow analysis, as used in SIC and MSC, introduces specificity to these rapid, simple and economic methods.

Despite the numerous applications of solvent extraction in flowing stream systems, sorbent extraction is the predominating sample processing method that has been rapidly growing in recent years as a consequence of the improved concentration factors and considerable reduction of organic solvent consumption. Solid-phase extraction (SPE) is the most popular sample treatment implemented in-line in multi-syringe flow injection analysis (MSFIA), the multi-channel operation offered by multi-syringe and the discontinuous flow attained through the commutation valve provides unique features for implementing SPE protocols. Among then is the possibility of accommodating a loading solution and an eluent in different syringes, and by activating the respective commutation valve to change the solution that passes through the solid-phase extractant. Moreover, the application of time-based sampling enables the establishment of calibration based on the mass of the analyte retained in the extraction phase. This approach may also expand the concentration working range, since different sample volumes can be used [26]. The solid-phase extractants applied in MSFIA systems were either commercial resins or disks, actually, commercially available disk-sorbents (e.g., Empore disks) comprising chelating moieties, ion exchanger resins or reversed-phase materials are demonstrated to be optimum solid-phases for flow-through sorbent extraction methods [27–30].

In this paper, the combination of disk-based solid-phase extraction with multi-syringe chromatography (MSC) analysis is proposed for the on-line separation and enrichment of hydrochlorothiazide (HCTZ) and losartan potassium (LP) in environmental waters. Hydrochlorothiazide, 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, has been used as antihypertensive agent due to its diuretic action. It is supplied as tablets for oral use and can be prescribed alone, as the sole therapeutic agent or in combination with other antihypertensive drugs like losartan potassium. Losartan potassium, 2-butyl-4-chloro-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol monopotassium salt is the first member of a new class of non-peptide angiotensin II receptor antagonist. It reduces effectively hypertension by suppressing the effects of angiotensin II at its receptors, thereby blocking the rennin-angiotensin system. Several analytical procedures have been reported for the determination of the two drugs in pharmaceutical forms or in biological fluids, individually or in their combination with other drugs, these including flow injection [31], reverse-phase high performance liquid chromatography (HPLC) [32–36], capillary zone electrophoresis [37], spectrophotometry [38–41] and electrochemical techniques [42].

These two compounds are currently very used in the practice due to their synergic effects, and therefore, they are frequently found in the environment [43] and sewage effluents [44]. Due to this reason and due to our experience in analyzing these two compounds we have chosen them as a chemical model in the present work.

The structures of these two drugs are shown in Fig. 1.

2. Experimental

2.1. Reagents, samples and sorbent

The standard of hydrochlorothiazide was purchased from Sigma–Aldrich (St. Louis, MO, USA). The losartan potassium standard was difficult to find, we wrote to Merck and different chemical

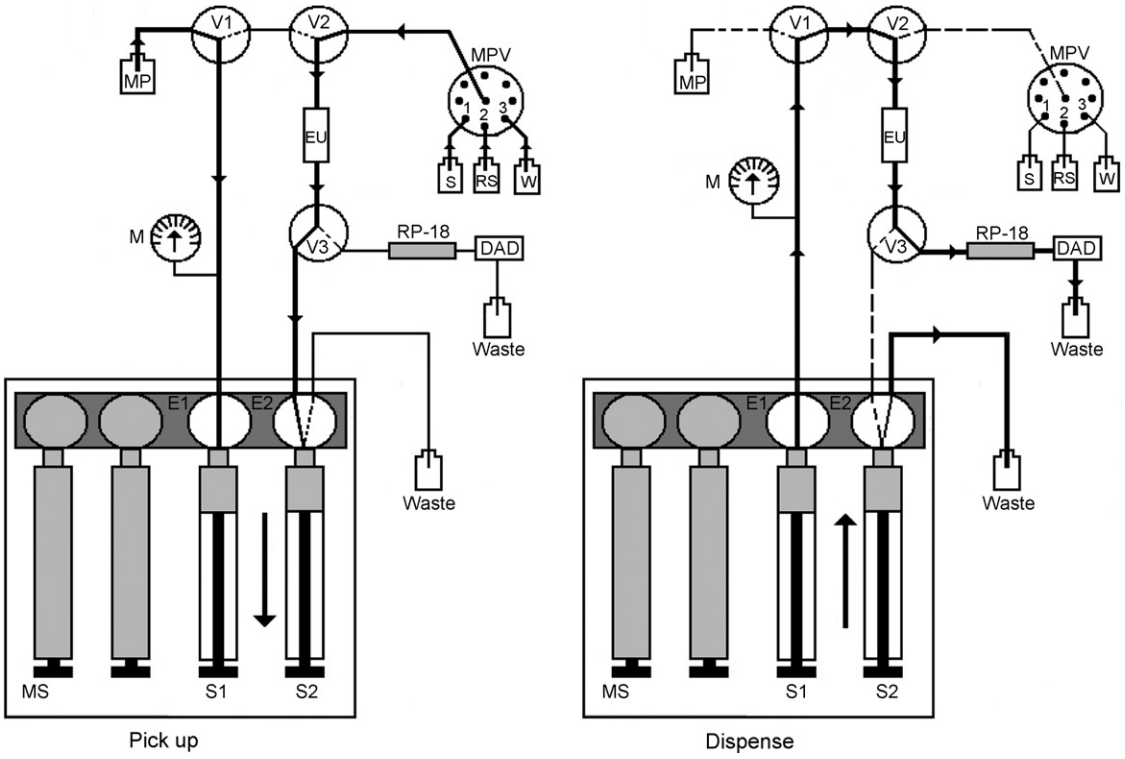

Fig. 2. MSC flow injection disk-phase extraction set-up for simultaneous enrichment and determination of HCTZ and LP. MS: multi-syringe burette, E_1: Delrin two-way connector, E_2: three-way solenoid valve, S_1–S_2: syringes, M: manometer, V_1–V_3: solenoid valves, EU: extraction unit, MPV: multiposition selection valve, RP-18: monolithic column, DAD: diode array detector, MP: mobile phase, S: sample, RS: regeneration solution, W: water.

suppliers, most of them never answered; Merck requested the preliminary results. Therefore, it was extracted and crystallized from the tablets. Five tablets of Cozaar (50 mg/tablet) were weighed and reduced to a fine powder in a porcelain mortar. A portion of the powdered composite equivalent to one tablet was quantitatively transferred with 3 mL of methanol to a centrifuge tube. After vortex mixing for 1 min the mixture was placed into the ultrasonic bath for 15 min and then centrifuged at 4000 rpm for 30 min. The clear supernatant was completely transferred into a centrifuge tube previously weighed. The residue was extracted once and the supernatant was collected in the same centrifuge tube and evaporated in a water bath under a stream of nitrogen. The residue was reconstituted in 25 mL of methanol. Analytical reagent grade potassium dihydrogen phosphate (KH_2PO_4) was purchased from Probus, S. A. (Barcelona, Spain), phosphoric acid (85%) p.a. and hydrochloric acid (1 N) was from Sharlau Chemie S. A. (Spain), Methanol Chromasolv® (HPLC grade, Sigma–Aldrich) and acetonitrile (HPLC – gradient grade PAI – ACS, Panreac) were used to prepare required mobile phase. The deionized water was purified by a Milli-Q-system (Millipore Corp. Bedford, MA). Stock standard solutions were prepared in methanol at concentration of 1000 $\mu g\,mL^{-1}$ and were stored at −20 °C for 1 month; working standard solutions were daily prepared by diluting the stock solution in the mobile phase. Octadecyl-bonded silica gel (C_{18}), poly(styrenedivinylbenzene) copolymer (SDB-XC) and cation-exchange-SR disks of 0.5 mm thickness were purchase from Empore 3 M (St. Paul, MN, USA).

2.2. Instrumentation

The multi-syringe chromatography flow injection analysis system used for the extraction and simultaneous determination of HCTZ and LP can be seen in Fig. 2. The system is basically constituted by a multi-syringe burette module (MS) and a multiposition selection valve (MPV), both from Crison Instruments, Alella, Spain. The multi-syringe burette module was equipped with two high-precision bidirectional syringes (S_1, S_2), (Hamilton, Switzerland); both with a capacity of 5.0 mL. The syringe S_2 has a three way solenoid valve (N-Research, Caldwell, NJ, USA) on its head (E_2), the position "off" of the valve connected syringes S_2 to waste and the position "on" connected syringes S_2 to the system.

The commutation valve of syringe S_1 was replaced by a delrin two-way connector (E_1), (Sciware, Palma de Mallorca, Spain); the MS module also comprised three additional solenoid valve (V_1–V_3), (MTV-3-N-1/4UKGH, Takasago, Japan). The extraction unit containing the disk or membrane consisted of two delrin cylinders. The disk is placed in an 8 mm i.d. gap as can be seen in Fig. 3. This gap contains a conical section where a polyethylene frit with an average pore diameter of 10 μm is attached in order to avoid distortion of the membrane [16]. Manifold was constructed with 0.8 mm internal diameter (i.d) polytetrafluoroethylene (PTFE, Teflon) tubing. The chromatographic separation was achieved on a Chromolith Flash RP-18e, (25 mm × 4.6 mm i.d. column) protected with a Chromolith RP-18e (10 mm × 4.6 mm) guard column (Merck). The optimal mobile phase for elution and separation of hydrochlorothiazide and losartan potassium was a mixture of 10 mM potassium dihydrogen phosphate:acetonitrile:methanol (60:30:10 v/v/v), the buffer pH was adjusted to 3.0 with orthophosphoric acid (85%) prior to mixing with the acetonitrile and the methanol. The mobile phase was filtered and degassed in an ultrasonic bath for 15 min before use and delivered at a flow-rate of 0.8 $mL\,min^{-1}$. A Hewlett Packard 8453 diode array spectrophotometer equipped with an 18 μL inner volume flow-cell (Hellma) was used as detector. Measurements were recorded at 226 nm. For instrument control, data acquisition and processing, AutoAnalysis 5.0 software (www-sciware-sl.com) was used.

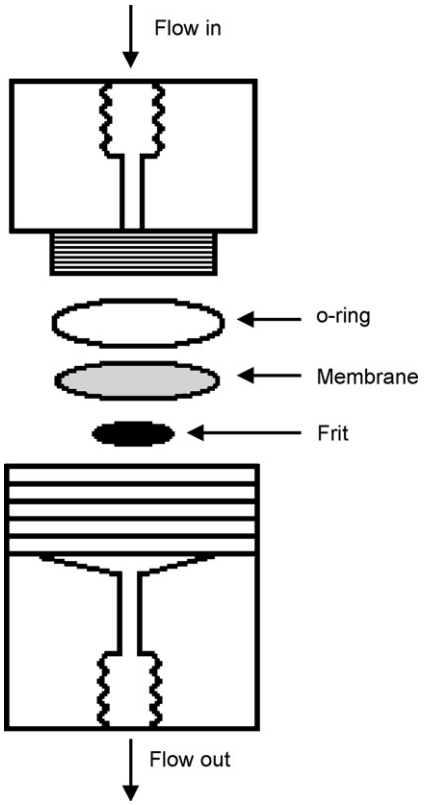

Fig. 3. Schematic view of the extraction unit for disk-based solid-phase pre-concentration.

2.3. Analytical procedure

The operational details of the MSC system for solid-phase extraction, pre-concentration and further chromatographic separation of the drugs are listed in Table 1 and summarized as follows:

1. Initially, the column was conditioned with 1.0 mL of mobile phase (step 3, Table 1). Thereafter, the central channel of the selection valve is directed to port 1 for the aspiration of 1.0 mL of sample, which is backward to the extraction module for the isolation of the analyte from matrix constituents (step 4–5, Table 1). After sample loading, 1.0 mL of the deionized water is aspirated through the sorptive membrane and tubes for removal of non-retained matrix species and rinses the tubes (steps 6–7, Table 1).
2. The HCTZ and LP retained on the extraction disk are eluated and transported to the monolithic column with the mobile phase (step 9, Table 1). The operational sequence is repeated three times (steps 2–11).
3. Regeneration of the cation extraction sorbent was carried out with 2.0 mL of 80% (v/v) methanol/0.02 mol L^{-1} HCl solution (steps 14–15, Table 1).

2.4. Analysis of samples

The technique proposed was applied to the determination of HCTZ and LP in superficial water, groundwater, as well as at the outlet stream of a wastewater treatment. A portion of the standard was added to a know volume of sample to give a final concentration of 1.0 mg L^{-1}, the samples were filtered through membrane filter of 0.45 μm pore size prior analysis.

3. Results and discussion

3.1. Selection of disk-sorbent material

Commercially available extraction membranes with entrapped adsorbed particles were tested in order to obtain satisfactory values for recovery of HCTZ and LP. Thus, octadecyl-bonded silica gel (C_{18}), poly(styrenedivinylbenzene) copolymer (SDB-XC) and cation-SR ion exchange disks, Empore 3 M, were evaluated as adsorptive surfaces. Bonded silica sorbents are commonly used for the solid-phase extraction of analytes from complex sample matrices. A variety of functional groups, such as octyl (C_8) and octadecyl (C_{18}) can be bonded to the silica surface to provide non-polar interactions. SDB-XC is a poly(styrenedivinylbenzene) copolymer used as a reversed-phase sorbent for solid-phase extraction. SDB-XC may be substituted into methods that use C_{18} or C_8 bonded silica and often demonstrates greater capacity. However, results from this investigation show that both sorbent only retained satisfactorily the LP. Cation-SR is a poly(styrenedivinylbenzene) copolymer that has been modified with sulfonic acid. This functional group imparts selectivity for cationic analytes, such primary, secondary and tertiary amines like HCTZ. Because cation-SR membrane displays reverse phase and cation-exchange interactions, allowed to retain the HCTZ and LP.

Table 1
Multi-syringe chromatography protocol for on-line enrichment and separation of hydrochlorothiazide and losartan potassium from environmental waters

Steps	Operation	Flow-rate (mL min^{-1})	Position of the solenoid valves			
			E_2	V_1	V_2	V_3
1. Start loop						
2. Adjustment of the piston bar position	Dispense 1.0 mL	1.5	Off	Off	Off	Off
3. Pre-condition of the system	Dispense 1.0 mL	0.8	Off	On	Off	On
4. Selection valve	Move to port 1					
5. Sample aspiration	Pickup 1.0 mL	0.5	On	Off	On	Off
6. Selection valve	Move to port 2					
7. Rinsing of manifold lines	Pick up 1.0 mL	0.5	On	Off	On	Off
8. Acquisition of the spectra						
9. Elution and eluate transportation to monolithic column	Dispense 5.0 mL	0.8	Off	On	Off	On
10. Stop measurement						
11. Adjustment of the piston bar	Pickup 5.0 mL	1.5	Off	Off	Off	Off
12. End loop						
13. Adjustment of the piston bar	Dispense 4.0 mL	2.0	Off	Off	Off	Off
14. Selection valve	Move to port 3					
15. Membrane regeneration	Pickup 2.0 mL	0.5	On	Off	On	Off
16. Selection valve	Move to port 2					
17. Rinsing of manifold lines	Pickup 2.0 mL	0.5	On	Off	On	Off

3.2. Eluent and chromatographic separation

The elution of HCTZ and LP from cation-SR membrane and its separation onto the chromatographic column was examined by studies of different mixtures of 0.01 M, pH 3.0 phosphate buffer, acetonitrile and methanol. Incomplete removal of the sorbed analytes was observed with ratios less than 10% methanol. Content of acetonitrile lower than 30% (v/v) increases the retention of LP and the analysis time. Additional studies were also done to check the effect that mobile phase pH and buffer concentration had on analytes retention, shape of the peaks and resolution. Results from this investigation showed that there was no significant change in retention, shape of the peaks and resolution of investigated drugs when the concentration of buffer was increased among 0.01–0.05 mol L^{-1}, and the concentration of 0.01 mol L^{-1} was chosen to prepare buffer phosphate. The effect of pH on the retention and separation was observed over the range 3.0–7.0 using phosphate as buffer salt. The retention of losartan potassium was affected and we observed that at pH 5.0 the resolution between hydrochlorothiazide and losartan potassium decreased and at pH 7.0 the peaks overlap totally. From these data it was determined that the optimal mobile phase for separation of the compounds consisted of 0.01 M buffer phosphate (pH 3.0):acetonitrile:methanol (60:30:10 v/v/v).

3.3. Selection of physical variables

Various parameters concerning the MSC operational sequence, such as the pre-concentration and elution flow-rates as well as sample loading volume were investigated. Variable flow-rates of sample loading, within the range 0.3–1.0 mL min^{-1} through the membrane were tried in order to investigate their effect on compounds retention. For this purpose 1.0 mL of a (0.5 mg L^{-1}) of HCTZ and (0.8 mg L^{-1}) of LP standards were pre-concentrated in this experiment. Flow-rates above 0.6 mL min^{-1} generated bubbles in the system; in this range change in retention of compounds was not observed.

Analogously, elution flow-rates were studied within the range 0.5–1.5 mL min^{-1}, under the same experimental conditions, using a pre-concentration flow-rate of 0.5 mL min^{-1}. It should be noted that flow-rates above 1.0 mL min^{-1} were not possible to exceed because of the percent of buffer in the mobile phase; if the percent of organic part is augmented, the flow-rate can be increased, and therefore, an elution flow-rate of 0.8 mL min^{-1} was chosen. For optimization of sample loading volumes, increasing volumes ranged from 1.0 to 5.0 mL of individual standard solutions of HCTZ and LP at 0.4 mg L^{-1} were aspirated into the MSC system. In both cases, no appreciable analyte breakthrough was observed for loading volumes up to 3.0 mL. However, the reproducibility was not affected by the sampling volume. A chromatogram obtained using the developed method conditions is illustrated in Fig. 4.

3.4. Life time and conditioning of the cation-exchange disk

Appropriate conditioning of the membrane was proven to be crucial for efficient sorption of the species of interest. According to manufacturer's recommendations, the membranes were soaked successively into acetone, methanol, nitric acid (50%) and distilled water prior to their implementation into the extraction unit. However, regeneration of the solid-phase disk was carried out by 80% (v/v) methanol/0.02 mol L^{-1} HCl solution after three injection and elution of the sample or standard. In order to investigate the effect of successive injections on the life of the cation-exchange disk, 1.0 mL of a 0.4 mg L^{-1} HCTZ and 0.8 mg L^{-1} LP standards were consecutively injected. It is possible to use the same disk up to 30 injections.

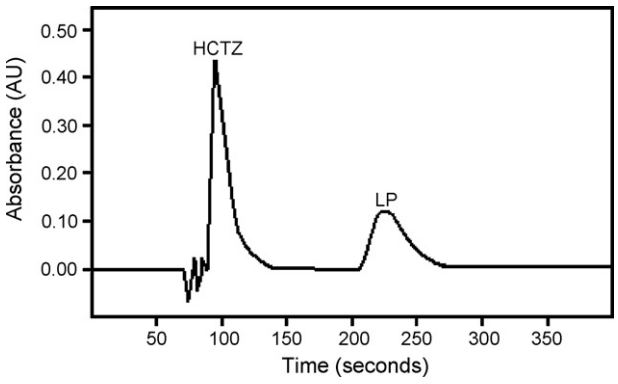

Fig. 4. MSC chromatogram obtained from a standard solution of hydrochlorothiazide (HCTZ: 0.8 mg L^{-1}, t_r: 98 s) and losartan potassium (LP: 1.2 mg L^{-1}, t_r: 237 s). Mobile phase: 0.01 M buffer phosphate (pH 3.0):acetonitrile:methanol (60:30:10 v/v/v), flow-rate 0.8 mL min^{-1}, UV detection at 226 nm, sample volume 1.0 mL.

After these injections, the peak shape for the HCTZ was deformed and the retention efficiency decreased for the HCTZ.

3.5. Analytical parameters

The figures of merit of the system, including linear dynamic ranges and calibration curves for a sample loading volume of 1.0 mL are summarized in Table 2. The detection limit (DL) was calculated as 3*Syx/b* and the determination limits was calculated as 10*Syx/b*. The repeatability (R.S.D.), calculated from 7 replicates using 1.0 mL injections of a 0.4 mg L^{-1} HCTZ and 0.8 mg mL^{-1} LP solutions was 2.72 and 2.54%, respectively. The repeatability between 5 cation-SR disks was 2.65% for HCTZ and 0.30% for LP; and injection throughput of 9 injections per hour for a sampling volume of 1.0 mL has been achieved.

3.6. Recovery tests

In order to assess the reliability of the proposed method and the influence of the bulk sample matrix on the multi-syringe chromatography solid-phase extraction system, surface, groundwater, as well as at the outlet stream of a wastewater treatment were spiked with the target compounds and analyzed. To obtain retention on ion exchange sorbents, the sorbent and analyte moiety must be in an ionized form. The sulfonic acid has a negative charge at any reasonable pH. To select a pH of the sample matrix containing the analytes, one must be aware of the pk_a values for the compound. Generally, the pH is adjusted to at least 2 units below the pk_a of the analyte cation. The pk_a (s) of the HCTZ are 7.9 and 9.2, the pH (s) of the analyzed samples ranged between 6 and 7. Therefore, we did not need to adjust the pH of the water samples. Table 3, summarizes the results of HCTZ and LP determination and percent recoveries of spiked water samples. Recoveries ranging from 95.6 to 118.0% were obtained for the samples analyzed.

Table 2
Figures of merit of the proposed MSC-extraction system

Analytical parameter	Hydrochlorothiazide	Losartan potassium
Detection limit (mg L^{-1})	0.07	0.09
Determination limit (mg L^{-1})	0.30	0.30
Sensitivity (L^{-1} mg) (n = 3)	30.0887	31.3829
Regression coefficient (n = 3)	0.9960	0.9962
Linear dynamic range (mg L^{-1})	0.3–1.7	0.4–1.8
Repeatability (%) (n = 7)	2.72 (0.4 mg L^{-1})	2.54 (0.8 mg L^{-1})
Reproducibility (%) (n = 5)	2.65 (0.5 mg L^{-1})	0.30 (0.8 mg L^{-1})
Sample throughput (h^{-1})	9	9

Table 3
Results obtained in the analysis of water samples

Sample	Hydrochlorothiazide			Losartan potassium		
	Added ($mg\,L^{-1}$)	Found ($mg\,L^{-1}$)	Recovery (%)	Added ($mg\,L^{-1}$)	Found ($mg\,L^{-1}$)	Recovery (%)
Superficial water	0	<LD*	–	0	<LD	–
	1.13	1.08 ± 0.01	95.6	1.00	1.05 ± 0.01	105.3
Groundwater	0	<LD	–	0	<LD	–
	1.13	1.14 ± 0.04	100.9	1.00	1.18 ± 0.01	118.0
Wastewater outlet[a]	0	<LD	–	0	<LD	–
	1.17	1.15 ± 0.03	98.3	0.98	1.01 ± 0.02	103.1

The results are expressed as the mean of three replicates ± standard deviation.
[a] Dilution factor 1:1.
* LD: detection limit.

4. Conclusions

In this work, multi-syringe chromatography analysis has been combined with extraction disk for on-line solid-phase extraction, pre-concentration and determination of hydrochlorothiazide and losartan potassium in superficial water, groundwater and wastewater outlet samples has been developed. The system developed was proved for the determination of these chemical compounds in spiked water samples with a recoveries ranging from 95 to 118%. As compared with earlier methods for the determination of these pharmaceuticals, the proposed MSC disk-based system should be regarded as a time and cost-effective alternative to conventional chromatographic technique, such as liquid or gas chromatography for determination and resolution of pharmaceuticals in water samples, due to the possibility of on-line sample pre-treatment (solid-phase extraction), simplicity and low consumption of the organic solvents.

However, it should be made more studies related with the augment of the sample loading volumes in order to improve the detection limit and sensibility of the proposed method. Indeed, more sensitivity could be also reached by the use of liquid waveguide capillary cells (which allow increasing the optical path length up to 2 m) and other kind of special detectors.

Acknowledgments

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