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Multiclass Determination of Pharmaceuticals in Surface Water Samples by SPE and UHPLC-MS/MS for Environmental Risk Assessment

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Abstract

The presence of pharmaceuticals in the environment is a reality, and the risk of serious problems to people and the environment is cause for great concern. To get a real overview of the current situation, it is necessary to know the concentrations at which these compounds are found in the aquatic environment. Therefore, the present work aimed to develop and validate a method for the multiclass determination of 36 pharmaceuticals in water using solid-phase extraction (SPE) and ultra-high-performance liquid chromatography with tandem mass spectrometry (UHPLC-MS/MS). The results of accuracy and precision obtained for the validated levels were between 53 and 113%, with a relative standard deviation (RSD) ≤ 17%. The method quantification and detection limits were 1 and 0.3 ng L^{-1}, respectively, for most of the compounds. The validated method was applied to surface water samples, and the results indicated that all samples were contaminated with at least 4 different compounds. Subsequently, an environmental risk assessment was carried out based on the calculation of the risk quotient (RQ). The pharmaceutical losartan was the only compound with RQ > 1 and, therefore, classified as having high environmental risk. The proposed method is considered suitable for the determination of multiclass pharmaceuticals in surface water at very low levels and can be applied in routine analyses due to its reliability and simplicity.

Keywords: water; pharmaceuticals; SPE; UHPLC-MS/MS; risk assessment

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1. Introduction

Although pharmaceuticals bring benefits to human health and quality of life, they can pose a serious environmental problem. After use, some of these substances are excreted and enter urban sewage systems, which may or may not be treated [1,2]. In the case of treatment, conventional wastewater treatment plants are not capable of completely removing all pharmaceuticals present. As a result, these compounds end up entering water bodies directly, which later serve as water intake points; the water then undergoes purification processes that are also unable to remove these compounds [3]. One of the major challenges related to pharmaceuticals is that they are persistent and can accumulate in the environment over time. Furthermore, several of these compounds can be toxic to aquatic organisms. Studies suggest that prolonged exposure to these substances can have negative impacts on animals and aquatic organisms, including behavioral changes, developmental alterations, and hormonal imbalances [4]. To truly grasp the scope of the problem, it is necessary to

know the concentrations of these compounds in the samples. Generating this information enables the establishment of monitoring programs.

The concentrations of most pharmaceuticals in aquatic matrices generally range from ng L^{-1} to μg L^{-1}, requiring a preliminary sample preparation step to concentrate these compounds prior to analysis [5]. In this context, solid-phase extraction (SPE) stands out as a well-established technique that allows for the concentration of analytes and the removal of most interferents. SPE, particularly when using polymeric sorbents, combined with liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS), has proven to be an efficient and widely used combination for the determination of pharmaceuticals in aquatic matrices [6–16]. The LC-MS/MS technique combines liquid chromatography separation with the sensitivity and selectivity of tandem mass spectrometry. This allows for the simultaneous determination of a wide range of compounds present in complex samples, such as water, effluents, soil, food, and others. Other advantages of using the LC-MS/MS technique include the ability to develop broad multi-class methods, which significantly reduces the cost of analysis [17].

World population growth has resulted in high demands on water supplies, whether for domestic consumption, industrial production, or agricultural irrigation [18]. The lack of adequate infrastructure for wastewater treatment leads to the contamination of water bodies by domestic and hospital effluents [19]. Brazilian legislation does not establish maximum limits for emerging contaminants, such as pharmaceuticals. The European Union (EU) has more comprehensive water monitoring programs that are constantly updated. In 2013, a watch list was created to improve the information available regarding the identification of substances of greatest concern, which includes certain pharmaceuticals. Member States must monitor the substances on the list at least once a year. The watch list was established in 2015 and updated in 2018, 2020, and again in 2022 [20]. The number of pharmaceuticals monitored has gradually increased over the years, and the trend is set to continue growing. The inclusion of these compounds is in line with the European Union's Strategic Approach to Pharmaceuticals in the Environment and, in the specific case of antibiotics, with the European "One Health" Action Plan against Antimicrobial Resistance [21].

Contaminants of emerging concern (CECs), such as pharmaceutical and personal care products (PPCPs), flame retardants, and plasticizers, constitute special classes of contaminants in aquatic matrices, as they have the potential to cause adverse effects on both the environment and human and animal health [22]. These compounds are not necessarily new pollutants, but their presence and significance have only recently begun to be assessed [23–25]. Wastewater treatment plants (WTPs), as well as the discharge of raw sewage, are the main entry points for these contaminants into water bodies, particularly surface waters, which serve as sources of water intake for WTPs. However, most of the treatments to which water is subjected at the WTPs are not effective in completely removing these compounds [1,3]. The environmental effects associated with CECs are attributed to chronic exposure of organisms, since they occur at extremely low concentrations. This aspect makes the management and risk assessment of these compounds even more complex. Most pharmaceuticals are water-soluble, which facilitates their transport in aqueous media, although some may be strongly adsorbed to soil or sediment [26]. In recent decades, contaminants from a broad spectrum of therapeutic classes have been detected in nearly all environmental matrices and on every continent, albeit at low concentrations. This includes surface water [27–30], groundwater [12,13,31], and wastewater [32–34].

Efficient and reliable preconcentration methods are necessary to assess the occurrence, distribution, and migration of pharmaceuticals in the environment [35]. Solid-phase extraction is a well-established and universally applicable sample preparation technique for the determination of pharmaceuticals in aquatic matrices [6]. According to Table S1,

there are many recent studies that involve the determination of PPCPs in water samples using SPE. Among these publications, some determine PPCPs, but most determine only pharmaceuticals. The remaining studies include, in addition to these compounds, pesticides, illicit drugs, plasticizers, disinfectants, biomarkers, stimulants, and perfluorinated compounds. Among the most used SPE sorbents, Oasis HLB stands out, as it is used in 73% of these applications. As a polymeric sorbent, it is widely used in the extraction of compounds with different polarities, such as pharmaceuticals. In second place (9%) is the Strata-X sorbent, which is also a polymer-based product. Regarding the analysis, liquid chromatography with tandem mass spectrometry is the predominant technique, due to the high solubility of these compounds in water. This technique allows for quantification at very low concentration levels.

Thus, considering the importance of analyzing pharmaceuticals in water samples at very low levels, this study aimed to develop, validate, and apply an efficient and easy-to-perform multi-class method for the determination of pharmaceuticals in surface water samples using SPE and UHPLC-MS/MS, as well as to assess the associated environmental risk.

2. Results and Discussion

2.1. UHPLC-MS/MS Established Conditions

For selected reaction monitoring (SRM) acquisition mode, the two transitions with the highest intensity were selected for each compound. The quantification and identification transitions for SRM mode, retention time, cone energy, and collision energy are presented in Table S2. Negative electrospray ionization (ESI-) mode was used only for mefenamic acid, aldosterone, nimesulide, and triclosan; the remaining compounds were analyzed in positive mode. Figure S1 shows the total ion chromatograms of some representative compounds from different drug classes, including analgesics, anti-inflammatory drugs, hormones, antibiotics, and beta-blockers, analyzed in this study.

2.2. Evaluation of the Sample Preparation Method

2.2.1. Selection of SPE Sorbents

Of the ten sorbents evaluated, using a blank sample spiked at 100 ng L^{-1}, the three best were selected for subsequent testing. Figure 1 shows the relationship between the sorbents and the number of compounds with recoveries from 60 to 115%, out of a total of 36 compounds initially under study.

Although the Oasis HLB (60 and 200 mg) and Strata-X (60 and 200 mg) sorbents recovered a similar number of compounds, it was decided to evaluate only those containing 200 mg, as they recovered more compounds than the 60 mg ones. The third sorbent chosen was Sep-Pak C18 500 mg, as it is a more affordable non-polymeric sorbent. Thus, the Factor A levels for the factorial design were: Strata-X 200 mg (−1), Oasis HLB 200 mg (0), and Sep-Pak C18 500 mg (+1). A full factorial design was conducted to evaluate whether varying the pH or increasing the amount of EDTA would improve the extraction efficiency of these sorbents. Initially, the intention was to evaluate a pH below 4 in this design. However, EDTA salts are more soluble in water as pH increases and less soluble as pH decreases, which would make it impossible to evaluate them at very low pH levels. The factorial design with the variables pH, amount of EDTA, and sorbents generated a total of 27 experiments, which were conducted simultaneously. This evaluation was performed using blank samples spiked at 100 ng L^{-1}. The number of compounds, out of a total of 36 analytes, with recovery considered satisfactory (60 to 115%) in each experiment is shown in Figure 2.

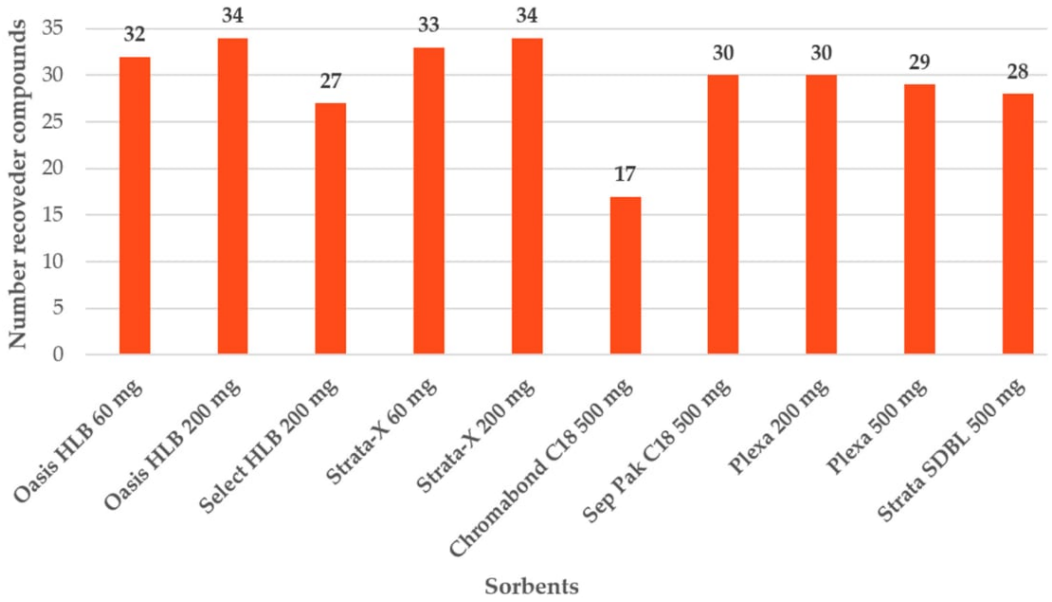


Figure 1. Number of compounds recovered between 60 and 115% using different sorbents.

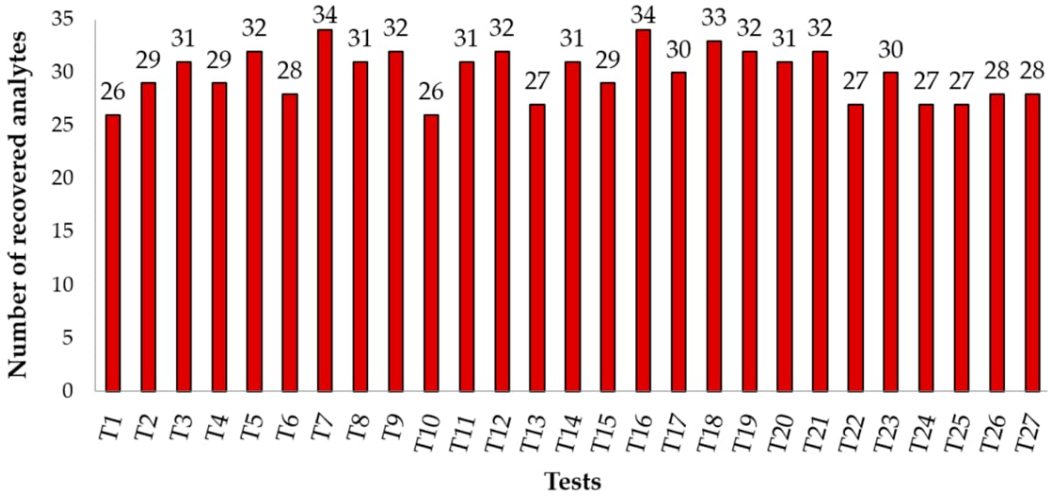


Figure 2. Number of compounds with recovery from 40 to 120% for the full factorial design tests.

The data from the factorial design were evaluated using a Pareto chart (Figure S2) to determine which variables had the greatest influence on the results. From the diagram, it was observed that none of the variables proved to be statistically significant ($p > 0.05$) at the 95% confidence level, although pH was the variable that came closest to the *p*-value of 0.05. Consequently, it was followed by an evaluation considering the parameters that yielded the highest number of compounds with recoveries in the range of 60 to 115% (T7, T16, and T18).

2.2.2. Selection of the Extraction Method Conditions Based on the Factorial Design

For tests T7 (Strata-X 200 mg, pH 6.0, and 0.1% EDTA), T16 (Oasis HLB 200 mg, pH 6.0, and 0.1% EDTA), and T18 (Oasis HLB 200 mg, pH 6.0, and 0.3% EDTA) in the factorial design, adequate recoveries (40 to 120%) were obtained for 34, 32, and 31 compounds, respectively. Several studies have reported that polymeric sorbents provide good results for analytes with a high polarity difference [7,36–42]. Figure 3 shows the recovery and RSD results obtained for the evaluated compounds in tests T7, T16, and T18.

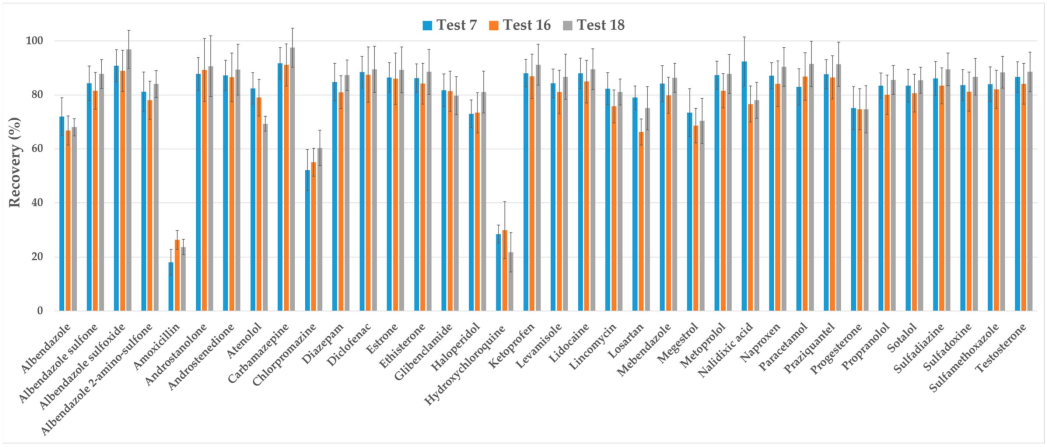


Figure 3. Recovery and RSD values for the compounds in tests T7, T16, and T18 ($n = 6$).

As shown in Figure 3, amoxicillin and hydroxychloroquine were the only compounds that exhibited recoveries below 30% in all three tests conducted. Domínguez-García et al. [34] obtained a recovery of 78% for hydroxychloroquine in river water samples only at pH 7 during the SPE step with Oasis HLB 200 mg. In the case of antibiotics, there is typically a dependence on the sample's pH, whether related to the retention of the compounds or to their degradation [43]. Several authors report the need to adjust the sample to more acidic pH levels (<4) to preconcentrate amoxicillin [44–47]. Fabregat-Safont et al. [48] also reported that the determination of amoxicillin in water samples is quite difficult due to its polar nature, which directly affects SPE-based procedures because of the risk of compound loss in both C_{18}-type and polymeric sorbents. These authors emphasize that the stability of amoxicillin in water samples under different storage conditions still needs to be carefully evaluated in further studies [48]. Furthermore, β-lactam antibiotics are difficult to analyze using multiclass methods due to the chemical instability associated with the β-lactam ring [47]. Therefore, we chose to proceed with the evaluation of the SPE method without the compounds amoxicillin and hydroxychloroquine. The test that yielded the highest number of compounds with recovery values within the 40–120% range was T7, with 34 compounds, which uses Strata-X (200 mg), pH 6.0, and 0.1% EDTA. These conditions were selected for the next tests.

2.2.3. Selection of Elution Volume

Elution volumes of 1 and 2 mL were evaluated to maximize the concentration factor as much as possible. A high concentration factor in the SPE step is especially important for the determination of pharmaceuticals, since these compounds are expected to be present at very low concentrations (ng L^{-1}) in surface water samples. The recovery results obtained in the elution tests using 1 and 2 mL, with a spiking level of 100 ng L^{-1}, indicated that all compounds evaluated showed acceptable recoveries for both volumes. Consequently, it was decided to use an elution volume of 1 mL, which resulted in a concentration factor of 50.

2.3. Established Sample Preparation Procedure

The sample preparation procedure established in this study for the determination of pharmaceuticals in surface water samples by UHPLC-MS/MS, after a preconcentration of the analytes by SPE using the polymeric sorbent Strata-X, is presented in Figure 4.

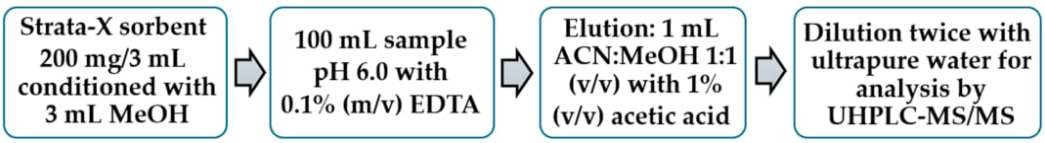


Figure 4. Schematic representation of the proposed method.

2.4. Validation of the Method

The selectivity of the proposed method proved to be satisfactory, given the presence of no interferents in the blank matrix. The linearity of the method, evaluated by plotting three calibration curves in the elution solvent, was considered adequate, with a coefficient of determination (r^2) between 0.9937 and 0.9996 and a linear range between 0.05 and 10 µg L^{-1}. The accuracy and precision of the method, evaluated at three spiking levels with seven replicates each (n = 7), yielded satisfactory results with recoveries between 53 and 113% and RSD ≤ 17%, both in the repeatability test and in the intermediate precision test. Considering the concentration factors for SPE and extract dilution, the final concentration factor of the method was 50-fold. The method limit of quantification (LOQ), considering the lowest spike level that could be validated with acceptable recoveries and RSD, was 1 ng L^{-1} for most of the compounds. Only albendazole, levamisole, paracetamol, and sotalol presented a limit of detection (LOD) of 2 ng L^{-1}. The method LOD, calculated by dividing the LOQ by 3.33, yielded results from 0.3 to 0.6 ng L^{-1}. Table 1 presents the results related to method validation.

Table 1. Results for the coefficient of determination (r^2), accuracy (recovery, %), and precision (relative standard deviation, RSD %) of the method at different spike levels.

Compounds	LOD (ng L^{-1})	LOQ (ng L^{-1})	Repeatability: Recovery (RSD), %			Intermediate Precision Recovery (RSD), %		
			Spike Levels (ng L^{-1}), n = 7			Spike Levels (ng L^{-1}), n = 7		
			1	2	20	1	2	20
Albendazole	0.6	2	35 (5)	53 (7)	73 (3)	60 (3)	72 (2)	79 (2)
Albendazole 2-aminosulfone	0.3	1	84 (3)	78 (5)	88 (3)	77 (5)	83 (4)	88 (5)
Albendazole sulfone	0.3	1	90 (6)	82 (6)	93 (2)	92 (3)	90 (3)	96 (2)
Albendazole sulfoxide	0.3	1	90 (9)	84 (8)	94 (4)	83 (5)	84 (3)	96 (5)
Androstanolone	0.3	1	101 (9)	89 (6)	94 (3)	99 (8)	86 (4)	95 (3)
Androstenedione	0.3	1	92 (4)	86 (7)	91 (2)	94 (3)	87 (4)	93 (5)
Atenolol	0.3	1	82 (9)	62 (4)	75 (6)	75 (3)	81 (4)	66 (6)
Carbamazepine	0.3	1	78 (12)	81 (10)	110 (5)	109 (5)	103 (6)	119 (6)
Chlorpromazine	0.3	1	59 (10)	62 (11)	64 (11)	57 (7)	61 (6)	72 (10)
Diazepam	0.3	1	104 (3)	97 (6)	110 (3)	96 (12)	99 (10)	112 (7)
Diclofenac	0.3	1	106 (4)	89 (7)	94 (3)	94 (4)	92 (4)	95 (4)
Estrone	0.3	1	100 (17)	107 (10)	101 (6)	111 (8)	90 (5)	97 (5)
Ethisterone	0.3	1	80 (7)	87 (7)	99 (2)	101 (6)	89 (3)	98 (7)
Glibenclamide	0.3	1	95 (6)	76 (10)	92 (4)	91 (16)	84 (5)	97 (3)
Haloperidol	0.3	1	48 (8)	61 (10)	83 (5)	57 (5)	73 (5)	86 (8)
Ketoprofen	0.3	1	104 (7)	84 (5)	88 (3)	94 (3)	87 (4)	89 (3)
Levamisole	0.6	2	-	65 (5)	96 (3)	47 (4)	91 (7)	101 (2)
Lidocaine	0.3	1	106 (11)	80 (5)	94 (1)	104 (3)	88 (4)	98 (3)
Lincomycin	0.3	1	54 (7)	56 (5)	79 (2)	73 (4)	80 (4)	84 (2)
Losartan	0.3	1	102 (5)	84 (6)	89 (4)	103 (5)	85 (4)	93 (5)
Mebendazole	0.3	1	78 (5)	76 (4)	91 (1)	88 (4)	87 (3)	95 (2)
Megestrol	0.3	1	70 (4)	74 (6)	79 (11)	75 (3)	78 (7)	84 (9)

Table 1. *Cont.*

Compounds	LOD (ng L^{-1})	LOQ (ng L^{-1})	Repeatability: Recovery (RSD), %			Intermediate Precision Recovery (RSD), %		
			Spike Levels (ng L^{-1}), n = 7			Spike Levels (ng L^{-1}), n = 7		
			1	2	20	1	2	20
Metoprolol	0.3	1	77 (7)	72 (6)	89 (1)	76 (4)	84 (3)	92 (4)
Nalidixic acid	0.3	1	86 (17)	74 (9)	102 (14)	61 (13)	79 (8)	91 (17)
Naproxen	0.3	1	96 (12)	96 (12)	94 (9)	106 (9)	93 (12)	96 (6)
Paracetamol	0.6	2	-	73 (14)	82 (14)	51 (6)	70 (6)	64 (5)
Praziquantel	0.3	1	108 (5)	96 (6)	105 (1)	97 (4)	96 (4)	108 (4)
Progesterone	0.3	1	81 (7)	76 (10)	80 (11)	82 (3)	80 (6)	82 (9)
Propranolol	0.3	1	65 (7)	67 (5)	87 (3)	80 (4)	82 (4)	92 (5)
Sotalol	0.6	2	-	90 (11)	86 (4)	50 (3)	80 (4)	87 (3)
Sulfadiazine	0.3	1	90 (8)	89 (7)	102 (2)	86 (3)	98 (4)	107 (4)
Sulfadoxine	0.3	1	113 (4)	102 (7)	98 (3)	107 (6)	97 (5)	104 (3)
Sulfamethoxazole	0.3	1	111 (5)	101 (6)	99 (2)	106 (4)	97 (3)	100 (3)
Testosterone	0.3	1	89 (4)	86 (6)	96 (1)	89 (3)	89 (4)	98 (5)

Chaves et al. [49] obtained slightly higher LOQ values (4 ng L^{-1}) for albendazole, glibenclamide, mebendazole, and propranolol using a method that also employed the Strata-X sorbent (200 mg) followed by LC-MS/MS analysis. However, to achieve these limits, the authors used a sample volume of 1 L, in addition to an additional evaporation step for the 4 mL of eluate. Alharbi et al. [41], on the other hand, reported higher LOQ values for atenolol (230 ng L^{-1}) and diclofenac (150 ng L^{-1}) when using the Strata-X sorbent (200 mg) and a sample volume of 500 mL, with an evaporation/reconstitution step required for the 6 mL of eluate. This procedure, in addition to demanding more time for sample preparation, can lead to loss of analyte due to evaporation or degradation.

Other studies in the literature that use polymeric sorbents, such as Strata-X and Oasis HLB, generally report low LOQ levels for drugs when large sample volumes are used [9–13,38,40,50] and/or evaporation/reconstitution steps [39,51–53]. The proposed method achieved low LOQ values without the need for additional steps or large sample volumes, which make the procedure more time-consuming and can lead to clogging of the SPE cartridge. Finally, the method developed made it possible to achieve low LOQs in less time compared to the other methods described in the literature.

2.5. Application to Surface Water Samples

Application of the proposed method to surface water samples from different regions of the state of Rio Grande do Sul, Brazil, revealed the presence of various pharmaceuticals in concentrations ranging from 1 to 254 ng L^{-1}. Table 2 presents the concentration values for each of the compounds detected in the samples, as well as their respective LOQ values. All 22 samples analyzed contained at least four different pharmaceuticals. The four most frequently quantified pharmaceuticals were albendazole (22 samples), albendazole sulfoxide (22 samples), carbamazepine (15 samples), and losartan (14 samples). Albendazole 2-aminosulfone, diazepam, praziquantel, and sulfadiazine were the only compounds that were not detected in the samples. Figure S3 presents the total ion chromatograms for albendazole (A21) and losartan (A16), along with their respective LOQ values of 2 and 1 ng L^{-1}.

Table 2. Concentrations of the pharmaceuticals in the analyzed surface water samples.

Compounds	LOQ ng L^{-1}	Concentration (ng L^{-1})																					
		A1	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**	**A8**	**A9**	**A10**	**A11**	**A12**	**A13**	**A14**	**A15**	**A16**	**A17**	**A18**	**A19**	**A20**	**A21**	**A22**
Albendazole	2	48	55	54	56	54	49	68	59	69	47	45	52	47	55	52	58	65	58	62	57	254	52
Albendazole 2-aminosulfone	1	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Albendazole sulfone	1	1	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Albendazole sulfoxide	1	5	6	5	4	5	6	2	2	2	2	3	3	3	4	3	3	2	3	3	4	11	3
Atenolol	1	3	n.d.	n.d.	n.d.	n.d.	31	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	49	n.d.	14	n.d.	n.d.	1	n.d.	n.d.	n.d.
Carbamazepine	1	4	1	1	1	1	4	n.d.	n.d.	n.d.	4	1	1	1	15	3	3	2	n.d.	1	n.d.	n.d.	n.d.
Diazepam	1	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Diclofenac	1	1	n.d.	n.d.	n.d.	n.d.	11	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	17	n.d.	8	n.d.	n.d.	1	n.d.	2	n.d.
Glibenclamide	1	n.d.	n.d.	n.d.	n.d.	n.d.	2	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1	n.d.	1	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ketoprofen	1	n.d.	n.d.	n.d.	n.d.	n.d.	12	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	6	n.d.	11	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Lidocaine	1	2	n.d.	1	1	1	3	n.d.	n.d.	n.d.	1	n.d.	n.d.	n.d.	9	1	3	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Lincomycin	1	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	6	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	28	n.d.	n.d.	n.d.	n.d.
Losartan	1	10	1	1	1	2	89	n.d.	n.d.	n.d.	6	1	1	1	167	4	82	n.d.	n.d.	5	n.d.	n.d.	n.d.
Metoprolol	1	1	n.d.	n.d.	n.d.	n.d.	10	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	16	n.d.	9	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Nalidixic acid	1	1	n.d.	3	1	4	1	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Naproxen	1	n.d.	n.d.	n.d.	n.d.	n.d.	9	n.d.	10	n.d.	n.d.	n.d.	n.d.	n.d.	25	n.d.	7	n.d.	n.d.	3	n.d.	n.d.	n.d.
Paracetamol	2	n.d.	n.d.	n.d.	n.d.	n.d.	23	12	4	3	n.d.	16	n.d.	n.d.	7	n.d.	8	5	9	6	4	n.d.	10
Praziquantel	1	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Propranolol	1	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Sotalol	2	n.d.	n.d.	n.d.	n.d.	n.d.	14	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	8	n.d.	12	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Sulfadiazine	1	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Sulfamethoxazole	1	n.d.	n.d.	n.d.	n.d.	n.d.	5	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	4	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.

n.d.: none detected.

Albendazole is an anthelmintic belonging to the benzimidazole class. In both humans and animals, albendazole and its active metabolites are excreted in urine or feces and can easily enter aquatic environments. It is known that these metabolites often retain pharmacological activity, making it essential to determine them alongside the unchanged compound [54]. The 22 samples analyzed were contaminated with albendazole and the metabolite albendazole sulfoxide at concentrations ranging from 45 to 254 ng L^{-1} and from 2 to 11 ng L^{-1}, respectively. Porto et al. [55] reported the presence of albendazole in influent and effluent samples from a wastewater treatment plant in Campinas-SP, Brazil, with average concentrations of 464 ng L^{-1} in the influent and 129 ng L^{-1} in the effluent, suggesting that albendazole may be partially degraded during treatment by photolysis and ozonation. Chaves et al. [49] observed a significant change in albendazole concentrations in river water samples during the rainy and dry seasons in the São Luiz-MA, Brazil, region. During the dry season, concentrations ranged from 8 to 22 ng L^{-1}, while during the rainy season, concentrations did not exceed 4 ng L^{-1}, indicating a probable dilution effect based on the different seasons of the year.

Ranked second among the most widely sold drugs in Brazil [56], losartan was detected in more than half of the samples analyzed, with concentrations ranging from 1 to 167 ng L^{-1}. Its widespread use in the treatment of hypertension makes this compound an imminent problem in water bodies. Roveri et al. [57] measured losartan concentrations in rivers in the São Paulo-SP region, Brazil, where concentrations ranged from 0.1 to 8 ng L^{-1}. The occurrence of losartan in coastal waters of Santa Catarina was evaluated in a study by Pisetta et al. [58], who detected concentrations ranging from 0.4 to 3 ng L^{-1}.

The fact that Brazil ranks among the world's top ten consumers of pharmaceuticals contributes to the presence of various compounds in the environment. According to Marson et al. [59], the anti-inflammatory drug diclofenac and the antiepileptic drug carbamazepine are the pharmaceuticals most frequently found in surface waters. Diclofenac and carbamazepine were detected in concentrations ranging from 1 to 109 ng L^{-1} and from 1 to 59 ng L^{-1}, respectively.

2.6. Environmental Risk Assessment

The Lethal Concentration 50% (LC_{50}) and Inhibition Growth Concentration (IG_{50}) values obtained using the TEST software (Version 4.2.1), as well as the PNEC values calculated for each of the three trophic levels regarding the compounds determined in the samples, are presented in Table S3. The drug concentration found in the samples (MEC) values were converted to mg L^{-1} for calculation purposes. The risk coefficients calculated for T. pyriformis, D. magna, and the fathead minnow are shown in Tables S4–S6. To evaluate the calculated risk quotient (RQ) values, the three levels of ecological risk proposed by Hernando et al. [60], (2016), where there is a "low" risk for the range $0.01 \leq RQ \leq 0.1$, a "medium" risk for $0.1 \leq RQ \leq 1$, and a "high" risk for $RQ > 1$, were applied. In the assessment of the protozoan *T. pyriformis*, the compounds albendazole, atenolol, carbamazepine, diclofenac, losartan, and metoprolol yielded RQ values in the range of 0.01 to 0.1, suggesting a "low" environmental risk associated with the presence of these compounds. Only in sample A8 was the RQ for carbamazepine associated with a moderate risk (0.13). For the crustacean *D. magna*, only carbamazepine and losartan achieved RQs considered to indicate low environmental risk (0.04 and 0.01, respectively). In the case of the fathead minnow, which in this study represented the highest trophic level evaluated, RQs were found to indicate low (albendazole, atenolol, diclofenac, glibenclamide, lidocaine, and losartan), moderate (diclofenac, glibenclamide, lincomycin, and losartan), and high environmental risk (losartan).

Samples A6 (1.46), A14 (2.74), and A16 (1.34) had the highest RQ values for losartan, suggesting a high environmental risk associated with the presence of this compound. Given that losartan is the second most widely sold active ingredient in Brazil [56], a high occurrence of this compound in aquatic environments is expected. Several studies demonstrate losartan's harmful potential to organisms at different trophic levels, particularly in terms of cytotoxicity and genotoxicity [60–62]. Results such as those obtained in this study serve as an important warning regarding the current state of water bodies in Brazil. Urgent monitoring programs are needed, and this requires greater commitment on the part of the relevant authorities. Many pharmaceuticals have the potential for bioaccumulation and biomagnification, meaning that their chronic effects on ecosystems can no longer be ignored. The reliability of the toxicity predictions obtained was evaluated by considering the statistical performance of the QSAR models. It is important to emphasize that QSAR-derived toxicity values represent estimates and should ideally be supported by experimental data.

3. Materials and Methods

3.1. Reagents and Materials

All standards of the compounds evaluated (Table S2) were purchased from LGC Standards (Wesel, Germany) with high purity (≥98%). The surrogate standards nalidixic acid-D5, albendazole-D3, lidocaine-D10, metoprolol-D7, naproxen-D3, and sulfadimethoxine-D6 were purchased from Witega (Berlin, Germany). Triphenyl phosphate obtained from Sigma Aldrich (San Luis, CA, USA) was used as the internal standard. Individual stock solutions of each compound were prepared in acetonitrile (ACN) at 1000 mg L^{-1} from the solid standards, taking their purities into account. The mixed solutions of the analytes and the surrogate mixed solutions were prepared in ACN, both with a final concentration of 10 mg L^{-1}. All solutions were stored at −10 °C.

The solvents acetonitrile, methanol, and glacial acetic acid were purchased from J.T. Baker (Phillipsburg, NJ, USA). Formic acid LC-MS grade was purchased from Sigma Aldrich (USA). Ethylenediaminetetraacetic acid (EDTA) was purchased from Merck (Rio de Janeiro, Brazil). Ultrapure water was obtained using a Milli-Q Direct UV3® system from Millipore (Molsheim, France). Argon 5.0 was from Air Liquide (São Paulo, Brazil). The SPE cartridges Bond Elut Plexa (200 mg/3 mL and 500 mg/6 mL) were from Agilent Technologies (Santa Clara, CA, USA), Strata-X (60 mg/3 mL and 200 mg/3 mL) and Strata SDBL (500 mg/3 mL) from Phenomenex (Torrance, CA, USA), and Oasis® HLB (60 mg/3 mL and 200 mg/6 mL) and Sep-Pak C18 (500 mg/6 mL) from Waters (Milford, MA, USA), Supel Select HLB (200 mg/6 mL) from Sigma Aldrich (USA), and Chromabond C18 ec (500 mg/3 mL) from Macherey-Nagel (Düren, Germany).

3.2. Instrumental Conditions

The analyses were performed using a UHPLC-MS/MS system from Waters (USA) equipped with an Acquity UPLC binary-pump liquid chromatograph with a Xevo TQ-XS MS/MS triple-quadrupole, an autosampler, and a column temperature controller. The system also used a nitrogen generator, model NM30L-MS (Peak Scientific, Inchinnan, Scotland), and an air compressor, model SF2 FF (Atlas Copco, Overijse, Belgium). An Acquity UPLC HSS T3 column (100 × 2.1 mm; 1.8 µm) from Waters (USA) was used for the chromatographic analysis. MassLynx 4.2 software from Waters (USA) was used for instrument control and data processing. The injection volume was 5 µL, and the flow rate was 0.250 mL min^{-1}. The mobile phase consisted of (A) water and (B) ACN, both containing 0.1% (*v*/*v*) formic acid. The gradient program began at 5% B (held for 0.25 min), increased linearly to reach 100% B in 7 min (held until 7.4 min), and then decreased to 5% B at 7.8 min. The mass spectrometer was operated with electrospray ionization in

positive mode (ESI+), using SRM mode with two transitions for each compound. The most abundant ion, corresponding to the first transition, was selected for quantification, while the second most intense transition was used to confirm the identity of the pharmaceuticals. The conditions used in the MS were: source temperature, 150 °C; desolvation temperature, 600 °C; desolvation gas (nitrogen), 1000 L h^{-1}; cone gas (nitrogen), 150 L h^{-1}; capillary voltage, 2.4 kV; and collision gas (argon), 0.15 mL min^{-1}. Table S2 presents the selected transitions for SRM mode, retention time, cone energy, and collision energy.

3.3. Evaluation of Sample Preparation Conditions

Initial tests to select the best sorbent were conducted under the conditions described by de Oliveira et al. [63], which consisted of percolating, through the different cartridges, 100 mL of water sample with pH adjusted to 6.0 and 0.1% (*m*/*v*) EDTA added. Elution was performed with 1 mL of ACN:MeOH (1:1, *v*/*v*) containing 1% (*v*/*v*) acetic acid. The extract was diluted twice with ultrapure water and analyzed by UHPLC-MS/MS * (Waters, Milford, MA, USA). Ten different SPE sorbents were evaluated for sample preparation: Bond Elut Plexa (200 mg/3 mL and 500 mg/6 mL), Chromabond C18 EC (500 mg/3 mL), Oasis® HLB (60 mg/3 mL and 200 mg/6 mL), Sep-Pak C_{18} (500 mg/6 mL), Strata-X (60 mg/3 mL and 200 mg/3 mL), Strata SDBL (500 mg/3 mL), and Supel Select HLB (200 mg/6 mL). Based on the results of the initial sorbent tests, the three best sorbents were selected, and a full factorial design (3^3) was conducted using Statistica© 10 software from StatSoft (Krakow, Poland). Table S7 presents the experiments conducted using a complete factorial design 3^3. The sorbents Strata-X 200 mg, Oasis HLB 200 mg, and Sep PAK C_{18} 500 mg were evaluated using a blank sample spiked at 100 ng L^{-1}. The amount of EDTA (0.1, 0.2, and 0.3%), the sample pH (4.0, 5.0, and 6.0), and the sorbent were evaluated simultaneously, resulting in 27 experiments.

After conducting the full factorial design, the three best tests were selected based on the number of compounds recovered within the range of 60 to 115%. Each test was performed in triplicate, and based on these results, the best sorbent, pH, and amount of EDTA were selected. To ensure the highest possible concentration factor, elution volumes of 1 and 2 mL were also evaluated in triplicate, in terms of recovery.

3.4. Method Validation

The method was validated according to the criteria established by AOAC International [64]. The parameters evaluated were selectivity, linearity, accuracy, precision, LOD, and LOQ. The deuterated standards were added before starting the extraction step to ensure the efficiency of the procedure. Instrumental stability was verified using the internal standard triphenyl phosphate. The selectivity was evaluated based on the analysis of the blank matrix and the spiked blank matrix. Linearity was evaluated using an analytical curve at concentration levels 0.05, 0.1, 0.5, 1, 5, and 10 µg L^{-1} prepared in the same solvent used in the SPE elution step. According to AOAC International [64], accuracy must be evaluated in terms of the recovery of analytes in blank sample spike assays with at least seven independent replicates per concentration level, in addition to a minimum of three levels covering the working range. From this evaluation, the precision of the method is determined using the relative standard deviation (RSD) of the recovery results. To evaluate the accuracy and precision of the method, spike levels 1, 2, and 20 ng L^{-1} (n = 7) were used in the repeatability test. The selection of these levels was based on the concentrations at which pharmaceuticals are typically found in surface water samples, as well as on the proposed sample preparation method and the detection limit of the UHPLC-MS/MS system. Intermediate precision was estimated from spiking experiments at the same spike levels on 3 different days. Considering the AOAC International [64] guideline, for the concentration

levels 1 and 2 ng L^{-1}, the acceptable recoveries are from 40 to 120% with RSD ≤ 30%. For the level of 20 ng L^{-1}, acceptable recoveries are from 60 to 115% with RSD ≤ 21%.

The method limit of quantification (LOQ) was defined as the lowest spiking level that presented satisfactory performance of accuracy and precision. The method limit of detection (LOD) was determined by dividing the LOQ value by 3.3.

3.5. Application to Surface Water Samples

The validated method was applied to the analysis of 22 river water samples from different regions of the state of Rio Grande do Sul, Brazil. The samples were collected in 500 mL amber glass bottles, transported to the laboratory under refrigerated conditions, and stored in a refrigerator until extraction, which was performed within 24 h. Prior to the SPE step, each sample was filtered through a 47 mm membrane filter of porosity 0.45 µm, and the pH was adjusted to 6.0.

3.6. Environmental Risk Assessment

An environmental risk assessment was conducted for all analytes quantified in the surface water samples for which chronic toxicity values, such as Lethal Concentration 50% (LC_{50}) and Inhibition Growth Concentration (IG_{50}), were available in the free software Toxicity Estimation Software Tool (TEST) version 5.1 (EPA, USA), which uses the Quantitative Structure–Activity Relationship (QSAR) method to predict chemical toxicity of a molecule directly from its chemical structure. Most of the LC_{50} and IG_{50} values used to calculate the Predicted No Effect Concentration (PNEC) were predicted using the QSAR method [65]. However, when available, experimental LC_{50} and IG_{50} values were used. Toxicity results were evaluated for three different trophic levels representative of the aquatic ecosystem: *Tetrahymena pyriformis* (protozoan), *Daphnia magna* (crustacean), and *Pimephales promelas*/fathead minnow (fish). The PNEC was calculated by dividing the LC50 or IG50 values by the assessment factor of 1000. The Risk Quotient (RQ) was calculated by dividing the drug concentration found in the samples (MEC) by the PNEC value [66].

4. Conclusions

This study successfully developed and validated a method for determining pharmaceuticals in surface water using SPE and the UHPLC-MS/MS technique. The main variables involved in SPE were optimized using a factorial design, which identified the most suitable sorbent (Strata-X 200 mg), pH (6.0), and amount of EDTA (0.1%) for the compounds evaluated. The method's 50-fold concentration factor, combined with UHPLC-MS/MS analysis, enabled rapid and efficient simultaneous determination of 34 pharmaceuticals with detection and quantification limits suitable for monitoring applications.

Applying the method to 22 surface water samples from different regions of the state of Rio Grande do Sul, Brazil, indicated the occurrence of at least four different pharmaceuticals in concentrations from 1 to 254 ng L^{-1}. The most frequently quantified compounds were albendazole and albendazole sulfoxide, present in all samples, as well as carbamazepine and losartan, present in 15 and 14 samples, respectively. All four of these compounds are frequently detected in surface waters in different regions of Brazil. Based on the concentrations of the compounds in the samples, it was possible to conduct an environmental risk assessment using the risk quotient (RQ). All samples contained at least one compound with an RQ value classified as having low, medium, or high environmental risk. Losartan, which is the second most widely consumed drug in Brazil, was the only compound with RQ values considered to be high risk (>1), demonstrating a direct relationship between consumption and occurrence in aquatic environments. It should be noted that the QSAR assessment predicts toxicity but lacks chronic toxicological data and data on bioaccumulation, which

affects the RQ results. The method developed in this study proved to be simple, effective, and reliable, and can be applied in routine laboratory analyses, toxicological tests, and environmental monitoring, since all established validation parameters were met.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/molecules31224177/s1. Figure S1. UHPLC-MS/MS total ion chromatograms from compounds representative of different classes of pharmaceuticals at 10 μg L^{-1}; Figure S2. Pareto chart of the factorial design conducted; Figure S3. UHPLC-MS/MS total ion chromatograms of the compounds albendazole and losartan in samples A21 and A16, respectively, along with their LOQ; Table S1. Recent SPE applications for the determination of pharmaceuticals in different water samples; Table S2. Analyzed compounds and deuterated compounds, along with their respective retention times, cone energy, and collision energy for each of the SRM transitions; Table S3. LC_{50} and IG_{50} values obtained using the TEST software for the compounds quantified in the samples, and PNEC values; Table S4. Risk quotient values for *T. pyriformis*; Table S5. Risk ratio values for *D. magna*; Table S6. Risk Quotient Values for Fathead Minnow; Supplementary Table S7. Experiments were conducted using a complete factorial design 3^3 [60–92].

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Data Availability Statement: Data are contained within the article.

Conflicts of Interest: The authors declare no conflicts of interest.

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