DETERMINATION OF IBUPROFEN AND 1-HYDROXYIBUPROFEN IN AQUEOUS SAMPLES USING CORK AS A NATURAL PHASE IN ROTATING-DISK SORPTIVE EXTRACTION

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ABSTRACT

Ibuprofen is one of the most widely used nonsteroidal anti-inflammatory drugs due to its analgesic, anti-inflammatory and antipyretic properties, as well as its low cost and easy accessibility. A fraction of the compound and its metabolites are excreted in the urine, being eliminated in the wastewater reaching river waters in the range of ng L^{-1} to µg L^{-1}. In this context, highly sensitive and selective analytical methods are required to quantify them, including these methods a pre-concentration step. In this work, the use of a microextraction technology based on rotating-disk sorptive extraction, involving a sorptive phase of laminar cork, was implemented for the extraction of ibuprofen and 1-hydroxyibuprofen from aqueous samples and their subsequent determination by gas chromatography coupled to mass spectrometry.

The optimal conditions for determination of the analytes were: 20 mL of sample volume, pH 2, 20 % w/v NaCl (to increase the ionic strength), 90 min of extraction time and 2000 rpm of rotation velocity of the disk. Recoveries of 118 and 39 % and relative standard deviations of 6 and 13 % for ibuprofen and 1-hydroxyibuprofen were obtained, respectively. The presence of both compounds in river waters (Mapocho river, Santiago of Chile) at a concentration of 2.56 to 4.08 µg L^{-1} were found. The use of laminar cork as a natural sorbent phase immobilized in the rotating-disk allowed to extract the analytes from water samples through its lipophilic-hydrophilic balance that favors the interaction with the compounds under study.

Keywords: Cork, ibuprofen, 1-hydroxyibuprofen, natural sorptive phase, RDSE.

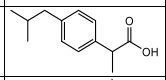
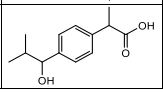
1. INTRODUCTION

Pharmaceutical products (PP) are natural or synthetic substances, or a mixture of both, whose purpose is to prevent, treat, cure or mitigate a disease or medical diagnosis, in many cases saving the life of a person or animal [1-2]. However, despite their indispensability for life, they are currently considered as emerging contaminants of the environment since they are excreted through urine and therefore, they can reach natural waters. This problem has generated a great controversy in recent years in the scientific community, since the presence of PPs in the environment impacts the environment that can be harmful to health [3-5]. It calls attention that something so fundamental to improve the quality of life can be at the same time causing damage to health and ecosystem.

Among the most popular and widely used PP worldwide are non-steroidal anti-inflammatory drugs (NSAIDs), including ibuprofen (IBU), which is frequently used for its anti-inflammatory, antipyretic, and analgesic properties [6]. Tons of IBU are generated each year, being considered by the Chilean Public Health Institute (ISP 2021, Chile) [7] third in the ranking of the most used drug after paracetamol and losartan in the January-October period in 2021. IBU is completely eliminated within 24 hours after its last dose and is excreted in relatively high amounts, approximately 70-80% of the drug, either in its original form or as a metabolite, being continuously disposed in wastewater [8-9]. Among its metabolites 1-hydroxyibuprofen (1-OH-IBU) is obtained by biological oxidation [10-11]. As shown in Table 1, both IBU and 1-OH-IBU are weak acids (pKa 4.5-5.3) and their ionizable properties allow them to have a high mobility in the aquatic environment. In the literature, the presence of IBU and 1-OH-IBU in wastewater has been reported to reach concentrations in the µg L^{-1} range for both influents and effluents of the wastewater treatment plants [12]. Since they are present in trace amounts and in highly complex matrices, a previous sample preparation step is generally required to isolate and preconcentrate the analytes of interest before introducing them to an analytical instrument for their determination. Since 2009, rotating-disk sorptive extraction (RDSE) has been successfully applied as a sample preparation technique, it has been applied for the determination of several emerging contaminants where different sorptive phases such as polydimethylsiloxane (PDMS), Oasis HLB, octadecylsilane (C18) and molecularly imprinted polymer (MIP) have been used [13]. Cork and montmorillonite clay have also been applied as natural phases in the RDSE to determine several compounds such as hormones, pesticides, BTEX, parabens and PAHS from water samples [14-16].

Cork is a natural raw material obtained from the bark of the cork oak (*Quercus surber L.*). It is cultivated in several countries where its largest world production (about 50%) occurs in Portugal [17]. Cork is characterized for being a renewable material, biodegradable, impermeable, good thermal and acoustic insulator, not very dense, elastic, rigid, stable, compressible, among others [18]. Its diverse chemical composition has motivated researchers to use it as a sorptive phase, since it is mainly composed of suberin (45%), lignin (33%) and polysaccharides (12%) (cellulose and hemicellulose) and contains some waxes and other compounds (15%) [19]. Although it is composed of hydrophobic molecules (lignin and suberin), interacting through Van der Waals forces and π-π type interactions (π-stacking) with low-polarity analytes, the variety of functional groups that it contains in its structure allows it to have a hydrophilic-hydrophobic balance that enables interactions through hydrogen bonds with more polar molecules. To the best of our knowledge, it is the first time that laminar cork is used as a natural sorptive phase in RDSE for the determination of IBU and 1-OH-IBU, in aqueous samples using gas chromatography coupled to mass spectrometry (GC-MS). Only analytes with more hydrophobic features had been studied by RDSE using cork as sorptive phase.

Table 1. Physico-chemical properties of target analytes.

Compound*	Structure	Molecular Formula	Molecular weight (g mol^{-1})	pKa	Log $K_{o/w}$	Water solubility (g L^{-1})	Ref.
IBU		$C_{13}H_{18}O_2$	206.285	4.91 – 5.3	3.97	0.021	[12,20]
1-OH-IBU		$C_{13}H_{18}O_3$	222.284	4.55	2.69	0.51	[12,20]

**IBU: ibuprofen, 1-OH-IBU: 1-hidroxyibuprofen.*

2. EXPERIMENTAL

2.1 Reagents

All reagents used in this study were of analytical grade. Deionized water obtained from a Simplicity® Water Purification System, Millipore (Darmstadt, Germany) was used for the experiments. Standards for the analytes IBU and 1-OH-IBU were purchased from Sigma-Aldrich (Milwaukee, United States). 3,3',4,4'-tetrachlorobiphenyl (PCB 77) purchased from Dr. Ehrenstorfer GmbH (Augsburg, Germany) was used as internal standard and ibuprofen-d_3 purchased from Cerillian Corporation (Texas, United States) was used as standard surrogate. The solvents acetonitrile (MeCN) and ethyl acetate (EtAc) (HPLC grade) used for phase conditioning and desorption of the analytes, respectively, were purchased from Merck (Darmstadt, Germany). N-methyl-N-(trimethylsilyl)trifluoroacetamide (MSTFA) derivatizing agent from Merck (Darmstadt, Germany) was used for the derivatization reaction.

Individual standard solutions of the analytes were prepared in methanol (MeOH, HPLC grade, 99.8% purity) from Merck (Darmstadt, Germany) at a

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concentration of 10 mg L^{-1} and the multistandard solutions of 2 mg L^{-1} were prepared in the same solvent. The solution of the internal standard (PCB 77) was prepared in ethyl acetate at a concentration of 1 mg L^{-1}. All standard solutions were stored at 4°C.

Nitrogen (purity ≥ 99.999%) and Helium (99.9999%) gases were obtained from Linde (Santiago, Chile) and were used for the evaporation of the final extract and as Carrier gas in GC-MS, respectively.

As sorbent phase, agglomerated laminar cork, made with 2 mm thick grains of 1 m x 1 m from Corchos Chile (Santiago, Chile), was used.

2.2 Instruments and Software

For the analysis of the samples, a Thermo Scientific Trace 1300 gas chromatograph (Milan, Italy) coupled to a Thermo Fisher Scientific ISQ (Austin, TX, USA) triple quadrupole mass selective GC-MS detector (Austin, TX, USA) was used as the analytical instrument. A Restek RTX-5MS (Bellefonte, PA, USA) fused silica capillary column (30 m x 0.25 mm i.d.; film thickness 0.25 µm) was used. Helium was used as Carrier gas at a rate of 1 mL min^{-1} and two microliters of the derivatized sample extract were injected into the chromatographic equipment where the splitless mode was used. The injector temperature was 280°C. The initial temperature program was 75°C (1 min) and increased to a temperature of 300°C at a rate of 15 °C min^{-1} (5 min). The analysis time for each run was 21 min with a solvent delay of 7 min. The transfer line temperature was 300 °C and the source temperature was 250 °C. The quantification of the compounds was based on the selective ion monitoring (SIM) mode. The quantifier and qualifier ions for IBU and 1-OH-IBU selected were 160, 234 and 323, 324 m/z, respectively, the retention times were 9.58 min for IBU and 10.91 min for 1-OH-IBU.

A Nicolet iS5 Fourier transform infrared spectrophotometer (FT-IR), Thermo Scientific, coupled to an iTX-iD7 attenuated total reflectance (ATR) smart sampling accessory with diamond crystal was used to characterize the sorbent phase. OMNIC 8.0 software (Thermo Scientific) was used to resolve the spectra. The wavenumber range was 4,000 to 400 cm^{-1}. A resolution of 4 cm^{-1} and with a scanner number of 16, for each sample.

A MR 300 magnetic multi-stirrer (Heidolph Instrument, Germany) was used for the extraction. The pH values were determined from a WTW pH-meter pH model pMX 3000 (USA). A KMC-1300V vortex shaker (Vision Scientific Co., Ltd., Korea) and an analog heat block evaporator (VWR, USA) were used in the sample preparation methodology.

Statgraphics Centurion XV statistical software for Windows (Magnugistics, USA) was used for the chemometric design employed in the optimization of RDSE.

2.3 Preparation of the rotating-disk

The device used in RDSE is shown in Figure 1. A 1.5 cm diameter Teflon-cover disk containing a mini magnetic bar inside (Teflon-coated Micro Stir bar from VWR International) and having a cavity of 0.1 cm^3 on one of its surfaces was used.

The preparation of the sorbent phase (laminar cork) was based on previously reported by Manzo *et al*. 2019 [14]. Circular pieces (of 47 mg) were cut with a punch, equivalent to the area of the disk cavity. The circular pieces were sonicated once with deionized water for 60 min and twice with methanol for 30 min. Then, the phase was dried in an oven at 37°C for 20 min. It was placed on the disk and sealed with the Teflon-cover. Prior to extraction, in a glass vial, the disk with the phase was conditioned with acetonitrile and deionized water for 10 min at 2000 rpm for each.

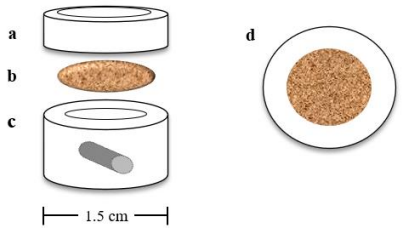

Figure 1. Rotating-disk with cork laminar sorbent used in this study. a) Teflon-cover; b) Laminar cork; c) Rotating-disk (including an inserted magnet); d) Top view of the rotating system.

2.4 Rotating-Disk Sorptive Extraction procedure

For extraction, a 20 mL aliquot of sample was added to a glass vial containing the disk with the sorbent phase. HCl 1 mol L^{-1} was used to adjust the pH of the samples (pH 2) and 20% NaCl for ionic strength. For the optimization experiments, the solution was spiked with a multistandard solution of the analytes at a concentration of 30 µg L^{-1} and stirred at 2000 rpm for 90 min at room temperature. For desorption of the analytes, the disk was transferred to another vial and 10 mL of ethyl acetate was added. It was stirred for 20 min at 2000 rpm. Then, the ethyl acetate extract containing the concentrated analytes was evaporated under a stream of N_2 to dryness at 60°C. For derivatization, 50 µL of MSTFA and 50 µL of ethyl acetate were added and shaken for 5 min at room temperature. Prior to injection into the GC-MS, 30 µL of PCB-77 (1 mg L^{-1}) was added as an internal standard.

2.5 Analytical figures of merit and application in environmental aqueous sample

Figures of merit such as calibration curve (determination coefficient), limit of detection, limit of quantification, precision and accuracy (ICH guidelines) were determined from the proposed method with the respective optimized conditions and using river water as matrix. The calibration curve and the determination coefficient (R^2) were studied in a linear range from 5 to 60 µg L^{-1} where 5 concentration levels were considered. The limits of detection (LOD) and limits of quantification (LOQ) were determined from six blank samples, based on the mean and the sum of 3 or 10 times the standard deviation of the blank ($LOD = \bar{X} + 3\sigma$, $LOQ = \bar{X} + 10\sigma$), then extrapolated on the calibration curve. The precision of the method was based on that of the relative standard deviation (%RSD, n = 6) and the accuracy was determined from the recovery (%Re).

The applicability of the method was studied in a real sample, river water (Canoa site, Mapocho river, Santiago of Chile), using the proposed method. Prior to analysis, the collected samples were filtered and stored in polypropylene bottles at 4°C. A 20 mL aliquot of sample was taken, adjusted to pH 2 and 20% NaCl was added (in duplicate), and analyzed by the optimized RDSE method.

3. RESULTS AND DISCUSSION

3.1 Sorbent phase characterization

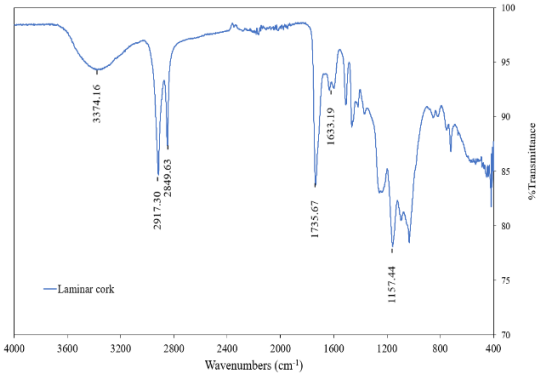

Figure 2. FTIR spectrum of the laminar cork.

Figure 2 shows the FTIR spectrum obtained from laminar cork. As can be observed, it is similar to the spectra previously reported in literature [21]. At higher wavenumber a broad band of low intensity is observed at approximately 3400 cm^{-1}, characteristic of the OH groups, and two sharp and intense bands between 2800 and 2900 cm^{-1}, in the stretching region of the CH groups. These bands are mainly associated with contributions from polysaccharides and biopolymers, lignin and suberin, in this case, molecules possessing several hydroxyl groups and aliphatic carbons. At 1736 cm^{-1} a sharp band of stretching is observed corresponding to the C=O groups of the ester functional groups that form the structure of suberin. In the aromatic region between 1500 and 1600 cm^{-1} two low intensity peaks are observed which are attributed to stretching of C=C bonds of the benzene rings that form the structure of both lignin and suberin. Between 1100 and 1300 cm^{-1} contributions from stretches of C-O bonds present in methoxy (OCH_3) groups of lignin, polysaccharides and suberin are observed.

This information helps to predict the types of interactions that may exist between the cork and the analytes, either by hydrogen bonding through the hydroxyl and carbonyl groups and hydrophobic interactions such as Van der Waals forces and π-stacking through the benzene rings, where the latter should be in the majority recalling the fact that the phase is composed mainly of highly hydrophobic suberin and lignin molecules.

3.2 Optimization of RDSE

The optimization of the different factors that could affect the extraction procedure of the analytes was carried out. To achieve the best extraction efficiency of IBU and 1-OH-IBU using the laminar cork biosorbent, the chemical and hydrodynamic variables were studied: pH, salt concentration (%w/v), extraction time, rotation velocity and sample volume.

3.2.1 Study of chemical variables

IBU and 1-OH-IBU are acidic substances that are affected (protonated or deprotonated) by pH changes, which directly influence in the adsorption of the analytes in the sorptive phase. Therefore, it was important to evaluate the effect of the pH of the medium, in order to carry out an efficient extraction. The analytical responses of the compounds as a function of four the different pH in the range 2 to 9 were studied. Different solutions were used (a 1 mol L^{-1} dibasic sodium phosphate buffer solution of pH 6.5, a 1 mol L^{-1} HCl solution and a 0.05 mol L^{-1} NaOH solution) to adjust the pH. As shown in Figure 3 the extraction was favored at pH 2 for both analytes, at this pH the compounds are fully protonated or in their neutral form favoring not only the Van der Waals and hydrophobic forces (π-π stacking) between the analytes and the sorbent phase, but also the interaction through hydrogen bonds. On the contrary, at pH higher than pKa of the analytes, these are ionized (with negative charge) causing hydrogen bonding interactions between analyte-sorptive phase, the main intermolecular force of IBU and metabolites, to be cancelled.

NaCl salt is an ionic modifier that increases the ionic strength of the aqueous sample, allowing polar or semi-polar analytes (such as IBU and its metabolite) to decrease their solubility and facilitate the transfer of the compounds from the water sample to the extraction phase (salting-out effect) [22]. In this study, different concentrations of NaCl from 0 to 30% w/v were studied. As shown in Figure 4 for IBU and 1-OH-IBU, the extraction efficiency increases at higher salt concentrations (20-30% w/v). It was established as optimal to use NaCl at 20% since a lower dispersion of the data is obtained, mainly for IBU, compared to the 30% concentration. The large dispersion of the data at higher salt concentrations is attributed to the fact that during the extraction process the salt is dragged, inside the disk, which can interfere in the final steps of derivatization and injection in the equipment, leading to larger experimental errors.

Previous reports where IBU has been determined using RDSE with others sorptive phases, have also shown that extraction is favored using sample at pH 2 [23-24]. On the other hand, it has not been reported a large amount of salt to improve the extraction process of IBU, however, Viera *et al*. 2018 [15] reported the use of large amounts of salt (30% NaCl) for the determination of parabens from water samples using cork powder as sorbent phase.

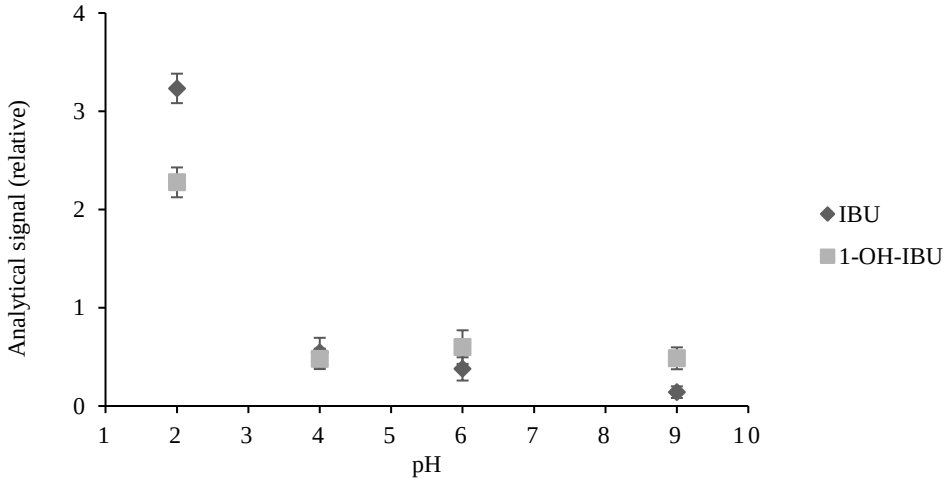

Figure 3. Effect of pH on the analytical signal (20 mL of sample, velocity of rotation 2000 rpm for 60 min, n = 3).

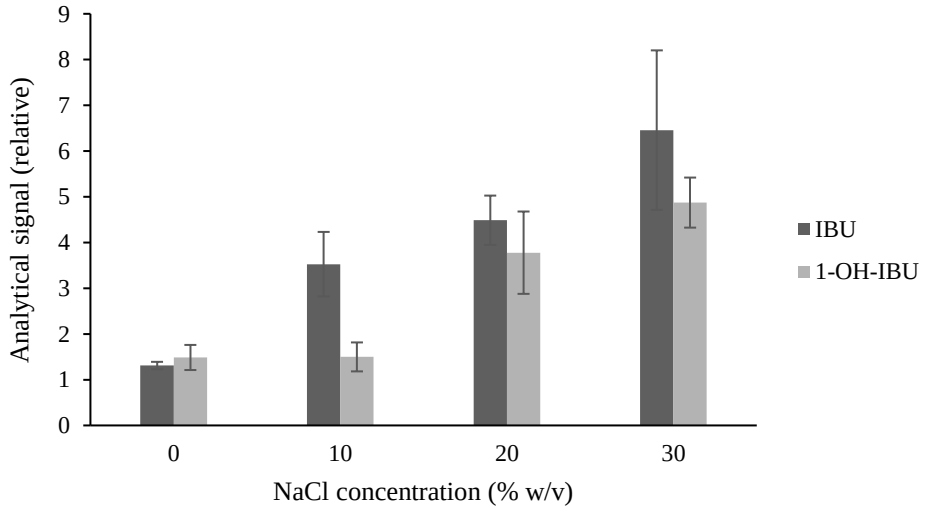

Figure 4. Effect of the NaCl concentration on the analytical signal (pH 2, 20 mL of sample, velocity of rotation 2000 rpm for 60 min, n = 3).

3.3 Study of hydrodynamic variables

Previous studies by RDSE shows that the most important hydrodynamic variables in the analyte extraction efficiency are rotation velocity of the disk, sample volume and extraction time [13], being rotation velocity the most important factor to be consider, mainly from a kinetic point of view (mass transfer of the analyte) [25-26]. To have a shorter extraction time, the rotation velocity must be increased to favor the mass transfer of the analyte in the sample. However, as the volume of the sample increases, rotation velocity should be increased concomitantly to kept a relatively constant equilibrium time. For this, it is important to evaluate the three factors simultaneously because they are interrelated.

A multivariate study was designed to evaluate the variables sample volume, extraction time and velocity of rotation using a response surface based on the Doehlert design. This design allows assigning different levels to each factor according to its weight or relevance [27]. Rotation was assigned 7 working levels (X2), considering it as the most significant variable, extraction time was assigned 5 levels (X1) and sample volume 3 levels (X3). The normalized chromatographic areas of the analytes were taken as the response variable and a total of 15 experiments were carried out, including three centers. Table 2 shows the matrix of experiments used in the optimization analysis. To evaluate the quality of the model, an ANOVA statistical analysis of the regression was performed where, for both responses, a p-value < 0.05 was obtained between the variance of the model and the residuals and a p-value > 0.05 between lack of fit and the pure error indicating that the model is adequate to describe the data.

In order to find the compromise zone and the optimal point between the study variables, multi-response optimization was analyzed using the desirability function (D), giving the same impact to each of the variables. Figure 5 shows the desirability contour surface for the study analytes. The overall desirability was 0.874781. The optimum values to achieve a higher chromatographic response are obtained with an extraction time of 90 min, 20 mL for the sample volume and a velocity of 2000 rpm. The latter is consistent with the fact mentioned above, higher velocity of rotation increases the mass transfer of the analyte from the sample to the phase and decreases the stagnant layer of water present in the aqueous system and the extractive phase.

Table 2. Matrix of experiments (Doehlert design) for the study of hydrodynamic variables using cork as sorbent phase in RDSE

Experiment	Coded values			Real Values		
	X1	X2	X3	Time (min)	Velocity (rpm)	Volume (mL)
1	0	0	0	60	1100	20
2	1	0	0	120	1100	20
3	0.5	0.866	0	90	2000	20
4	-0.5	0.866	0	30	2000	20
5	-1	0	0	0	1100	20
6	-0.5	-0.866	0	30	200	20
7	0.5	-0.866	0	90	200	20
8	-0.5	-0.289	-0.816	30	800	10
9	0	0.577	-0.816	60	1700	10
10	0.5	-0.289	-0.816	90	800	10
11	-0.5	0.289	0.816	30	1400	30
12	0	-0.577	0.816	60	500	30
13	0.5	0.289	0.816	90	1400	30
14	0	0	0	60	1100	20
15	0	0	0	60	1100	20

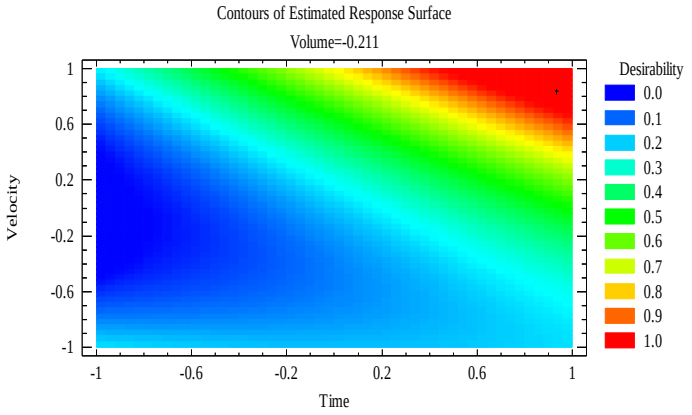

Figure 5. Response surface of global desirability for the study of hydrodynamic variables.

3.4 Figures of merit and determination of analytes in a real sample

For the validation of the method, the figures of merit associated with the optimized methodology were studied. Table 3 summarizes the analytical features of the method obtained for IBU and 1-OH-IBU. It was found a linear calibration graph using five levels of concentrations, with R^2 coefficients > 0.98, indicating an adequate linear fit. Low LOD and LOQ (in the order of ng L^{-1}) were obtained for both IBU and 1-OH-IBU, which were determined using a drinking water (n = 6) matrix. Accuracy and precision were studied through the recovery (%Re) and relative standard deviation (%RSD).

The %Re were between 39 and 118%, being IBU the most efficiently extracted analyte which can be associated to their higher affinity with cork. IBU had a recovery close to 100% since it is related to ibuprofen-d_3 (surrogate standard), whereas 1-OH-IBU had a recovery lower since it is a more polar compound and has a different behavior than labeled ibuprofen. Finally, % RSD were less than 13% for the analytes. Previously, the determination of pharmaceuticals in urine samples using cork as sorbent phase in disposable pipette extraction (DPX) has been reported. In this work, RSD of 20.9% and LOD and LOQ of 3 and 10 ng mL^{-1}, respectively were reported for IBU [28], which are higher than those reported in our work.

Table 3. Figures of merit for analytes.

Compound	Sensitivity (L μg^{-1})	Linearity (R^2)	Accuracy [a]	Precision [a]	LOD [b] (ng L^{-1})	LOQ [b] (ng L^{-1})
			%Re (relative)	%RSD (n = 6)		
IBU	0.0234	0.9866	118	6	12	26
1-OH-IBU	0.0161	0.9969	39	13	9	25

[a] river water, [b] drinking water.

The proposed methodology was applied in river water (Canoa site, Mapocho river, Santiago of Chile) where a calibration curve was performed in enriched matrix from 0 to 60 µg L^{-1} (n = 5, in duplicate) for both analytes (IBU and 1-OH-IBU). The concentrations obtained for IBU and 1-OH-IBU in river water were 2.6 ± 0.5 µg L^{-1} and 4.1 ± 0.8 µg L^{-1} respectively. This result is consistent with the fact that ibuprofen hydroxylated metabolites are excreted to a greater extent than the original compound.

Finally, the efficiency of the laminar cork phase was compared with other commercial phases (C18, Oasis HLB and S-DVB) by applying the proposed method for the extraction of analytes by RDSE. Figure 6 shows the results of the comparison. As can be seen, for IBU the laminar cork had similar extraction efficiencies to the other commercial phases and higher than the C18 film, however, although 1-OH-IBU in cork has a quite good analytical response, it provides lower efficiencies compared to the observed with other synthetic phases. Nevertheless, the laminar cork is a renewable, economical and biodegradable material that allowed detecting the analytes in a similar way to the commercial phases.

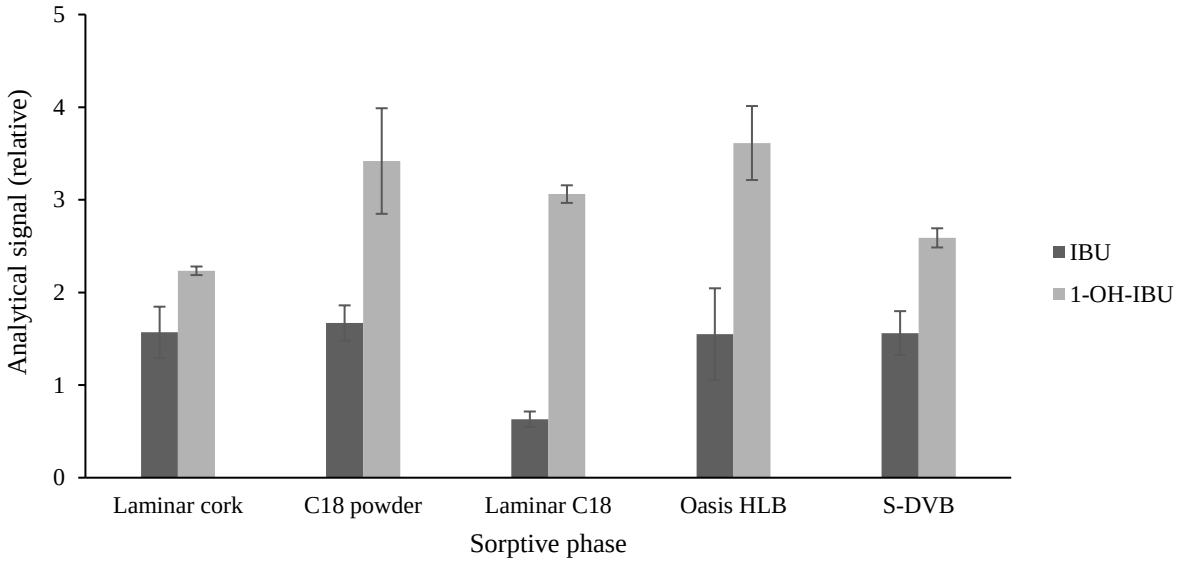

Figure 6. Comparison of commercial sorbent phases with laminar cork (This study was carried out with 20 ml of sample, 2000 rpm and 90 min).

CONCLUSIONS

The RDSE technique using laminar cork as a sorbent phase allowed the extraction of analytes with intermediate polarity range, such as ibuprofen and its metabolite, in water samples with efficiencies similar to commercial phases. In addition to this, cork allows a much greener and more economical methodology to be carried out. Ibuprofen was extracted to a greater extent than its hydroxylated metabolite, however both compounds could be extracted and determined in real samples of river water.

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