Dispersive liquid liquid microextraction spectrophotometric determination of metoclopramide in various biological samples

Hassan Mohammed Jasim M.
Department of Chemistry, College of Science, Mustansiriyah University, Baghdad, IRAQ
dr.moh2004@uomustansiriyah.edu.iq

Abstract

A sample pretreatment technique based on dispersive liquid–liquid microextraction followed by spectrophotometric determination of metoclopramide in biological samples has been developed. The procedure involves rapid addition of mixture of organic solvents consisting of ethylene chloride and ethanol to the ion pair solution prepared by reduction Mo-(VI) to Mo-(V) using ammonium thiocyanate in acidic medium.

After removing the aqueous phase, the sediment phase was measured at λmax 469 nm. Under optimal experimental conditions, the linearity ranged 0.025-3 µg mL^{-1} for standard, urine and serum. The suggested method was successfully applied for the determination of metoclopramide in serum and urine samples.

Keywords: DLLME, Microextraction, Metoclopramide.

Introduction

The sample preparation is an important step in bioanalysis. Therefore, microextraction techniques are suitable for the analysis of the target analyte in biological samples since the analyte is present at low level. Microextraction techniques offer some advantages over the traditional sample preparation methods such as reducing the consumption of organic solvent and minimizing the sample volume[1].

In 2006, Rezaee et al[2] presented dispersive liquid-liquid microextraction (DLLME). In this technique, a mixture of organic solvents (an extracting and disperser solvents) is injected into the sample solution (containing the target analyte) using a micropipette or syringe. After dispersing the extraction solvent as fine droplets in the cloudy sample and centrifugation step, the organic layer is measured using a suitable instrument [3]. Combination of DLLME technique with UV–Vis spectrophotometry has become very popular.

Combination of the techniques mentioned above offer some advantages such as high enrichment factor, usefulness, speed, and simplicity, inexpensive and environmental friendliness. Moreover, DLLME technique presents some major benefits such as the negligible extraction solvents volume used, the large surface area between the droplets of the extraction solvent and the aqueous sample and the fast extraction kinetics that results in rapid achieving of a state of equilibrium[4].

DLLME has been developed for the determination and analysis of insecticides[5], volatile polycyclic aromatic hydrocarbons[6], fungicides[7], fluoroquinolones[8], valproic acid[9] thiamine[10], salmeterol[11] and barbituric acid[12].

Metoclopramide (META, Fig. 1) is chemically known as [4-amino-5-chloro-N-[2-(diethylamino) ethyl]-2-methoxybenzamide]. It is an antiemetic and gastroprokinetic agent commonly used for the treatment of nausea and vomiting[13]. Generally, it is freely soluble in water and alcohol (like ethanol) but practically insoluble in ether. The activity of META is due to its antagonist activity at D2 receptors in the chemoreceptor trigger zone in the central nervous system, this action prevents nausea and vomiting. The activity of META is mediated by muscarinic activity, 5-HT4 receptor agonist activity and D2 receptor antagonist activity. The purity and assay of META. were unaffected by the presence of its impurities and degradation products[14].

Various methods have been developed for the determination of META such as HPLC[15,16], H-NMR spectroscopic[17], voltammetry[18], potentiometric[19], flow injection chemiluminescence[20,21], flow injection-spectrophotometric[22] and spectrofluorimetric[13]. Spectrophotometric determination via using colorimetric reaction of META with different reagents such as 2,5-dimethoxyaniline[23], dibenzoyl methane[24], imipramine hydrochloride[25], folin-ciocalteu[26] has been frequently used for the determination of META.

So, in this work, DLLME has been coupled with UV-Vis spectrophotometry for the determination of META. in serum and urine is developed. The proposed method is based on extracted ion-pair- META, formed after reduction of Mo-(VI) to Mo-(V) using ammonium thiocyanate in acidic medium. The parameters affecting efficiency of the suggested method were evaluated such as volume of extraction solvent and disperser solvent, time and speed of centrifuge and extraction time. The performance of the suggested method for the analysis of pharmaceutical preparation and the real sample was tested.

Material and methods

Apparatus: APEL PD (303 UV spectrophotometer, Japan) with 1cm quartz microcells was used. Acceleration of phase separation process was performed using HERMLE centrifuge (Z 200A, Germany) with 15-mL centrifuge tubes.

Materials: The chemicals and reagents were of analytical grade. Ethanol, ammonium molybdate, ammonium

thiocyanate, ascorbic acid were supplied from BDH (England). Ethylene chloride and HCl were purchased from GCC (UK) and Fluka (Germany. Pure Metoclopramide was supplied by Samarra Drug Industry (Iraq). Standard solution of META (1000 µg mL^{-1}) was prepared by dissolving 1g of pure META in 1L of distilled water and stored at 4 C^0 in PVC container. The working solution (10 µg mL^{-1}) was prepared freshly in distilled water. Ammonium molybdate (VI) solution 0.04% was prepared by dissolving 0.04 gm to 100 mL. Ascorbic acid and ammonium. thiocyanate solution (10% each) were prepared by dissolving 10 gm for each one into 100 mL volumetric flask and then complete volume to the mark with D.W. 4 mol. L^{-1} HCl solution was prepared by dilution of concentrated HCl.

Dispersive liquid-liquid microextraction procedure: The mixture of 1 mL ammonium molybdate (0.04%), 1.25 mL of HCl (4 mol. L^{-1}), 1.25 mL of ascorbic acid (10%) and 1.5 mL of ammonium thiocyanate (10%) were placed in 15 mL centrifuge tube and hold it for 5 min. after that, different volumes of META (10 µg mL^{-1}) were added and diluted to 10 mL with D.W. ethylene chloride (300 µL) as an extraction solvent and ethanol (700 µL) as disperser solvent were rapidly injected into the solution using microsyringe to induce the formation of a cloudy solution. The mixture was then centrifuged for 4 min at 4000 rpm. The orange red ion-pair complex was collected by using microsyringe, placed into 1 cm quartz microcell, then measure the absorbance at 469 nm against blank. A blank solution was prepared under the same condition but without META addition.

Procedure for biological samples (serum and urine): 1 mL of serum was centrifuged for 10 min at 4000 rpm to remove proteins, then diluted to the mark with D.W. A urine sample was prepared by transferring 1 mL into 100 mL volumetric flask and diluted to the mark with D.W. Serum and urine samples were spiked with META working solution and then separately subjected to the DLLME procedure as described above.

Results and Discussion

Mo-(VI) is reduced by ascorbic acid and/or HCl to Mo-(V) upon its reaction with ammonium thiocyanate to form a red binary Mo-(V) thiocyanate complex. The formation of ion pair complex between Mo-(V) thiocyanate and the tertiary amine group occurs by the protonated nitrogen atom of the drug[27]. When META solution is added, an orange red complex is formed extracted by mixture of ethylene chloride (300 µL) and ethanol (700 µL). The absorbance spectra of ion pair complex after DLLME showed that the maximum abs. was obtained at 469 nm against the reagent blank. So, all subsequent measurements were performed at the selected wavelength (Fig. 2).

Optimization of the formation of ion pair: The effect of ammonium molybdate on the formation of the ion pair at various concentrations (0.01-0.12%) was studied. As show in fig. 3 a, the data appears that 0.04 % give the maximum value. Also, the effect of ascorbic acid and ammonium thiocyanate was studied. It was found that the reduction of Mo (VI) to Mo (V) occurs using ammonium thiocyanate in acidic media. Moreover, the addition of ascorbic acid enhances the sensitivity, stability and rapidity of Mo(v)-thiocyanate complex[27]. Therefore, the influence of ascorbic acid and ammonium thiocyanate was investigated in the range of 2.5-15 % (w\v).

The results show that maximum absorbance was obtained with 10 % (w\v) for ascorbic acid and thiocyanate respectively (Fig. 3 b, c). The effect of acidity on the formation of ion pair has also been studied in the range of 1-5 mol L^{-1}. As shown in fig. 3 d, 4 mol L^{-1} gave max absorbance. Therefore, optimization of DLLME method was carried out using chosen optimum conditions.

Optimization of DLLME techniques

Selection type of extraction and disperser solvents: In DLLME technique, selection of extraction solvent and disperser solvent is an important step. Generally, the suitable extraction should have high affinity to analysts, low solubility in water, higher density and lower miscibility than the aqueous sample[28]. To achieve this characterization, chloroform, dichloromethane, dichloromethane, benzene, hexane and carbon tetrachloride were chosen. While, the main feature of disperser solvent is the miscibility with both organic solvent and the aqueous phase that helps the dispersion of extraction solvent into small droplets in the aqueous phase. Therefore, ethanol, methanol, acetonitrile and acetone were studied as a disperser solvent. As shown in fig. 4, a mixture of ethylene chloride and ethanol gave higher absorbance signal than the others. Thus, this combination was chosen and subjected to further experiments.

Effect of extraction and disperser solvent volume: The value of the preconcentration factor and the sensitivity of the DLLME method are strongly dependent on the volume of the organic phase[29]. A volume range of 200- 500 µL of ethylene chloride containing 700 µL of ethanol was examined (Fig. 5 a). The results show that the absorbance decreases with increasing the volume of ethylene chloride. This is due to the dilution effect that helps to decrease the concentration of an analyte in the sedimented phase. So, 300 µL of ethylene chloride was selected. On the other hand, for the effect of disperser solvent volume, various volumes of ethanol ranged 500-1500 µL mixed with 300 µL of extraction solvent were investigated (Fig.5 b). It was found that by increasing the volume of disperser solvent, the absorbances increase up to 700 µL, but decrease thereafter (i.e. from 700 to 1500 µL). This is probably due to an increase of the solubility of analyte in water sample [30]. Therefore, 700 µL of ethanol was selected.

The effect of ionic strength: The influence of ionic strength was also studied to enhance transferring the analyte to the organic phase. The study was performed by the addition of different concentrations of NaCl (0-10 % (w/v)). The result

shows that the addition of salts had no effect on signal. Thus, the method was performed without salt addition.

Effect of extraction time: The effect of extraction time has also been studied using different intervals (1–20 min). The results show that the time did not contribute to an improvement in the signals. This is because of fast transition of the analyte from aqueous phase to the organic phase. Subsequently, the equilibrium state is achieved quickly. This was because the surface area between the extraction solvent and aqueous layer was infinitely large. Thereby, the method was rapid; this was the most important advantage of DLLME technique.

Effect of centrifugation speed and time: Centrifugation speed and time were also investigated to obtain excellent separation; the centrifugation time and speed were studied in the range of 1-10 min and 1000-6000 rpm respectively. The results show that 4 min at 4000 rpm gave higher absorbance signal so that they were chosen as optimum.

Stoichiometry of the ion pair: The nature of the Mo-(V) in the presence of excess amounts of ammonium thiocyanate was determined by continuous variation (Fig. 6 a) (Fig. 6 b) methods. The results indicate that the ratio of 1:1 (Reagent: drug), ion pair is formed.

Method validation: Under the experimental conditions, calibration graphs values, molar absorptivity, sandal sensitivity and regression line equations for each sample are illustrated in table 1. The results show that correlation coefficients were 0.9984. The enrichment factor was calculated from the slope ratio of the calibration graph after and before DLLME.

Five replicate determinations using four different concentration levels were tested for the precision and accuracy calculation. RSD% values were found to be less than 1.8 % indicating that reasonable repeatability of the selected method.

The recovery was investigated for serum and urine samples by spiked with four different concentrations of META and subjected to the proposed DLLME method. Good recoveries for biological samples in the range of 93.1-101.5 were obtained (Table 2).

The sample solution containing different concentrations (0.0025-3 µg mL^{-1}) of META was examined according to the proposed procedure of DLLME and the corresponding spectra of the organic phase were recorded in the range of 190-1100 nm. As shown in fig.7, the absorbance increased upon increasing of META concentration.

Interference study: The effect of potential compounds and ions was established using sample spiked with 1 µg mL^{-1} of META at different ratio (i.e.10, 100,1000-fold) of each one. The results shown in table 3 indicate that there is no interference effect for the studied ions and compounds.

Application: The proposed method was applied for extraction and determination of META in different real samples (i.e. serum, urine). Samples solutions were spiked with four different concentrations of META and subjected to the proposed DLLME method. Good recoveries for real samples in the range of (92-100.98) were obtained (Table 2). Comparable with other reported methods, the results show that the suggested method is more sensitive and accurate (Table 4).

Table 1
Analytical parameter of DLLME method

Parameters		**Real samples**			
	Std.		**Drug**	**Urine**	**Serum**
	Before DLLME	After DLLME			
Regression equation	Y= 0.0162x+ 0.1037	Y=0.5652x+0.116	Y=0.4995x+0.1428	Y=0.5045x+0.1356	Y=0.5605x+0.1427
Correlation coefficient r	0.9985	0.9984	0.9983	0.9984	0.9984
Linearity percentage r^2%	99.70	99.76	99.66	99.76	99.76
Linear range (µg mL^{-1})	2-65	0.025-3	0.025-3	0.025-3	0.025-3
Ɛ [a] (L mol^{-1} cm^{-1})	$4.9x10^3$	$1.69x10^5$	$1.5x10^5$	$1.51x10^5$	$1.68x10^5$
LOD [b] (µg mL^{-1})	0.2350	0.0067	0.0076	0.0075	0.0068
LOQ [c] (µg mL^{-1})	0.7757	0.0222	0.0251	0.00249	0.0224
S [d] (µg cm^{-2})	0.061	0.0018	0.002	0.0019	0.0017
[E] Enrichment factor	……..	34.88	30.83	31.14	34.60

Table 2
Accuracy and precision of the suggested method

Conc. (µg/ mL)	Intra-day repeatability (RSD [a] %, n=5)				Inter-day reproducibility (RSD%, n=5)				Rec. [b] % (n=5)			
	Std.	Drug	Urine	Serum	Std.	Drug	Urine	Serum	Std.	Drug	Urine	Serum
0.025	1.24	1.50	0.84	1.24	1.95	2.17	1.73	1.68	99.10	96.10	95.14	92.76
0.1	1.15	1.78	1.15	1.05	1.45	2.03	1.58	1.76	100.85	98.90	98.32	94.01
1	0.28	0.29	0.31	0.45	0.47	0.69	0.38	0.52	100.67	99.78	100.98	98.13
3	0.17	0.27	0.12	0.11	0.24	0.29	0.19	0.18	100.08	100.50	100.05	100.07

[a] Relative standard deviation; [b] Average of five determination

Table 3
Effect of interference ion

Coexisting ions	Tolerance ratio
Creatinine, urea, uric acid, SO_4^{-2}, K^+, Ca^{+2}, $PO4^{-3}$	1:1000
Creatinine, urea, uric acid, SO_4^{-2}, K^+, Ca^{+2}, $PO4^{-3}$	1:100
Creatinine, urea, uric acid, SO_4^{-2}, K^+, Ca^{+2}, $PO4^{-3}$	1:10

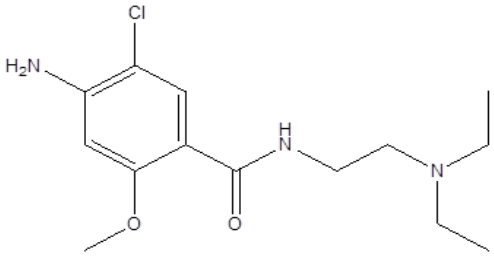

Fig. 1: Chemical structure of metaclopramide

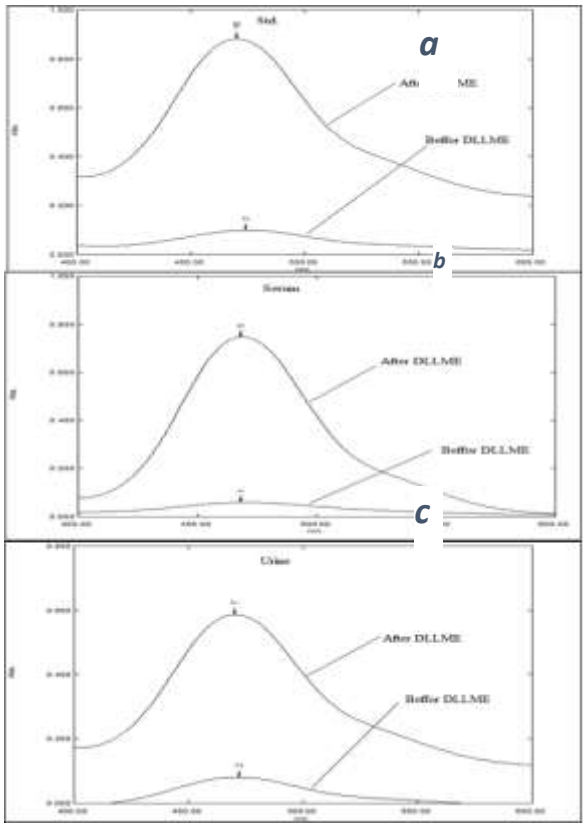

Fig. 2: Absorption spectra of metoclopromide spiked with 1 µg mL^{-1} before and after DLLME for (a) std. (b) serum and (c) urine

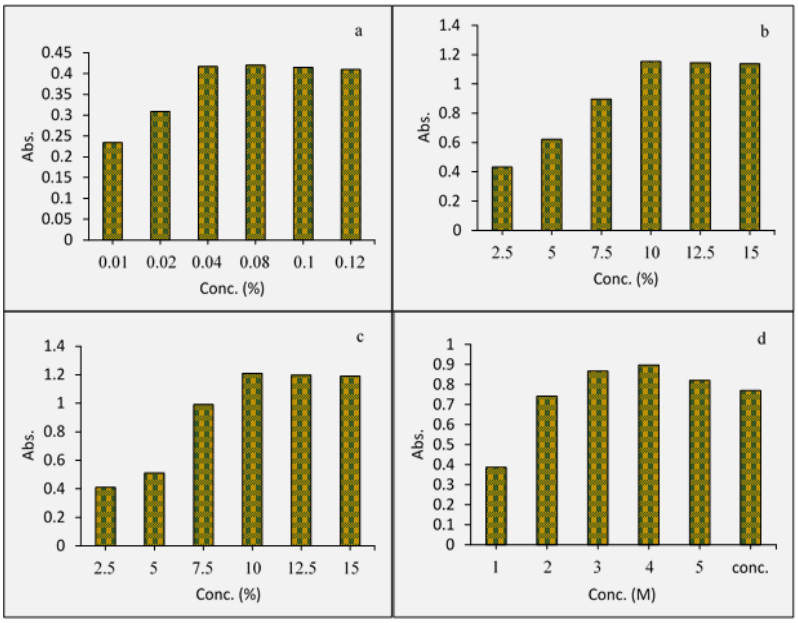

Fig. 3: Effect of concentration of a) am. molybdate b) ascorbic acid c) am. thiocyanate d) HCl

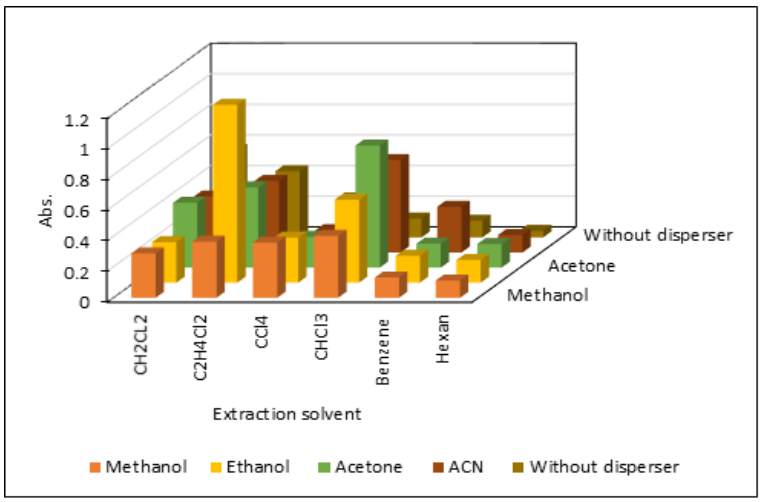

Fig. 4: Type of extraction and disperser solvents

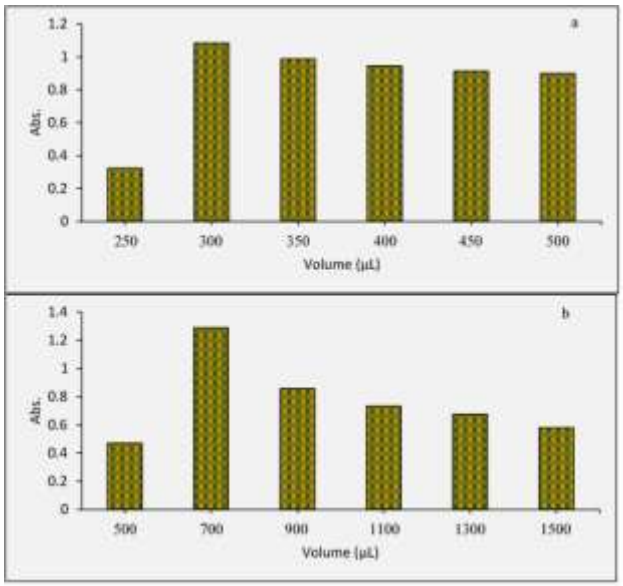

Fig. 5: Effect of volume of (a) ethylene chloride (b) ethanol solvents

Table 4
Comparison linear range, LOD and LOQ for the determination of Meta.

Method	Linearity ($\mu g\ mL^{-1}$)	LOD ($\mu g\ mL^{-1}$)	Samples
FI/UV-Vis.[22]	500-85000	500	Pharmaceutical formulation
RP-HPLC[16]	0.005-0.12	0.002	Serum
FI/CL[21]	0.005-3.5	0.001	Pharmaceutical preparation & biological fluid
Spectrophotometry[32]	0.1-10	0.012	Pharmaceutical preparation
DLLME/UV-Vis.*	0.025-3	0.0067 0.0075	Std. Urine
		0.0068	Serum

* Present study

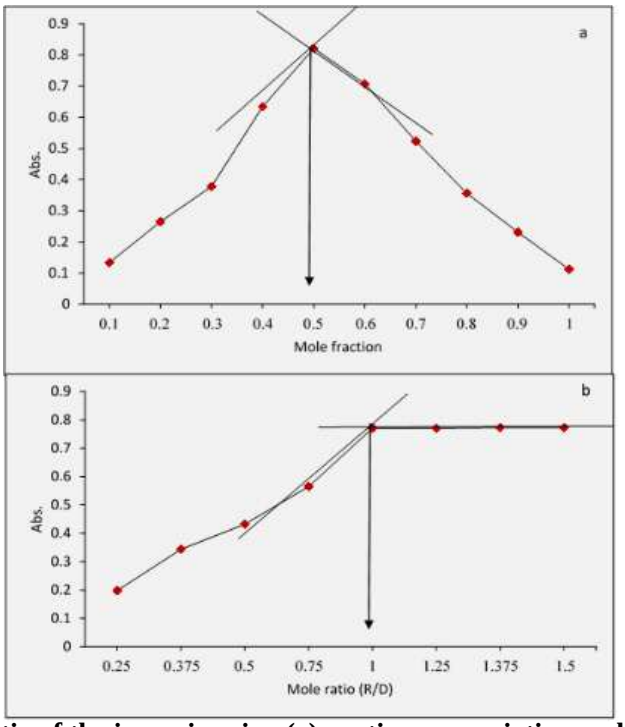

Fig. 6: Stoichiometric ratio of the ion pair using (a) continuous variation and (b) molar ratio method

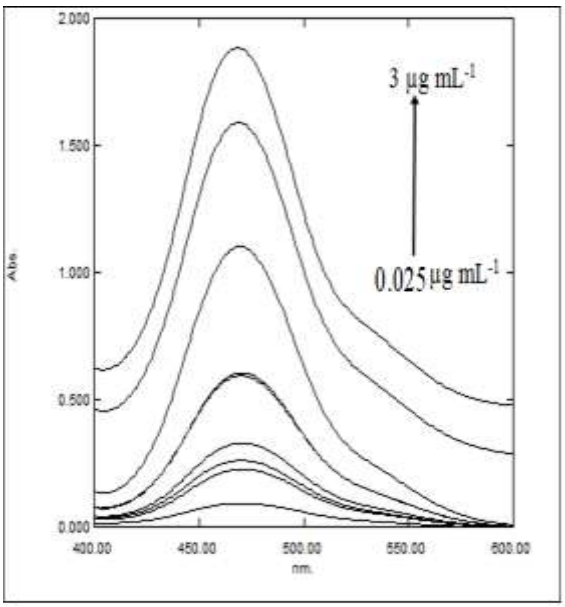

Fig. 7: UV-Visible absorbance spectra of sedimented phase in the presence of different concentration of Meta

Conclusion

Combination of DLLME with UV-Vis spectrophotometry for the extraction and preconcentration of META in biological samples is introduced. The developed DLLME method is simple, rapid and provides good enrichment factors (~32). Moreover, the method outlined a successful application and permits separation and preconcentration of META at a trace level in biological samples without requiring sophisticated instruments such as electrophoresis and/or HPLC.

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