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ENVIRONMENTAL CHEMICAL CONTAMINANTS

Dispersive Liquid-Liquid Microextraction Based Preconcentration of Selected Pesticides and Escitalopram Oxalate, Haloperidol, and Olanzapine from Wastewater Samples Prior to Determination by GC-MS

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Abstract

Background: Determination of emerging pollutants including pharmaceuticals, pesticides, industrial chemicals and hormones in different environmental samples is very important for human health.
Objective: Experimental design enabled parameters to be evaluated for their effects onextraction output as well as their interactive effects.
Method: A multivariate experimental design was used to attain optimum conditions of a dispersive liquid-liquid microextraction method for preconcentration of pesticides and pharmaceuticals for determination by GC-MS.
Results: The optimum parameters suggested by the design model were 200 μL of chloroform, 1.96 mL of ethanol, and 40 s vortexing period. LOD and LOQ were calculated using linear calibration plots of the analytes developed in the standard concentration range of 2.0 μg/L–2.0 mg/L.
Conclusions: Enhancement in detection power of the analytes recorded by the optimized method with respect to direct GC-MS determination (based on LOD values) was in the range of 3.6 and 539 folds. Spiked recovery experiments for municipal, medical, and synthetic wastewater samples yielded low recovery results when calculated against aqueous standard solutions. Matrix matched calibration standards were used to mitigate interferences from the waste samples and the percent recoveries obtained were close to 100%. This established accuracy and applicability of the developed method.
Highlights: The detection limits were found between 0.50 ng/mL and 37 ng/mL. An accurate, simple and sensitive analytical method was developed for the analytes.

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Over the past years, emerging pollutants have been an important matter to be dealt with because of their potential damaging effects on the environment and living organisms (1). Emerging pollutants consist mainly of pesticides, pharmaceuticals, industrial chemicals, personal care products, and steroid hormones (2, 3). Pesticides and pharmaceuticals are two major chemical groups that are widely used, and this wide application makes them ubiquitous in the environment with potential threats to humans and other organisms (4). These pollutants usually end up in water bodies at trace levels (ng/L to μg/L) and are, therefore, referred to in the literature as micropollutants (5). Pesticides are chemicals that are used for controlling or eradicating pests such as insects, weeds, and fungi in order to improve the quality, quantity, and storage period of agricultural products (6, 7). They are also used in controlling pests such as mosquitoes and ticks that effectively transmit parasites, viruses, bacteria, and other pathogenic microorganisms (8). Pesticides can also severely affect non-target organisms and several reports have been presented on their carcinogenic, mutagenic, and endocrine disruptive effects (9–12). Pharmaceutical drugs are medicinal products that are used to prevent, treat, or cure diseases and are also used in making diagnoses (13). With improvements in healthcare systems, the global use of both prescribed and self-medicated drugs have increased, leading to large amounts of disposed and excreted drug products into the environment (14). Aquatic organisms in both fresh water and the oceans are most affected by pharmaceutical drugs that are released into the environment (15, 16). In this study, three obsolete (dioxacarb, fenitrothion, and trifluralin) and two approved (flumetralin and tefluthrin) pesticides with known toxic effects were studied together with three pharmaceutical drugs, namely escitalopram oxalate, haloperidol, and olanzapine.

Both volatile and non-volatile compounds are efficiently separated and determined by chromatographic techniques, where GC and LC are respectively employed for the former and latter (17). Both chromatographic techniques are conveniently coupled to mass spectrometry detectors and this allows further separation of compounds according to different mass to charge ratios for their specific and selective determinations (18). Tandem mass spectrometry (MS/MS) is a very powerful tool that involves multiple fragmentations for a more efficient elucidation of unknown compounds and their determination at trace levels (19). GC-MS lacks the sensitivity of its tandem analogue (GC-MS/MS) and therefore requires preconcentration techniques that separate analytes from complex matrices into appreciable amounts to lower detection limits. Extraction is the most common sample cleanup and preconcentration technique employed for organic compounds and it is broadly grouped into liquid-liquid extraction (LLE) and solid phase extraction (SPE; 20). Advancements in the classical LLE and SPE methods have resulted in the use of very low amounts of solvents and sorbent materials and these are respectively referred to as liquid phase microextraction (LPME) and solid phase microextraction (SPME; 21). Dispersive liquid-liquid microextraction (DLLME) was developed in 2006 by Rezaee et al. and has since become a very popular extraction method for both organic and inorganic analytes (22, 23). The efficiency of the DLLME method stems from the use of disperser solvents that provide a high surface area of extraction, due to a high dissemination of extractant throughout the sample solution (24). The DLLME method is simple, economical, and records high analyte concentration and recovery (25). Despite the high efficiency of microextraction methods, complex samples may cause significant interference on analytes and affect the accuracy of quantification. Matrix matching and standard addition methods can be used to mitigate interference effects for accurate quantification of analytes.

The aim of the study was to develop and validate an extraction method for simultaneous preconcentration of the analytes for determination by GC-MS. Applicability of the method was tested on three wastewater matrices (synthetic, municipal, and medical) and accuracy of analyte quantification was enhanced using the matrix matching calibration technique.

METHOD

Chemicals

The drug samples (escitalopram oxalate, olanzapine, and haloperidol) used in the study were obtained from Ali Raif Pharmaceutical Company (İstanbul, Turkey) and all had purities >99%. The pesticides (dioxacarb, trifluralin, tefluthrin, fenitrothion, and flumetralin) also had purities >98% and all four were obtained from Dr. Ehrenstorfer (Augsberg, Germany). Standard stock solutions (1000 mg/L) of the analytes were prepared gravimetrically for high accuracy and subsequently diluted into working and calibration standards volumetrically. The solvents used to dissolve the standards included methanol, ethanol, and acetonitrile, all purchased from Merck (Darmstadt, Germany). The standard solutions were stored in a deep freezer at –18°C. Solvents used in the optimization experiments (chloroform, 1,2-dichloroethane, carbon tetrachloride, cyclohexane, toluene, acetonitrile, and isopropyl alcohol) and all chemicals used for the preparation of synthetic wastewater were purchased from Merck.

Instruments

The pesticides and pharmaceuticals were separated from each other by eluting them through an HP-5MS (30 m × 250 μm, 0.25 μm) capillary column fixed in the oven section of a 6890 model Agilent gas chromatograph. The temperature program employed was as follows: 50°C/min ramp from 70 to 200°C (4.0 min hold time), 60°C/min ramp from 200 to 250°C (6.0 min hold time), and a final ramp of 60°C/min ramp from 250 to 300°C (1.0 min hold time). Helium (carrier gas) was maintained at a constant flow rate of 2.5 mL/min and 1.0 μL sample/standard injection volume was used in the splitless mode. The analytes were detected with a 5973 model Agilent mass spectrometry detector and data acquisition was made in the scan mode (*m/z* 60–600). Dioxacarb, trifluralin, tefluthrin, fenitrothion, flumetralin, escitalopram oxalate, olanzapine, and haloperidol were quantified/qualified using the respective prominent ions (*m/z*) 121/166, 306/264, 177/197, 277/125, 143/145, 58/238, 242/229, and 224/237, respectively. The electron ionization source was operated at 70 eV and the respective temperatures of the MS Quad, MS Source, MS transfer line, and injection port were 150, 230, 280, and 250°C.

Procedure

The disperser (1.96 mL ethanol) and extraction solvents (200 μL chloroform) were mixed in a clean tube, withdrawn with a 5.0 mL plastic syringe, and injected into 8.0 mL of sample/standard solution. The solution was then vortexed for 40 s before centrifuging for 120 s at 6000 rpm for rapid separation of phases.

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The upper aqueous phase was carefully discarded with the aid of a clean Pasteur pipette and the settled chloroform phase was taken into micro insert vials for GC-MS determination of analytes.

Samples

Municipal wastewater was sampled from an aerated activated sludge wastewater pool by rinsing the polypropylene plastic bottle five times before filling to the brim. Medical wastewater was sampled from the sewer of a hospital into a plastic bottle and stored at 4.0 °C together with the municipal wastewater. Both municipal and medical wastewater samples were taken from different positions into 5.0 L plastic bottles. Both samples were filtered successively through 11 μm pore sized filter papers and 0.45 μm PTFE filters. Synthetic wastewater (1.0 L) was prepared and used instantly according to the following formulation (concentration of all chemicals is mg/L): glucose, 400; magnesium sulfate, 15.63; bactopeptone, 115; yeast extract, 14; iron(III) chloride, 0.075; ammonium sulfate, 104.8; sodium bicarbonate, 255.5; monopotassium phosphate, 21.75; calcium chloride, 2.45; and manganese sulfate, 1.8 (26).

Results and Discussion

All optimization studies were carried out with 200 μg/L aqueous standard solutions, extracted in three replicates, and the highest mean was selected as optimum parameter. Experimental design parameters were determined in a stepwise optimization process, where only one parameter was varied at different values while the other parameters were kept at one value.

Selection of Experimental Parameters

One of the reasons for choosing the experimental design was to develop an experimental model around a design space of experimental parameters, to allow evaluation of parameter combinations without necessarily performing experiments. In order to cut down the number of experimental variables in the design, univariate optimizations were performed to select the most influential parameters. The type of extraction solvent was first determined by trying three solvents with densities higher than 1.0 (chloroform, 1,2-dichloroethane, and carbon tetrachloride) and two solvents with densities lower than 1.0 (toluene and cyclohexane). Ethanol (2.5 mL) was used to disperse 300 μL of each solvent under identical experimental conditions. Based on density differences, toluene and cyclohexane were taken from the upper phase, while the other solvents were taken from the bottom phase into vials for instrumental reading. Chloroform showed optimum efficiency for four out of the eight analytes while 1,2-dichloroehtane and carbon tetrachloride were optimum for two analytes each as shown in Figure 1. It can also be seen from the figure that 1,2-dichloroehtane could not extract one analyte and cyclohexane could not extract three analytes. Hence, chloroform was selected as the optimum extraction solvent and it was mixed with acetonitrile, methanol, ethanol, and isopropyl alcohol to ascertain the most efficient disperser solvent. Ethanol showed a more efficient dispersion of chloroform for all eight analytes followed by methanol (Figure 2), which was slightly lower. The results obtained for acetonitrile and isopropyl alcohol were more than two times lower than the results of ethanol. Vortex was selected for its practical use as a mixer and added to chloroform and ethanol as the three experimental parameters for the experimental design.

Box-Behnken Experimental Design

A response surface methodology (Box-Behnken design) was used to optimize the DLLME method by evaluating the effects of three influential parameters on extraction output and their interactions with each other. Each parameter was tested at three levels (high: +1, mean: 0, and low: −1), making up a total of 17 parameter combinations including five center points distributed randomly through the runs. The respective levels tested for chloroform (A), ethanol (B), and vortex period were 200–350–500 μL, 1.0–2.0–3.0 mL, and 15–30–45 s. The second order polynomial expression given below was used to predict the response of parameter combinations as a function of independent parameter variables.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4 + \beta_{12} X_1 X_2 + \beta_{13} X_1 X_3 + \beta_{14} X_1 X_4 + \beta_{23} X_2 X_3 + \beta_{24} X_2 X_4 + \beta_{34} X_3 X_4 + \beta_{11} {X_1}^2 + \beta_{22} {X_2}^2 + \beta_{33} {X_3}^2 + \beta_{44} {X_4}^2 \quad (1)$$

where Y represents response; β_0 is a constant term; β_1, β_2, β_3, and β_4 are linear effects; β_{12}, β_{13}, β_{14}, β_{23}, β_{24}, and β_{34} are interaction effects; and β_{11}, β_{22}, β_{33}, and β_{44} are quadratic effects. Analysis of variance was used to ascertain significant effects of parameter variables and interactions on response. The quality of the polynomial model to experimented results was indicated by coefficient of determination (R^2) and adjusted R^2 values. The Design-Expert 7.0.0 software was used to analyze regression and graphical data.

The relevance/significance of parameter variables and variable interactions to the model was determined with *P*-values <0.05 and *F*-values greater than F-critical at 95% confidence level. All eight analytes recorded a similar pattern of results and as such, the statistical results of tefluthrin are presented as a representative analyte. The respective *F*- and *P*-values obtained for the model were 74.99 and <0.0001, and these were statistically significant. As shown in Figure 3, the plot indicated a good fit between experimented and predicted values, by making adjustments based on the number of model variables (adjusted R^2). The R^2 and adjusted R^2 values of the model were obtained as 98.9 and 97.6%, respectively. The lack of fit of the model was insignificant as observed for a *P*-value of 0.0594, an indication that experimental results are adequately explained by the model.

Positive (+1) and negative (–1) main effects represent optimum results obtained for the highest and lowest tested parameter variables, respectively. The lowest volume of chloroform recorded the highest extraction response and this negative main effect can be attributed to the inverse relationship between preconcentration factor and extraction solvent volume. Ethanol volume and vortex period showed positive main effects as increasing their amounts resulted in higher extraction response values by reason of a more efficient dispersion of chloroform. Chloroform and ethanol were determined to be significant to the design model according to their *P*-values of <0.0001 and 0.0077, respectively. Chloroform was more significant than ethanol, but the different periods of vortexing did not have a significant impact on extraction outputs (*P*-value = 0.0782). The interaction between chloroform and ethanol (AB) and the quadratic effects of chloroform (A^2) and ethanol (B^2) were also significant to the model. The AB interaction effect is depicted in the 3-D response surface chart of Figure 4, where analyte response increases with decreasing chloroform volume and increasing ethanol volume. Optimum experimental

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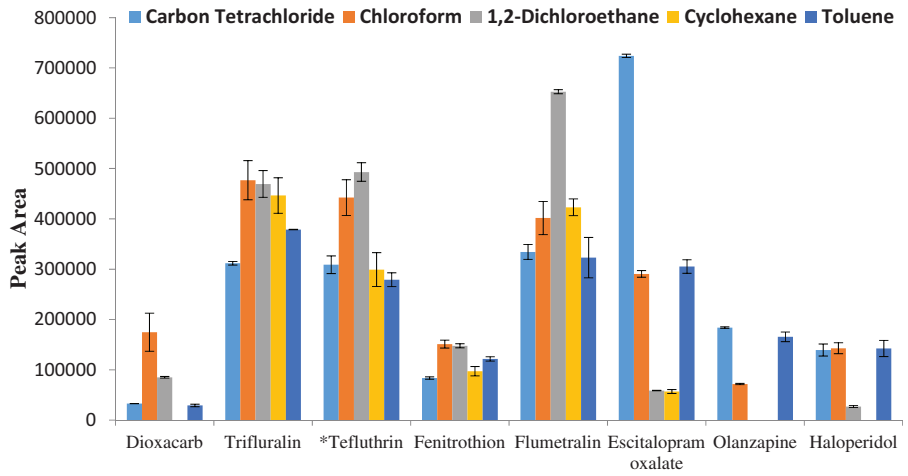


Figure 1. A plot of extraction solvent types against peak area values, $n = 3$ for error bars (*represents peak area values of tefluthrin scaled down three times).

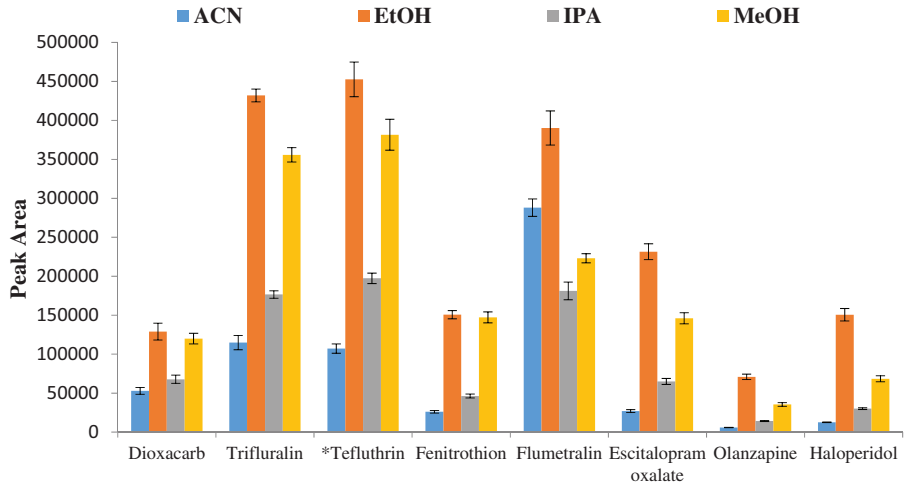


Figure 2. A plot of disperser solvent types against peak area values, $n = 3$ for error bars (*represents peak area values of tefluthrin scaled down three times).

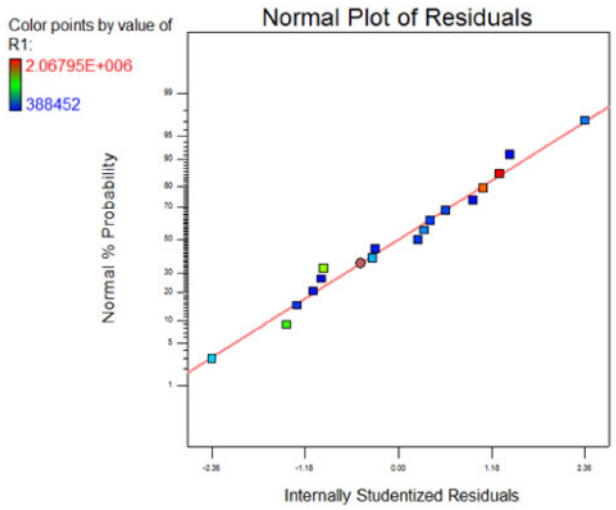


Figure 3. Normal probability plot for the average response values of tefluthrin.

conditions obtained from the model predictor were 200 μL chloroform, 1.96 mL ethanol, and 40 s vortex period.

Analytical Figures of Merit

Aqueous calibration standards prepared in the concentration range of 2.0 μg/L–2.0 μg/mL were analyzed under the optimum experimental conditions to determine the analytical figures of merit presented in Table 1. The calibration plot of the analytes covered broad linear dynamic ranges (LDRs) with correlation coefficient values ≥0.9993. The precision of the extraction process and instrumental measurement of analytes were expressed as relative standard deviation (RSD, %) of the lowest calibration standard (LCS). The RSD, % values obtained for all analytes were lower than 10%, signifying good repeatability. The limits of detection and quantification were calculated from the SD of the lowest calibration concentration and the slope (m) using the expressions $3.SD_{LCS}/m$ and $10.SD_{LCS}/m$, respectively. The LODs were calculated in the range of 0.57–37 μg/L and according to the instrumental detection limits of the analytes, the optimum

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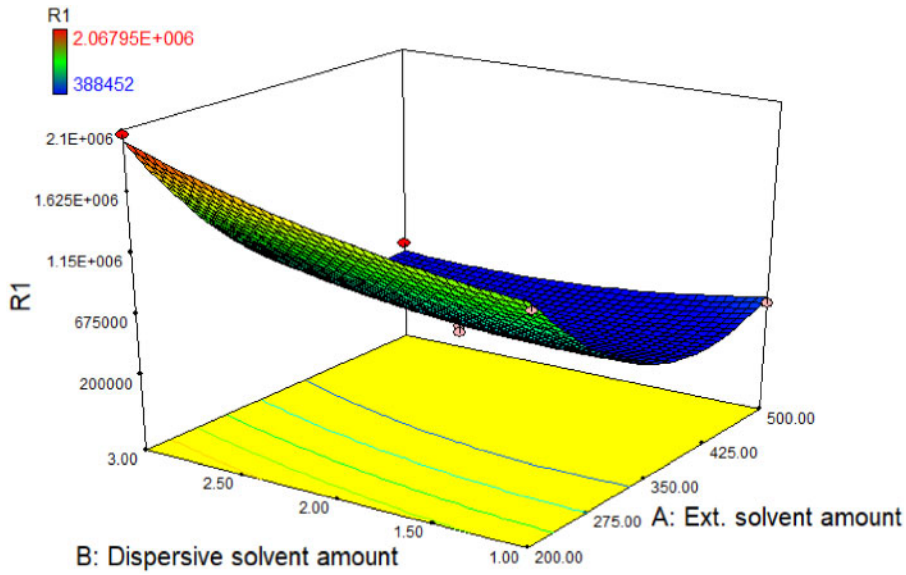


Figure 4. 3-D response surface plot of (A) chloroform volume and (B) ethanol interaction effects on the response of tefluthrin (fixed value: 30 s vortex period).

Table 1. Analytical figures of merit for analytes obtained using the optimized DLLME-GC-MS method

Chemical	LOD, μg/L	LOQ, μg/L	RSD, %	LDR, μg/L	R^2	EDP
Dioxacarb	5.4	18	9.2	20–2000	0.9996	50
Trifluralin	0.57	1.9	6.7	2.0–500	0.9993	105
Tefluthrin	0.66	2.2	4.1	2.0–2000	0.9999	91
Fenitrothion	2.6	8.6	4.5	10–2000	0.9997	539
Flumetralin	4.2	13.8	3.5	10–1000	0.9995	38
Escitalopram oxalate	17	56	6.9	50–2000	0.9991	3.6
Olanzapine	31	103	9.8	100–2000	0.9997	11
Haloperidol	37	122	8.8	100–2000	0.9995	39

Table 2. Comparison of LOD, LOQ, and RSD, % values of this study with other methods in the literature

Chemical	LOD, μg/L	LOQ, μg/L	RSD, %	References
Dioxacarb	5.4	18	9.2	This study
	2.0	6.5	8.0	(27)
	40 μg/kg	80 μg/kg	–	(28)
Trifluralin	0.57	1.9	6.7	This study
	0.15	0.495	–	(29)
Tefluthrin	0.66	2.2	4.1	This study
	1.7 μg/kg	5.0 μg/kg	–	(30)[a]
	8.0 μg/kg	25 μg/kg	–	(30)[b]
Fenitrothion	2.6	8.6	4.5	This study
	3.0	–[c]	2.1–4.1	(31)
Flumetralin	4.2	13.8	3.5	This study
	10 μg/kg	20 μg/kg	–	(28)
Escitalopram oxalate	17	56	6.9	This study
	5.0	17	1.8–7.5	(32)

[a] Ultrasound-assisted DLLME.
[b] Salting-out assisted liquid–liquid extraction.
c No information.

method recorded about 3.6–539 folds enhancement in detection power (EDP). EDP values were calculated as the ratio of the optimized method's LOD values to direct GC-MS LOD values.

Figures of merit from other studies reported in the literature are compared to this study's figures in Table 2. The methods compared include switchable solvent liquid phase microextraction (27), solid phase extraction (28), DLLME (29), ultrasound-assisted DLLME (30), and salting-out assisted liquid-liquid extraction (30), all coupled with GC-MS. The other comparisons were DLLME combined with micellar electrokinetic chromatography (31) and DLLME combined with ultra-performance liquid chromatography with photodiode array detector (32). The LOD values of this study are comparable or better than the values of the other methods given in Table 2. This study presents an alternate method for determination of the analytes at trace levels.

Recovery Studies in Wastewater Matrices

The method development process was performed with ultrapure deionized water and therefore, the analytes had very little or close to no matrix interferences. Environmental samples contain a wide range of compounds that make the matrix very complex. Wastewater is a typical example and it contains both organic and inorganic substances at varying concentrations. This method was tested on medical wastewater and municipal wastewater to ascertain the applicability of the method to real samples and the accuracy of quantifying the analytes. Since synthetic wastewater is conveniently used for developing wastewater treatment strategies in the laboratory, it was also tested in the recovery experiments to determine its matrix effects on the determination of analytes. All three wastewater samples were analyzed in triplicates under the optimum experimental conditions to determine whether or not the analytes were present. All three analyses did not produce signals at the retention times of the analytes, indicating their absence or amounts below the method's detection limits. The samples were, therefore, spiked at 50, 100, and 200 μg/L final concentrations. The spiking experiments were performed by adding very low amounts from high concentration intermediate stock solutions to ensure that the matrix of the samples would not be diluted, but its full effects exerted on the analytes. Aqueous calibration standards were measured alongside the spiked samples and the percent recoveries were determined using

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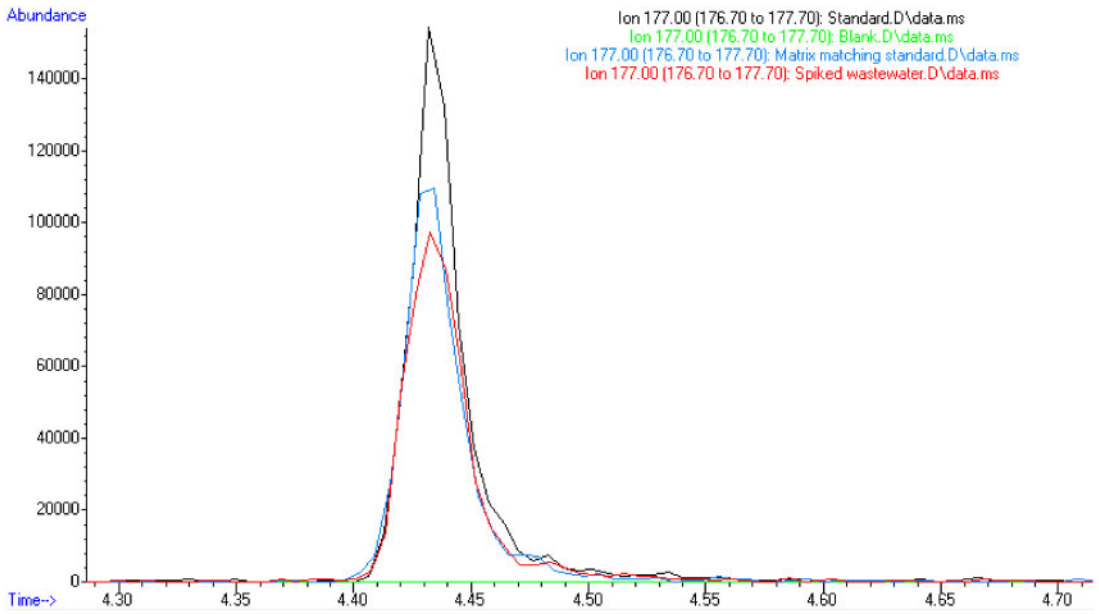


Figure 5. Overlay chromatograms of blank wastewater sample (green baseline), 50 μg/L spiked wastewater sample (red peak), 50 μg/L matrix matched calibration standard (blue peak), and 50 μg/L aqueous standard (black peak) for tefluthrin analyte.

Table 3. Percent recoveries calculated for spiked municipal and medical wastewater samples ($n = 3$ standard deviation)

	Municipal wastewater, %			Hospital wastewater, %		
Analyte	50 μg/L	100 μg/L	200 μg/L	50 μg/L	100 μg/L	200 μg/L
Dioxacarb	91.6 ± 4.0	103.2 ± 2.3	105.1 ± 10.2	105.8 ± 1.9	99.9 ± 1.4	99.4 ± 1.6
Trifluralin	97.6 ± 1.2	99.8 ± 1.6	107.9 ± 1.9	86.9 ± 1.2	106.9 ± 3.3	99.4 ± 2.3
Tefluthrin	90.4 ± 3.0	113.7 ± 0.3	110.5 ± 2.0	84.3 ± 4.4	105.9 ± 3.6	102.5 ± 1.8
Fenitrothion	108.5 ± 10.0	105.9 ± 6.6	91.6 ± 5.6	105.1 ± 9.3	97.7 ± 2.6	95.7 ± 0.9
Flumetralin	81.6 ± 3.5	111.7 ± 5.0	103.9 ± 1.7	81.3 ± 3.0	104.5 ± 1.1	100.0 ± 2.4
Escitalopram oxalate	105.4 ± 0.1	108.3 ± 1.3	100.3 ± 2.5	85.1 ± 0.4	106.2 ± 5.5	102.7 ± 0.7
Olanzapine	100.1 ± 1.8	98.7 ± 3.6	88.6 ± 3.3	99.5 ± 0.8	96.1 ± 10.6	100.1 ± 1.4
Haloperidol	99.8 ± 3.7	95.3 ± 3.0	100.3 ± 2.3	95.7 ± 9.2	112.6 ± 10.8	108.1 ± 7.5

each analyte's linear equation. According to the results obtained, the matrix of municipal and medical wastewater significantly hindered the extraction of the analytes with percent recoveries lower than 90%. The synthetic wastewater recorded appreciably high recoveries for some analytes, while others were low. In order to alleviate the low and irregular recovery results, matrix matching calibration method was employed for all three matrices. Here, calibration standards were prepared in similar matrices as the spiked samples. An overlay chromatogram showing a significant difference between 50 μg/L aqueous standard solution and 50 μg/L spiked wastewater sample is given in Figure 5. The figure also shows the closeness of the spiked sample to the matrix matched standard. The calibration plots of the matrix matched standards showed good linearity with R^2 values in the range of 0.9989–1.000. The percent recoveries calculated for the analytes spiked in synthetic wastewater were in the range of 85–113%. Presented in Table 3 are the percent recoveries for spiked municipal and medical wastewater samples and it can be seen that analyte recovery improved using the matrix matching calibration strategy. These results validate the method as accurate and applicable to the selected matrices.

Conclusions

This study made use of the efficient DLLME method for preconcentration of pesticides and pharmaceuticals from wastewater matrices for determination by GC-MS. An experimental design was used to optimize variables that affect the output of the extraction method and using the optimum values predicted by the design model, satisfactory analytical figures of merit were obtained for the analytes. The LODs were all below 40 μg/L and the analytes recorded enhancements in detection power between 3.6–539 folds. None of the analytes were determined in wastewater samples and spiked recovery tests were therefore performed to validate the method's accuracy and applicability. A matrix matching calibration strategy was used to overcome poor recovery results caused by high matrix content and this proved that the method can be used to quantify the analytes in different wastewater matrices with high accuracy and precision.

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Conflicts of interest

Authors have no interests to declare.

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