ORIGINAL ARTICLE

DETERMINATION OF IBUPROFEN BASED ON SCREEN-PRINTED ELECTRODES MODIFIED WITH CARBON NANOFIBERS

IRINA MIRELA APETREI[1], ADRIANA AURORA BEJINARU[2], MONICA BOEV[1], CONSTANTIN APETREI[3]*, OLIMPIA DUMITRIU BUZIA[1]

[1]*Department of Pharmaceutical Sciences, Medical and Pharmaceutical Research Centre, Faculty of Medicine and Pharmacy, "Dunărea de Jos" University of Galați, Romania*
[2]*Department of Dental Medicine, Faculty of Medicine and Pharmacy, "Dunărea de Jos" University of Galați, Romania*
[3]*Department of Chemistry, Physics and Environment, "Dunărea de Jos" University of Galați, Romania*

**corresponding author: apetreic@ugal.ro*

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Abstract

Electrochemical determination of ibuprofen has been employed by cyclic voltammetry and differential pulse voltammetry, using a screen-printed carbon electrode modified with carbon nanofibers. The mechanism of the oxidation process for ibuprofen is controlled by diffusion. A well-defined anodic oxidation peak has been obtained at + 1.08 V *vs.* Ag in 0.2 M acetate buffer (pH 4.5). The quantitative determination of ibuprofen has been conducted in optimal experimental conditions by differential pulse voltammetry, in the linear range between 8×10^{-7} M and 3×10^{-5} M and a detection limit of 3.5×10^{-7} M was established. The sensor has shown stability and good reproducible voltammetric response, which recommends its use in the analysis of pharmaceutical products. The quantity of ibuprofen acquired in the analysis of pharmaceutical products is compliant with the quantities obtained by using the usual methods.

Rezumat

Detecția electrochimică a ibuprofenului s-a realizat cu un electrod serigrafiat pe bază de carbon, modificat cu nanofibre de carbon, folosind voltametria ciclică și voltametria puls diferențială. Mecanismul procesului de oxidare al ibuprofenului este controlat de difuzie, prin baleierea potențialului în sens anodic, obținându-se un pic de oxidare bine definit la + 1,08 V *vs.* Ag în soluție tampon acetat 0,2 M (pH 4,5). Determinarea cantitativă a ibuprofenului s-a realizat prin voltametrie puls diferențială, în condiții experimentale optimizate, pe un domeniu liniar cuprins între 8×10^{-7} M și 3×10^{-5} M și o limită de detecție de $3,5 \times 10^{-7}$ M. Senzorul este stabil, iar răspunsul voltametric reproductibil îl recomandă pentru utilizarea lui în analiza produselor farmaceutice. Cantitatea de ibuprofen obținută la analiza produselor farmaceutice s-a dovedit a fi în concordanță cu rezultatele metodelor folosite în mod uzual.

Keywords: ibuprofen, carbon nanofibers, screen-printed electrodes, differential pulse voltammetry, pharmaceutical analysis

Introduction

Ibuprofen (IBP) is one of the most commonly used drugs, an analgesic, antipyretic and anti-inflammatory drug, encountered in the OTC (over the counter) category [1]. It is a non-steroidal drug primarily used in the cure of muscle or toothaches, rheumatoid arthritis, fever and migraines [1]. Chemically speaking, ibuprofen is (RS)-2-(4-(2-methylpropyl)-phenyl)-propionic acid, an optically active compound with an asymmetrical (chiral) carbon atom [2]. Of the two isomers, isomer S is more biologically active, being the pharmacological active compound known as dexibuprofen [3]. Nevertheless, most of the pharmaceutical products containing ibuprofen contain a racemic mixture of R and S isomers [1, 2].

Ibuprofen presents side effects, such as nausea, heartburn, gastrointestinal bleeding and may induce an increase in the risk of heart failure [1]. Ibuprofen overdose may induce abdominal pain, vomiting, headache and an increase in the risk of myocardial infarction [1, 4]. Therefore, the development of sensitive analytical methods for the determination of ibuprofen in biological and pharmaceutical samples is of utmost importance for the medical and pharmaceutical fields.

Numerous analytical methods for the identification and/or dosage of IBP have been presented in the literature, worth mentioning being spectrophotometry [5], spectrofluorimetry [6], capillary zone electrophoresis [7], high performance liquid chromatography (HPLC) [8], etc. In addition, the electro-analytical methods have also been employed in the IBP determination [9]. The electro-analytical methods used in drug-quality control are particularly useful in screening analyses as they are fast, accurate and require small sample volumes. The sensors used for IBP determination were the usual ones, based on glassy carbon electrode [10], boron-doped diamond electrode [9], various composite materials [11, 12] and

the detection has been carried out by voltammetric methods. In order to increase the sensitivity and selectivity of electrochemical sensors, nanomaterials were used, the carbon-based ones (nanotubes, nanofibers, graphene) being the most commonly used [13].
A new electrochemical sensor based on screen-printed electrodes, modified with carbon nanofibers, for the detection and quantification of ibuprofen was developed.
Cyclic voltammetry has been employed for the characterization of the electrochemical behaviour of the sensor at the IBP detection. In the end of the study, a simple and sensitive method has been elaborated for the quantitative determination of IBP in pharmaceutical products, using differential pulse voltammetry as a detection method. This method was used for the analysis of ibuprofen in pharmaceuticals and validated at the laboratory level with the help of the official method presented by the Romanian Pharmacopoeia.

Materials and Methods

Chemicals
Acetone, ethanol and IBP were purchased from Sigma-Aldrich, Germany, and were of analytical grade, used without further purification.
Various pharmaceutics in the form of IBP-based tablets were purchased from local pharmacies in Galați, Romania. The IBP in the pharmaceuticals was purified by recrystallization. 10 - 15 caplets of ibuprofen were triturated using a pestle mill until a fine powder was obtained. Over this powder, 50 mL of acetone was poured, and the mixture was agitated for 20 minutes using a magnetic agitator. After the dissolving of IBP in acetone, the mixture was filtered and the acetone evaporated in a rotary evaporator *in vacuum* at 40°C. After the almost complete evaporation of acetone, the heating and rotation stopped and the solution was kept in the *vacuum* airship until the complete evaporation of acetone. In order to check the purity of ibuprofen crystals, the melting point was determined. Thus, by reaching a value of 75°C, an identical value with the specific value of pure ibuprofen was obtained [2].
The standard 10^{-3} M ibuprofen solution was prepared from purified IBP and absolute ethanol. For the electrochemical measurements, the stock solution of IBP was diluted with a 0.2 M acetate buffer solution (pH 4.5).
All reactive solutions used in this study had analytical purity. The solutions were prepared using ultrapure water as solvent (resistivity of 18 MΩ × cm).
Preparation of sensor
The screen-printed carbon electrodes (SPCE), model 110 DRP, were acquired from Dropsens Ltd. (Spain). The commercial electrode was made up of a working electrode (carbon, diameter = 4 mm), an auxiliary carbon electrode and an Ag pseudo-reference electrode. The working electrode was chemically modified by a dispersion of carbon nanofibers in order to obtain a sensor of high sensitivity and selectivity. The carbon nanofibers (D × L: 100 nm × 20 - 200 μm) were acquired from Sigma-Aldrich, Germany. The dispersion of the carbon nanofibers in absolute ethanol was obtained by ultrasonication using the ultrasound bath Elmasonic S10H for 20 minutes. The dispersion of carbon nanofibers contained 25 mg of CNF dispersed in 10 mL absolute ethanol. SPCE was cleaned with a water/ethanol solution and dried in a desiccator. 10 μL of CNF/ethanol dispersion were deposited on the working electrode of the SPCE and the solvent was left to evaporate at room temperature for 2 h.
Electrochemical measurements
Electrochemical measurements were carried out with a Biologic SP 150 potentiostat/galvanostat (Bio-Logic Science Instruments, Seyssinet-Pariset, France). The electrochemical cell used had a 20 mL volume, so that only 10 mL of electrolytic solution was necessary for the voltammetric measurements. The sensor was connected to the potentiostat through a special cable, so that the three electrodes immersed in the solution in order to be analysed could fulfil their role in optimum conditions. The cyclic voltammograms were recorded at different scan rates, from 0.01 to 0.5 V/s, the optimal rate for practical applications being that of 0.05 V/s.
The differential pulse voltammetry technique (DPV) was used for the quantitative determinations due to its better performance compared to cyclic voltammetry (CV). The optimal parameters of DPV were 0.05 V of amplitude, 0.5 s of pulse time, 0.01 V of pulse width and 0.02 V/s of scan rate.
The pharmaceuticals analysed were: Ibufen® (200 mg, film-coated tablets, S.C. Antibiotice S.A., Romania), Brufen® (400 mg, film-coated tablets, BGP Products AB, Sweden) and Paduden Forte® (400 mg, tablets, Terapia S.A., Romania). The results obtained were validated by comparing them with the values obtained by using the reference method presented by the Romanian Pharmacopoeia, the analytical method based on the UV spectroscopy at 264 nm in 0.1 M NaOH solution [2]. The results were also compared to the values reported by manufacturers in the specifications of the drugs analysed.

Results and Discussion

The preliminary studies showed that the best electrochemical behaviour, the best sensitivity and selectivity for the IBP detection were obtained when the solution used as a counter electrolyte was the 0.2 M acetate buffer solution of pH 4.5. The analysed solution, obtained after adding the ethanol solution of IBP in 0.2 M acetate buffer solution of pH 4.5

contained ethanol, which was compulsory because of the low solubility of IBP in water.

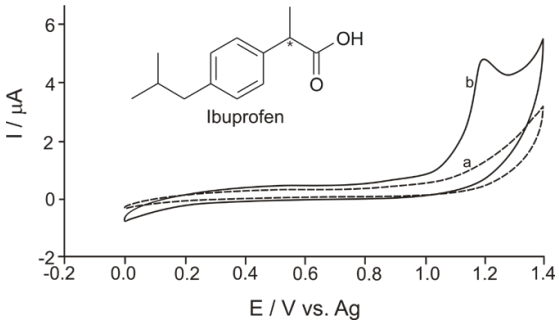

Figure 1.

Cyclic voltammograms of CNF/SPCE immersed in (a) 0.2 M acetate buffer of pH 4.5 and (b) 10^{-5} M IBP in 0.2 M acetate buffer of pH 4.5. Scan rate was 0.05 V/s. Inset figure: Chemical structure of IBP (*asymmetric carbon)

The cyclic voltammograms of the CNF/SPCE sensor immersed in acetate buffer of pH 4.5 and 0.2 M concentration and respectively IBP 10^{-5} M (counter electrolyte: 0.2 M acetate buffer of pH 4.5) are presented in Figure 1. The inset figure illustrates the chemical structure of IBP.

As apparent from Figure 1, the curve (a), the cyclic voltammograms of CNF/SPCE immersed in the support electrolyte solution does not present redox peaks. The current presents low values and, therefore, this sensor is appropriate for the voltammetric determination of electroactive substances. The voltammograms presented in Figure 1, curve (b) presents an irreversible oxidation peak at + 1.19 V.

The mechanism of the IBP electrochemical oxidation reported in the literature consists in the transfer of an electron with the formation of a radical-cation, followed by a decarboxylation process, and the process is not influenced by the pH [9-12]. Therefore, the electrochemical oxidation of IBP corresponds to an EC mechanism (electrochemical-chemical reaction) which comprises the transfer of an electron followed by a homogeneous chemical reaction. The electrochemical process of IBP at the surface of the sensor is similar to the one reported in the literature [9-12].

The advantages of this sensor when compared to other sensors used in IBP detection are lower detection potential and higher peak current (Table I) [9-12].

Table I

The main characteristics of the sensors used in the detection of IBP

Sensitive material	Electrochemical technique	Detection potential (V)	Peak current (µA)	LOD	Reference
Boron-doped diamond	DPV	+ 1.72	0.75	3.8×10^{-6} M	[9]
Glassy carbon	CV	+ 1.29	5.5	not reported	[10]
	SWV	+ 1.3	6.0		
HKUST-1 metal-organic framework-carbon nanofiber	CV	+ 1.25	10	21.7 µg/L	[11]
Graphite	SWV	+ 1.1	1.1	0.1 µg/cm^3	[12]
Carbon nanofibers	CV	+ 1.19	4.8	3.5×10^{-7} M	This work
	DPV	+ 1.08	12		

LOD – limit of detection; SWV – square wave voltammetry

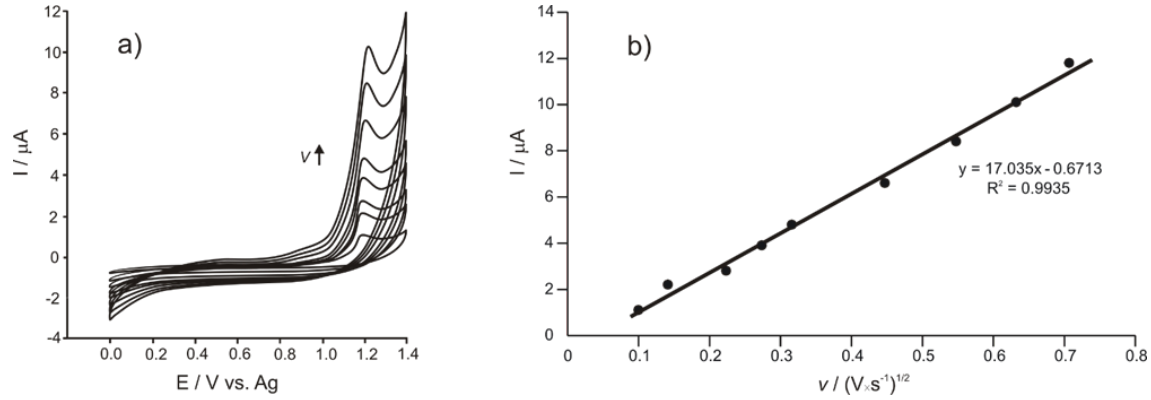

Figure 2.

(a) Cyclic voltammograms recorded at CNF/SPCE in 0.2 M acetate buffer of pH 4.5 supporting electrolyte in the presence of 10^{-5} M IBP at different scan rates: 0.01, 0.02, 0.05, 0.075, 0.1, 0.2, 0.3, 0.4 and 0.5 V/s. (b) The anodic peak current *vs*. square root of the scan rate

In order to determine the influence of the scan rate over the electrochemical detection of IBP by the CNF/SPCE sensor and the kinetic factor which controls the IBP oxidation process, cyclic voltammograms at various scan rates were recorded.

Figure 2a presents the cyclic voltammograms recorded with CNF/SPCE in IBP solution of 10^{-5} M at various scan rates from 0.01 to 0.5 V/s.

An increase of the current peak is observed when the scan rate is increased. The dependence between the anodic peak current and the square root of the scan rates is linear (Figure 2b). This result corresponds to an electro-catalytic process of IBP oxidation controlled by the diffusion process [14].

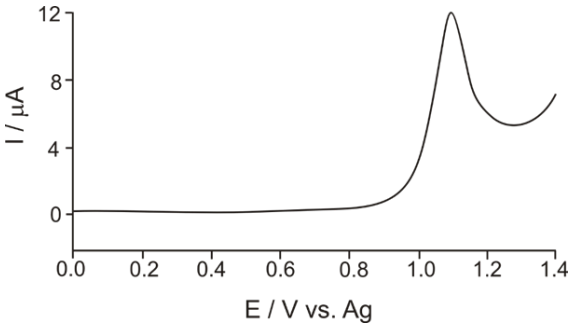

Figure 3.

DPV curve of CNF/SPCE immersed in 10^{-5} M IBP in 0.2 M acetate buffer of pH 4.5. Scan rate is 0.02 V/s

In view of increasing the sensitivity of the method in the studies on the quantitative determination of IBP, the DPV was employed, a technique by which the current background is significantly diminished and the peaks related to the redox process at the voltammetric sensor surface are better outlined [14]. The specific parameters of DPV technique were optimized, the best results being acquired when 0.05 V of amplitude and 0.020 V/s of scan rate are used. Figure 3 presents the DPV curve of the sensor CNF/SPCE immersed in 10^{-5} M IBP solution in 0.2 M acetate buffer of pH 4.5.

When compared to the signal obtained by CV, the DPV curve presents the oxidation peak of IBP at a lower potential (+ 1.08 V compared to + 1.19 V) and a higher current (12 µA compared to 4.8 µA). It follows that the DPV technique ensures an increased sensitivity of the sensor for the IBP detection. DPV was also used for the determination of the analytical performance of the CNF/SPCE sensor in the detection and quantification of IBP. The potential domain was preserved identical to the one used in CV, from + 0.0 V to + 1.4 V. The DPV curves were recorded in IBP solutions of various concentrations, ranging from 8×10^{-7} to 5×10^{-5} M (Figure 4).

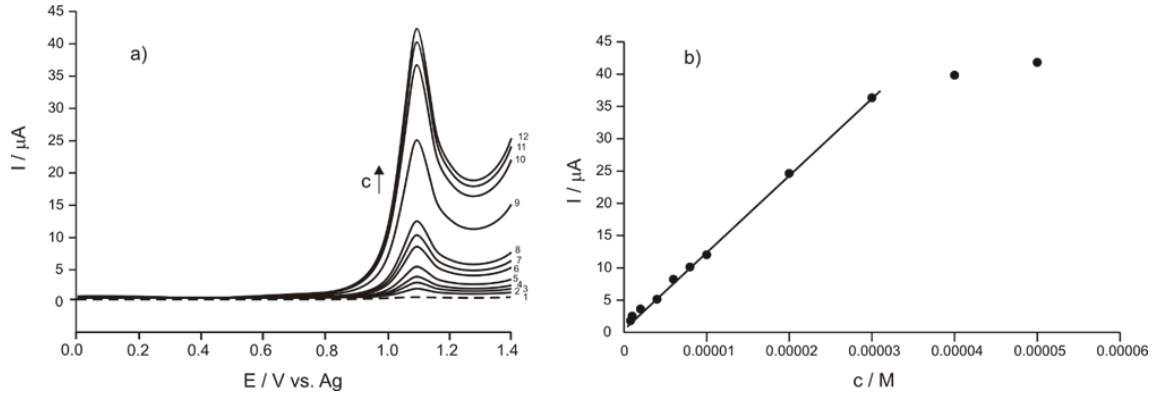

Figure 4.

(a) DPVs recorded on CNF/SPCE in 0.2 M acetate buffer of pH 4.5 supporting electrolyte (curve 1) and in the presence of different IBP concentrations ranged from 8×10^{-7} to 5×10^{-5} M IBP (curves 2 - 12). (b) The calibration curve between the current of the anodic peak and the IBP concentration, with the accentuation of the linearity domain.

As obvious from Figure 4a, the anodic peak current increases with the increase of concentration. However, at higher concentration values (over 3×10^{-5} M), the anodic peak current does not increase. A relation of linearity between the peak current and the IBP concentration in the domain 8×10^{-7} to 3×10^{-5} M is obtained (Figure 4b). The equation of the calibration curve is I (µA) = 1.17 × c (µM) + 0.88, and the correlation coefficient is $R^2 = 0.9989$. From the calibration curve, sensitivity (S) and the limit of detection (LOD) were calculated. The values S (1.17 µA × µM) and LOD (3.5×10^{-7} M) indicated that the sensor developed in this study has improved performance when compared to other sensors used for IBP determination (Table I) [9, 12]. These better results are owed to carbon nanofibers which increase the electroactive area and the transfer rate of the electrons.

The repeatability of the DPV measurements was determined by the successive recording of 10 DPV curves in 10^{-5} M IBP solution in 0.2 M acetate buffer of pH 4.5. The results obtained are relevant, indicating that the CNF/SPCE sensor does not suffer passivation or contamination processes, issues which often occur in electro-analytical methods. Relative standard deviation (RSD) calculated for the ten determinations is of 1.8%, a small value which proves the viability of the sensor in what concerns the ibuprofen detection in complex samples.

Studies concerning the influence of various interfering substances over the sensor response were based on the modification of the anodic peak current. In Figure 5 are presented the DPV curves of the sensor immersed in 10^{-5} M IBP solution and 10^{-5} M IBP solutions also containing 10^{-5} M paracetamol, 10^{-5} M ascorbic acid or 10^{-5} M glucose, respectively.

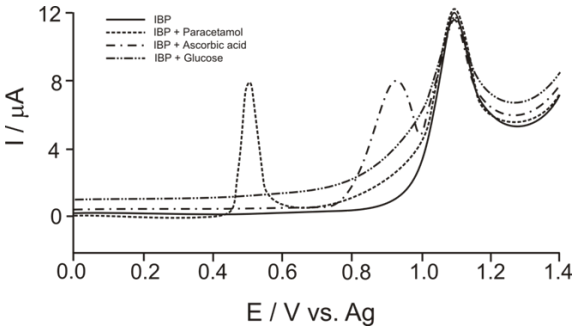

Figure 5.

DPV curves recorded on CNF/SPCE in 10^{-5} M IBP solution, 10^{-5} M IBP + 10^{-5} M paracetamol solution, 10^{-5} M IBP + 10^{-5} M ascorbic acid solution and 10^{-5} M IBP + 10^{-5} M glucose solution (supporting electrolyte was 0.2 M acetate buffer of pH 4.5)

As can be seen in Figure 5, in the case of paracetamol or vitamin C, besides the characteristic peak of IBP (+ 1.08 V), the characteristic peaks of interfering substances are obtained, but the difference between the peaks' potentials is sufficiently large and there are no significant differences in the simultaneous detection of the two compounds. No additional peak was observed in the case of glucose.

The quantification of the interfering substances influence over the anodic peak of IBP was carried out by calculating the relative deviation of the peak current. The values obtained were 2.5% for paracetamol, 3.7% for ascorbic acid and 1.7% for glucose. Therefore, the relative deviations of the IBP peak current are below 4% at 10^{-5} M concentration levels, highlighting the good selectivity of the sensor.

The new sensor developed in this study was used for the quantitative determination of IBP in various pharmaceutical products. The reference method was the official method in the Romanian Pharmacopoeia [2]. The results obtained for the quantitative determination are presented in Table II. The IBP amount obtained by using the method reported in the present study is compliant with the quantity obtained by using the reference method and to that reported by manufacturers.

Table II

Amounts of IBP measured in pharmaceutical samples

Pharmaceutical sample	Ibuprofen		
	a/mg	b/mg	c/mg
Ibufen®	200	200 ± 4	200 ± 6
Brufen®	400	400 ± 9	400 ± 12
Paduden Forte®	400	400 ± 10	400 ± 14

a = amount of IBP in the pharmaceutical sample (label value); b = amount of IBP determined by the developed method ± standard deviation (n = 5); c = amount of IBP determined by the reference method ± standard deviation (n = 5)

The validity of the method which uses the CNF/SPCE sensor and DPV as detection technique was demonstrated through five replicates in the course of a single day (intra-day assay), using a standard solution of IBP 5×10^{-6} M and for a ten - days period using a standard solution of IBP 10^{-5} M (inter-day assay). The results obtained are presented in Table III. The studies regarding recovery were conducted by the standard addition method, being also presented in Table III. The obtained results confirmed the accuracy of the voltammetric determination of IBP.

Table III

The precision of the assay for standard IPB solution (n = 5)

	IBP concentration taken (M)	IBP concentration found (M)	Precision (% RSD)	Recovery (%)
Intra-day	5×10^{-6}	4.99×10^{-6}	2.2	99.8
Inter-day	1×10^{-5}	1.012×10^{-5}	3.0	101.2

Table IV

Recovery test for IBP in pharmaceutical samples

Sample	Ibuprofen		
	IBP added ($\times 10^{-6}$ M)	IBP found ($\times 10^{-6}$ M)	Recovery (%) ± RSD (n = 5)
Ibufen®	2	2.01	100.5 ± 0.8
	4	3.98	99.5 ± 0.9
	6	6.05	100.8 ± 0.8
Brufen®	3	2.98	99.3 ± 0.5
	5	4.98	99.6 ± 0.7
	7	6.95	99.2 ± 0.5
Paduden Forte®	2	2.02	101.0 ± 0.5
	5	5.11	102.2 ± 1.0
	8	8.07	100.8 ± 0.9

In order for the method to be validated at the laboratory level, a recovery study was conducted using more pharmaceutical products (Table IV).
The IBP recoveries obtained for all pharmaceuticals analysed are close to 100%, which proves that the method reported in this study has very good precision, including in complex samples.

Conclusions

A-novel sensor based on CNF/SPCE for the detection and quantification of IBP, with possible applications in pharmaceuticals quality control, was developed. The employed approach has proven that the sensor is reproducible and highly sensitive, therefore feasible for practical applications. In addition, it was demonstrated that the sensitive nanocomposite material has excellent electrochemical properties, a large active surface and a good capacity of transferring electrons. The sensor's sensitivity in IBP detection is very good and the limit of detection is in the submicromolar level. The developed method of IBP quantification could be significant for the analytical practice, as it is sensitive, requires a limited time and the costs are low.

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