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Experimental design of switchable solvent–based liquid phase microextraction for the accurate determination of etrimfos from water and food samples at trace levels by GC-MS

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Abstract Presented in this study is a simple but efficient switchable polarity solvent microextraction strategy for etrimfos preconcentration from water and food samples for quantification by gas chromatography mass spectrometry. Repeatability of the extraction process and instrumental measurements were enhanced by using deuterated bisphenol A as internal standard. Significant parameters of the extraction method were fitted into an experimental design model to study the effects of parameters on extraction output, as well as mutual effects of combined parameters. The design model was formed with 51 experimented data obtained from the combination of sodium hydroxide volume, switchable solvent volume, and vortex period at three levels. The method was validated by applying optimum conditions attained from the model predictor. The detection limit was found to be 1.3 ng/mL and it corresponded to an enhancement factor of about 54 folds when compared to direct GC-MS measurement. Etrimfos was not detected in the water and food samples tested but the results (92–107%) obtained from spiked recovery experiments established that etrimfos when present in the selected matrices can be accurately and precisely quantified.

Keywords Etrimfos · Switchable solvent · GC-MS · QuEChERS · Experimental design

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Introduction

Ever since Rachel Carson's *Silent Spring* created awareness on the impact of pesticides on the ecosystem, several regulations have been introduced to evaluate all pesticides for their approval, safe usage, or prohibition (Grung et al. 2015). There are several studies that have reported adverse effects of pesticides on humans, the environment, and other organisms. The endocrine system basically controls the day-to-day function of the human body and some pesticides are capable of disrupting this normal function, leading to adverse health effects such as cancer (Monneret 2017; Balaguer et al. 2017). Producers and applicants of pesticides through occupation exposure stand the greatest risk to acute effects but consumers and other organisms accumulate low amounts that manifest into chronic effects over time (Gangemi et al. 2016; Mamane et al. 2015). Despite these negative effects, pesticides are being safely used in large quantities because of their benefits such as increased food quality and quantity, longer storage period and prevention of vector borne diseases (Popp et al. 2013; Damalas and Eleftherohorinos 2011). Etrimfos belongs to the organophosphate chemical class of pesticides and this chemical was formerly used as an effective insecticide against infestation of food products during storage, especially against driller insects. However, the European Union and the World Health Organization classify etrimfos as an obsolete pesticide, prohibited from use in the year 2009 (WHO 2010; EU 2009).

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Even after prohibition, some pesticides are capable of existing in the environment for very long periods due to their non-biodegradable nature and low water solubility (John et al. 2016; Kumar et al. 2014). These contaminants cannot be directly determined in their matrix form and therefore require sample preparation methods to isolate the analyte(s) of interest from its matrix into a form suitable for the instrumental technique being used (Slack and Snow 2007). Extraction methods are commonly used for a variety of samples and the focus of recent studies has greatly shifted to the use of green solvents that yield high results and produce very little or no waste (Z. Li et al. 2016; Wei et al. 2015). Microextraction methods are preferred over the classical solid phase and liquid-liquid extraction methods because they overcome disadvantages such as the use of toxic and large volume solvents, long periods of extraction, low enhancement factors, and low analyte recovery (Y. Li et al. 2015).

Among the new generation of green solvents, switchable polarity solvents possess unique properties that make them very useful in chemical processes such as separation, extraction, synthesis, and as catalyst for reactions (Domínguez de María 2017). The stand-out property of switchable solvents is the ability to change their polarities by simple protonation and deprotonation processes. Low polarity amines are used in producing switchable solvents by adding a hydrogen atom to the lone electron pair bearing nitrogen atom, forming a soluble conjugate acid. The protonation process is aided with periodic addition of carbon dioxide gas or solid carbon dioxide to the amine/water mixture until a single solvent is formed (Memon et al. 2017). When used as an extraction solvent, switchable polarity solvents (SPSs) do not need auxiliary solvents such as dispersive solvents to increase their surface area for extraction, but their polar nature ensures that they mix homogenously with the sample solution to extract the analyte(s). After extraction, polarity of the SPS is reverted to its non-polar state by adding an acid, a base, or flushing carbon dioxide out with an inert gas (Soylak et al. 2016). The extract obtained from SPS extraction is compatible with most instrumental systems and does not usually require further processing. SPS extracts are also suitable for gas chromatography mass spectrometry (GC-MS), where analytes are separated from the extraction solvent and from each other based on vapor pressure differences. The mass selective detector also allows simultaneous identification/quantification of analytes and separates them according to their different retention times and mass-to-charge ratios (m/z) (Mbughuni et al. 2016).

This study used an experimental design to optimize a switchable solvent liquid phase microextraction method (SS-LPME) to enrich etrimfos from water and food samples for its determination by GC-MS at trace levels. Isotopically labelled bisphenol A (BPA-D16) was added to all sample/standard solutions to ensure high precision for replicate determinations. The labelled standard was selected because of its extremely low probability of being found in the natural environment, and its distinct signal from the analyte of interest (Fig. 1). QuEChERS is a well-established sample pretreatment method widely used for routine pesticide analysis (N. Li et al. 2013; Chen et al. 2014; Zhao et al. 2012) and it was employed in this study for the food samples which could not directly analyzed by the SS-LPME method.

Materials and methods

Reagents

Etrimfos (CAS# 38260-54-7) was purchased from Dr. Ehrenstorfer (Augsburg, Germany) and an appropriate amount dissolved in methanol to prepare 2000 mg/L standard stock solution. Aliquots were then taken to prepare calibration standards in methanol for direct GC-MS analyses, and working standard solutions with ultrapure deionized water for method development. N,N-Dimethylbenzylamine (DBA) purchased from Merck (Darmstadt, Germany) was used to prepare the switchable solvent together with deionized water with the aid of solid carbon dioxide (dry ice) obtained from a local ice cream vendor. Sodium hydroxide, methyl cyanide, and acetic acid were purchased from Merck. Deuterated bisphenol A used as internal standard was purchased from Dr. Ehrenstrorfer (Augsburg, Germany).

Instrument

An Agilent 6890 model gas chromatograph system fitted with an HP-5MS column (length 30 m, internal diameter 250 μm, film 0.25 μm) and connected to an Agilent 5973 model mass selective detector was used to identify and quantify etrimfos in this study. The temperature program employed to elute etrimfos from the column was 50 °C/min ramp from 70 to 180 °C, and a final ramp of 40 °C/min to 280 where it was held for 1.3

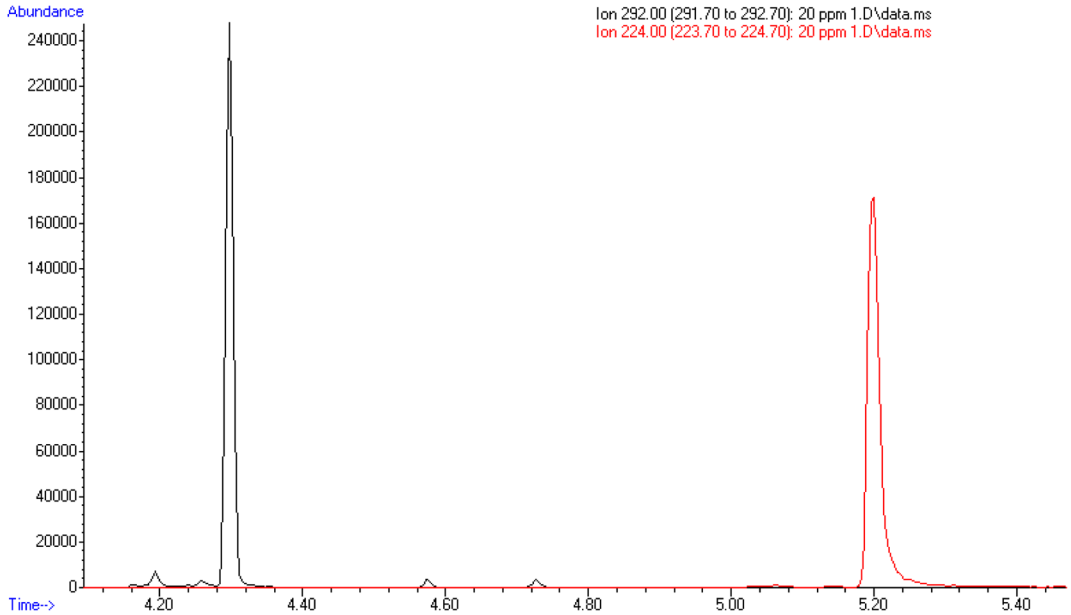


Fig. 1 An extract ion chromatogram showing the separated peaks of 20 mg/L etrimfos (4.29 min) and 10 mg/L BPA-D16 (5.20)

min. The carrier gas (99.999% helium) was kept at a constant flow rate of 1.4 mL/min, while the injection port (splitless inlet) temperature and injection volume were set at 250 °C and 1.0 μL, respectively. Temperatures of the MS transfer line, MS source, and MS quad were respectively set at 280 °C, 230 °C, and 150 °C, and the standard electron ionization energy of 70 eV was used. The most intense ions (*m/z*) used to quantify/qualify etrimfos and deuterated bisphenol A were 292/181 and 224/223, respectively. An ISOLAB (M1010002) vortex device was used for mixing samples and a Hettich Zentrifugen (EBA 20) centrifuge device was used to quicken phase separation.

SPS preparation

The switchable solvent used in this study was prepared by mixing equal volumes (100 mL each) of N,N-dimethylbenzylamine and ultrapure deionized water in a 250 mL Erlenmeyer flask. Broken pieces of dry ice were added at regular intervals (10–20 min) to the mixture and the flask was placed on a magnetic stirrer operating at 400 rpm. In order to prevent rapid escape of dissolved carbon dioxide gas, parafilm with a few perforated holes was used to cover the flask. Perforating the parafilm was done to prevent sudden jerk of the cover due to in-built pressure. The addition of dry ice under constant mixing was continued until a single-phase solvent was formed. The SPS was kept in the refrigerator (4.0 °C) when not in use.

SS-LPME procedure

Prior to extractions experiments, the prepared SPS was removed from the refrigerator to warm up to room temperature and checked to ensure the single solvent phase was intact. For all experiments, 8.0 mL of standard/sample solution was pipetted into clean plastic tubes and 1.3 mL of SPS immediately added. The solution was vortexed for 5.0 s followed by the addition of 1.1 mL sodium hydroxide for deprotonation, which was visualized as a cloudy white solution. After 30 s of vortexing for homogenous deprotonation, the resulting solution was centrifuged for phase separation and a sufficient amount taken from the low volume upper phase for instrumental determination.

Samples

Water samples from three lakes (Istanbul, Turkey), an irrigation canal (Antalya, Turkey), underground well (Samsun, Turkey), and wastewater treatment pools (Istanbul, Turkey) were taken into 1.0 L polypropylene plastic bottles. The bottles were thoroughly washed with the samples and filled to fullness. The samples were stored in a dry and cool wooden cabinet. Particulate

materials present in the samples were removed by filtering through 12 μm pore-sized filter papers. Rice and potato samples were purchased from a local market for the study.

Results and discussions

An experimental design was employed in this study in order to develop a model that could be used to navigate untested ranges of experimental parameter values. Only influential parameters to the extraction method were fitted into the experimental design. A pre-run performed with 50 ng/mL aqueous standard solution produced sufficiently high peak area values and all further experiments were therefore performed with 50 ng/mL. Deuterated bisphenol A was used as internal standard (IS) for all standards and samples.

Experimental design for SS-LPME

Significant parameters selected for the experiment were SPS volume, sodium hydroxide concentration, sodium hydroxide volume, and vortex period. The Box-Behnken design included 29 combinations (87 experimental runs for 3 replicates each) of the parameters at three value levels (low − 1, mean 0, and high + 1) with five common center combination points randomly distributed throughout the run order. In order to cut down on the number of combinational runs, the concentration of sodium hydroxide was optimized univariately by testing 0.50, 1.0, 2.0, 3.0, and 5.0 M. This was considered a logical choice because the concentration and volume of sodium hydroxide could become redundant in the experimental design. That is, the effect of a high volume of low concentration would be similar to a low volume of high concentration, based on final molarity of the two in the sample solution. After testing 2.0 mL of each concentration, 0.50 M emerged as the optimum concentration based on it recording the highest peak area value.

The new design therefore comprised of 17 combinations (5 center points), and the levels selected for SPS volume, sodium hydroxide volume, and vortex period were 1.0–1.5–2.0 mL, 1.0–1.5–2.0 mL, and 15–30–45 s, respectively. Three replicate extractions were performed for each combination run, making up a total of 51 experimental results. The expression below was used to evaluate the effect of independent variables (X_1, X_2, and X_3), linear coefficients ((β_1, β_2, and β_3), quadratic coefficients (β_{11}, β_{22}, and β_{33}), interaction coefficients, (β_{12}, β_{13}, and β_{23}), and a constant (β_0) on extraction outcome (Y) (Chormey et al. 2018).

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

The *Design-Expert 7.0.0* software was used to develop the experimental design and the software's analysis of variance (ANOVA) tool was used to establish the conformity between experimented and theoretical results. The linear regression coefficient (R^2) value obtained for the experimental data plotted in Fig. 2 was 98.6% and this validated its agreement to predicted values.

The reliability and accuracy of the model was also validated by the adjusted R^2 value (97.6%), which is the R^2 value modified according to the number of model predictors. The decrease (≈ 1.0%) in R^2 value signifies that the model is improved by the predictor by a less margin as supposed to chance. The F-value of the model was 142.91 while a value lower than 0.0001 was obtained for the model's P value. Significant parameters were determined based on P values being less than 0.05 and F-values being greater than F-crit. As denoted by the sign in Eq. 2, the main effects of switchable solvent and sodium hydroxide volumes were negative while vortex showed a positive effect.

$$\mathrm{R1} = +103,500 - 1.02300\mathrm{A} - 44825.52\mathrm{B} + 1101.04\mathrm{C} + 46670.38\mathrm{AB} + 38026.42\mathrm{A}^2 - 23884.12\mathrm{C}^2 \quad (2)$$

The negative effects imply that the lowest values of the parameters yielded the highest extraction results and the positive effect implied the opposite. Switchable solvent and sodium hydroxide volumes were very significant to the model with their P values lower than 0.0001. The higher volumes of SPS and sodium hydroxide produced high upper phase volumes after extraction leading to dilution of etrimfos. The low volumes on the other hand produced low upper phase volumes with concentrated etrimfos. The different vortex periods did not have significant impact (P value = 0.8204) on extraction output and this suggested that the deprotonation process caused separation of phases with effective

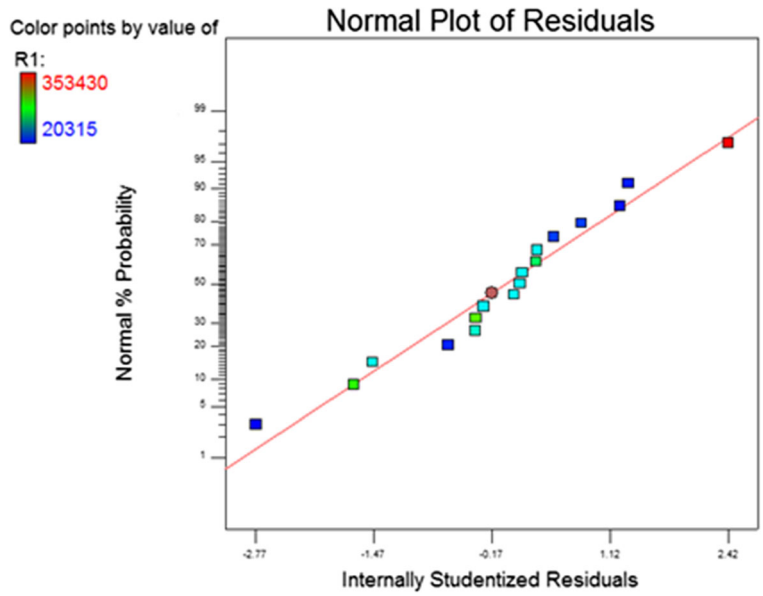


Fig. 2 A normal plot of residuals for experimented data

collection of the analyte. However, the extraction outputs increased marginally with increasing period as denoted by the positive main effect. The interaction between SPS and sodium hydroxide volumes was also very significant to the model as shown in the response surface plot in Fig. 3. Using the design model's predictor tool, optimum experimental conditions were determined as 1.3 mL of SPS, 1.1 mL of 0.50 M sodium hydroxide, and 30 s mixing by vortex.

Analytical figures of merit

Aqueous standard solutions in the range of 5.0–1000 ng/mL under optimum extraction conditions were used to develop a calibration plot that was used to validate the optimized method. Table 1 compares the figures of merit calculated for direct GC-MS and SS-LPME-GC-MS. For both methods, the use of deuterated bisphenol A significantly enhanced the linearity of the calibration plots (0.9999 for both methods) over wide concentrations ranges. The respective IS concentrations used for direct GC-MS analysis and method development were 5.0 mg/L and 20 ng/mL. The lowest concentration (5.0 ng/mL) was measured six times to calculate standard deviation (SD), which was in turn used to calculate limits of detection (LOD) and quantification (LOQ), and percent relative standard deviation (%RSD). The expressions 3 × SD/slope and 10 × SD/slope were used to calculate LOD and LOQ, respectively. Enhancement in detection power was calculated as the ratio of direct GC-MS (instrumental limit) LOD to the optimized method's LOD (1.3 ng/mL), and it yielded about 54 folds enhancement. The limit of quantification also fell below the default maximum residual limit (0.01 mg/kg) set for most vegetables, fruits, and food samples by the European Union (EU 2009). A study performed on cereals and cereal food products in the UK between 1994–2004 revealed residues of etrimfos between 0.06 and 0.30 mg/kg (Berry 2006). Repeatability of triplicate measurements was satisfactory, as expressed by the low values of percent relative standard deviation.

Spiked recovery test for aqueous samples

The developed SS-LPME-GC-MS method was tested on water samples from a well, an irrigation canal, three lakes, and two municipal wastewaters. Triplicate extractions and measurements were performed for each sample (blank analysis) but no analytical signals were recorded at the analyte's retention time. The well water sample and one lake water sample were selected for spike recovery studies in order to determine the amount of etrimfos that can be extracted and quantified when present. The lake water sample was selected to represent surface water, which is prone to aerial contamination and run-off from rain fall. The well water sample represented underground water, which is also prone to contaminants that leach down the soil beds. The spiking

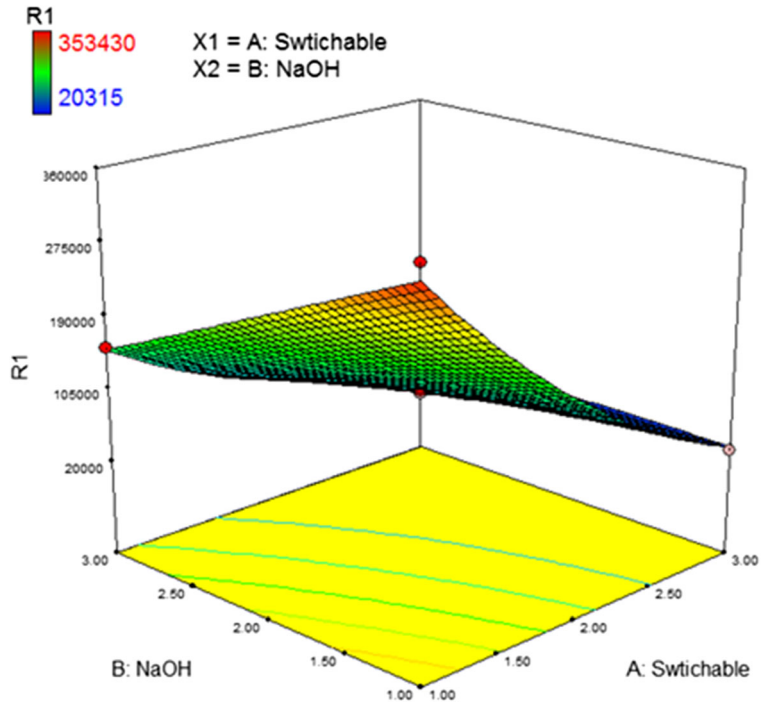


Fig. 3 A response surface plot depicting the interaction between SPS (A) and sodium hydroxide (B) with vortex held constant at 30 s

experiments were performed by diluting standards by 100 folds, to obtain a true representation of the sample matrices. The final spiked concentrations were 20, 50, and 100 ng/mL, and these were measured against five-point aqueous calibration standards. The respective percent recoveries calculated for the samples are given in Table 2. The proximity of the results to 100% and low %RSDs verified the method's accuracy and precision, respectively, making it suitable for the matrices tested.

Spiked recovery test for QuEChERS matrices

QuEChERS was employed as a pretreatment procedure for rice and potato samples. Ample amounts of the samples were blended for uniformity and weighed into 50 mL plastic tubes. The procedure reported by Lehotay (2007) was used in this study because the sample pretreatment process does not result in analyte dilution, as 15 g of sample is extracted with 15 mL of 1.0% CH_3COOH in methyl cyanide, using dispersive solid phase sorbents for matrix cleanup (Lehotay 2007). The QuEChERS extracts of the rice and potato samples (8.0 mL each) after filtration through 0.45 μm filter were spiked and subjected to the optimum SS-LPME method but deprotonation with the addition of sodium hydroxide did not produce a separate phase. The QuEChERS extraction solvent was totally miscible with the switchable solvent both in its polar and non-polar states. To mitigate this effect, the extract was diluted five times with deionized water to reduce the miscibility of the solvents and to lower matrix effects. The method detection limit for the solid samples therefore increased just five times. Distinct non-polar amine phases were

Table 1 Analytical performance of etrimfos determined for direct GC-MS and SS-LPME-GC-MS

Parameters	GC-MS	SS-LPME-GC-MS
LOD	70 ng/mL	1.3 ng/mL
LOQ	230 ng/mL	4.4 ng/mL
Linear dynamic range	200 ng/mL–100 mg/L	5.0–500 ng/mL
%RSD	6.5%	4.8%
R^2	0.9999	0.9999

Table 2 Percent recovery results calculated for etrimfos spiked in lake and well water

Sample	20 ng/mL	50 ng/mL	100 ng/mL
Lake water	95.9 ± 6.5%	92.1 ± 7.4%	105.3 ± 7.5%
Well water	106.9 ± 2.6%	100.8 ± 9.6%	98.1 ± 3.1%

obtained for the diluted matrices but they were very low relative to aqueous standard extractions. The peak area values for the spiked samples were significantly lower than their corresponding aqueous calibration standards resulting in percent recoveries lower than 80%. This suggests that the low volume was not sufficient to effectively collect the analyte in the deprotonation process. Matrix matched calibration standards were prepared in similar QuEChERS extracts of the respective samples and the calibration plots used to quantify spiked samples. The percent recoveries obtained for the potato and rice samples using matrix matching ranged between 94 and 102% as given in Table 3.

Conclusions

A switchable solvent liquid phase microextraction method was developed to preconcentrate etrimfos from aqueous media and food samples for trace determination by gas chromatography mass spectrometry. A multivariate experimental design was used to obtain optimum conditions of the extraction method after examining the main variables and their interaction effects. The optimum method produced an enhancement factor of 54 folds and its corresponding limits of detection and quantification were 1.3 and 4.4 ng/mL, respectively. The precision of the extraction method and measurements were enhanced by using deuterated bisphenol as internal standard. The precision calculated for the lowest concentration of the calibration plot expressed as relative standard deviation was lower than 5.0%. Several environmental water samples were analyzed but etrimfos was not detected in any of them. Application of the developed method to well and lake water samples spiked at different concentrations gave recovery results between 92 and 107%. Rice and potato matrices after QuEChERS extraction also produced recovery results between 94 and 102% using the matrix matching calibration method. The recovery results validated the accuracy and suitability of the developed method to the matrices selected. This method uses environmentally friendly solvents for an extraction process which is simple, inexpensive and efficient for the determination of etrimfos at trace level.

Table 3 Percent recovery results calculated for etrimfos spiked in potato and rice QuEChERS matrices

Spiked concentration	Potato matrix	Rice matrix
10 ng/mL	95.5 ± 6.2%	94.6 ± 2.5%
20 ng/mL	95.8 ± 6.1%	99.6 ± 1.5%
50 ng/mL	101.4 ± 8.5%	100.9 ± 4.5%
100 ng/mL	101.0 ± 3.7%	100.3 ± 8.0%
200 ng/mL	98.7 ± 7.2%	99.5 ± 5.3%

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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