Paracetamol Sensitive Cellulose-Based Electrochemical Sensors

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ABSTRACT: Electrochemical determination of paracetamol (PCT) was successfully performed using carbon paste electrodes (CPEs) modified with treated coffee husks (CHt) or cellulose powder (Ce). Scanning electron microscopy was used to characterize unmodified or modified CPEs prior to their use. The electrochemical oxidation of PCT was investigated using square wave voltammetry (SWV) and cyclic voltammetry (CV). The oxidation current density of PCT was two-fold higher with the CPE-CHt sensor and 30% higher with CPE-Ce in comparison with the unmodified CPE, and this correlated with the higher hydrophilicity of the modified electrodes. Using SWV for the electrochemical analysis of PCT, carbon paste electrode modified with raw coffee husks (CPE-CHr) showed the presence of impurities at +0.27 V/SCE, showing the interest in using pure cellulose for the present analytical application. Furthermore, CPE-Ce presented a higher real area compared to CPE-CHr, which explains the increase in the limit of saturation from 400 mg/L to 950 mg/L. The better saturation limit exhibited by CPE-Ce justifies its choice for electroanalysis of PCT in commercialized tablets. The proposed method was successfully applied in the determination of PCT in commercialized tablets (Doliprane® 500) with a recovery rate close to 100%, and no interference with the excipients contained in the tablets analyzed was observed.

This novel sensor opens the way for sustainable development of electroanalytical control of drugs sold individually in developing countries.

KEYWORDS: Paracetamol, carbon paste electrode, coffee husks, cellulose fibers, square wave voltammetry, electroanalysis

1 INTRODUCTION

Paracetamol (4'-hydroxyacetanilide or N-acetyl *p*-aminophenol, hereafter referred to as PCT) is one of the most widely used drugs in the world, because of its great activity against mild to moderate pain associated with headache, backache and arthritis [1] and its efficiency against fever [2]. Generally, PCT does not exhibit any harmful side effects but hypersensitivity or overdose ingestion in a few cases leads to the formation of toxic metabolites that can cause severe nephrotoxicity and hepatotoxicity [3, 4], accompanied in some cases by renal failure [5, 6]. Traditional analytical methods used for the determination of PCT include titrimetry [7], UV-visible spectrophotometry [8–10], spectrofluorometry [11], chemiluminescence [12], and chromatography [13–15]. Although these methods operate quite well, they are generally time consuming and laborious.

As alternatives, electrochemical methods offer several advantages in terms of cost, accuracy, selectivity and sensitivity [16–18]. Resorting to electroanalytical methods is also afforded by the electroactive character of PCT, which can be easily oxidized under proper conditions due to the hydroxyl and amino groups on its aromatic ring. During the past few years, many works have been carried out focused on the electrochemical determination of PCT. Some recent reports on its quantification by means of chemically modified electrodes include the use of multiwalled carbon nanotubes/graphene oxide nanocomposite-modified glassy carbon electrode [19], a graphene oxide-nafion composite film glassy carbon modified electrode [6], and a

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boron-doped diamond electrode modified with Nafion© and lead films [20]. Likewise, carbon paste electrodes (CPEs) chemically modified by an active compound and/or material displaying affinity towards PCT have been shown to be useful tools for the detection of PCT. As typical examples, Beitollahi *et al*. [21] reported the use of a carbon paste electrode modified with 5-amino-3′,4′-dimethyl-biphenyl-2-ol/carbon nanotubes for the simultaneous determination of PCT and other drugs. Shahmiri *et al*. [22] reported a simple and rapid method for the analysis of PCT and glutathione, based on a CPE modified with ethynylferrocene and NiO/MWCNT nanocomposite. More recently, Mashhadizadeh and Rasouli [23] designed a CPE modified with TiO_2 nanoparticles for the simultaneous determination of codeine and PCT in human plasma. These last studies demonstrate that CPE introduced in electroanalysis in 1958 by Adams [24] remains to date a convenient device for the qualitative and quantitative analysis of various compounds. CPEs are easy to prepare, inexpensive and generally give rise to reproducible signals [25]. Also, they display low background and long-term stability, as well as high polarization limits in both anodic and cathodic directions [26]. Taking into consideration these features, the development of low-cost, simple and accurate electrochemical sensors for the detection of PCT is of permanent interest for quality control analysis of pharmaceutical formulations, as recently reported in the literature [27, 28].

On the other hand, the exploitation of ligno-cellulosic materials (LCMs) as effective sorbents for organic compounds, such as dyes and pesticides, has been largely investigated during the last decade [29–32]. The uptake of such organic compounds is commonly achieved via hydroxyl and carbonyl groups found abundantly in polysaccharides (cellulose and hemicelluloses) and lignin, which together constitute about 90% of dried LCMs [33]. Their attractiveness results from their great availability, low cost, biodegradability and organophilic character. Coffee, one of the most popular beverages, is cultivated in about 80 countries around the world [32]. In the western region of Cameroon, two main varieties of coffee are largely produced: Arabica coffee and Robusta coffee. Their transformation generates large amounts of by-products, such as coffee husks, that are obtained when coffee berries are processed by the drying method [34]. Coffee husk is the part enclosing coffee beans; it represents about 12% of the berry dry-weight, and contains cellulose, hemicellulose, lignin and ash [35, 36]. This attractive composition explains why coffee husks have recently been exploited for PCT analysis in a LCM modified CPE amperometric sensor [27]. Therefore, in the present study we were interested in investigating the exploitation of pure cellulose fibers in comparison to coffee husk, for the elaboration of a sensor useful in electrochemical analysis of PCT which could be applied to quality control for low-cost and/or out-of-date commercialized PCT tablets in developing countries. The surface of the electrodes was characterized using scanning electron microscopy, cyclic voltammetry (not shown) square wave voltammetry (SWV) and contact angle techniques. Finally, the analytical performance of a novel modified CPE for quantification of PCT was evaluated by SWV on commercialized pharmaceutical tablets.

2 MATERIALS AND METHODS

2.1 Reagents

Paracetamol (PCT) was purchased from Sigma-Aldrich as powder and used as received. A 0.1 M phosphate buffer solution of pH 7.4 (PBS) was used as supporting electrolyte. All other aqueous solutions were prepared from analytical grade chemicals, using deionized water obtained from an ELGA LabWater ultrapure water system (PureLab UV/UF, ELGA, France) (pH 6.5, conductivity < 1 µS cm^{-1} and TOC < 0.1 M). Doliprane® 500 tablets (manufactured in February 2014) were purchased from Sanofi-Aventis (France) delivered under the batch n°5768.

2.2 Coffee Husks/Cellulose Powder

Coffee husks used in this study were collected from a coffee-processing mill in Santchou (Menoua Division, West Cameroon) and dried under sunlight for 3 days. They were ground and crushed, and a series of sieves allowed obtainment of their fine fraction (0–100 µm mean average size) which was used for the preparation of modified CPE.

According to the literature data, lingo-cellulosic materials are essentially composed of cellulose, hemicelluloses and lignin. They also contain extractible matter (2 to 8% of dry matter), metallic cations, such as Mg^{2+}, Ca^{2+}, K^+, Na^+, and other chemical elements like P, N, S or Si [37–38]. As expected, the EDX spectrum of the coffee husk powder used here revealed the presence of K, C, Ca and O as major components, as well as traces of P, Si, S, Na and Mg, as recently reported in the literature [27]. The percentage of cellulose, hemicellulose and lignin in the coffee husk powder was determined using the ADF-NDF method. Cellulose, hemicelluloses and lignin accounted for 55%, 5% and 9% of the total dry weight, respectively, a composition which is different from that reported for coffee husks from Ethiopia [35] where percentages were found to be 24%, 29% and 23%, respectively, for cellulose, hemicelluloses and lignin. However, the chemical composition of coffee husks varies from

one country to another, and within a country it depends on geographic location, climate, age and soil condition [34]. For instance, our results are in agreement with those reported in another study performed in Portugal [39] in which 43.0% of cellulose and 9.0% of lignin were found.

Cellulose powder from spruce was purchased by Honeywell Fluka™ (Batch n°345768/1 595) and the length of the fibers ranged between 0.02 and 0.15 mm.

2.3 Apparatus

The electrochemical measurements were performed using an electrochemical analyzer PG580 (Uniscan Instruments, UK) connected to a personal computer. The electrochemical software used was UiEchem version 3.27, from Uniscan Instruments. A classical three-electrode cell configuration was employed, consisting of bare or modified CPEs serving as working electrodes, a saturated calomel reference electrode (SCE) and a platinum wire counter electrode.

2.4 Preparation of CPEs

The unmodified CPE was prepared by thoroughly hand mixing 30 mg of silicone oil with 70 mg of graphite powder (analytical grade, ultra F, < 325 mesh, from Alfa Aesar) in a mortar. A portion of the composite mixture was packed into the cylindrical hole of a Teflon® tube equipped with a copper wire serving as electrical contact with the rest of the circuit. Before use, the surface exposed to the solution was polished on a weighing paper to give a smooth aspect. Raw coffee husks-modified carbon paste electrodes (CPE-CHr) and cellulose-modified (CPE-Ce) ones were prepared as described for the bare CPE by using 65 mg of graphite powder, 30 mg of silicone oil and 5 mg of raw coffee husks powder or cellulose powder. When not in use, the CPEs were removed from supporting electrolyte and kept at room temperature.

2.5 Other Procedures

For the determination of PCT in pharmaceutical formulations, each commercial tablet was carefully weighed, then finely powdered and dissolved in 1 L of phosphate buffer solution 0.1 M pH 7.4 (PBS). A 1.25 mL aliquot of this solution was then diluted to the mark with PBS in a 50 mL volumetric flask. The samples were finally spiked with known amounts of PCT and the concentration of PCT in solution was determined using the standard addition method.

Morphological analysis of CPEs tested was achieved by field emission gun-scanning electron microscopy (FEG-SEM) on a JSM-6301F apparatus from JEOL (SCIAM, Angers University, France). Coffee husk and cellulose modifiers carbon paste were immobilized on a SEM sample holder using adhesive carbon tape. Images obtained were from secondary electrons of 3 keV, with magnifications x100.

An estimation of the respective amount of the three cell wall components (cellulose, hemicellulose and lignin) in the coffee husks was made using the ADF-NDF method of Van Soest and Wine [36, 40]. Solubility in the ADF, NDF and ADF-$KMnO_4$ solutions was also extrapolated. Solubilization and filtration were done in a Fibertec M2 system, equipped with a heating and reflux device (from FOSS, France). All determinations were carried out in duplicate.

The contact angle measurements were performed on the unmodified or modified CPEs by the sessile drop technique, which allows comparison between materials. Toward this aim, the electrodes were freshly prepared and dried at room temperature in a desiccator tank. After complete drying, a droplet of ultra-pure water (20 µL) was deposited onto the CPE surface by means of a microsyringe and the contact angle of the droplet with the surface was measured with a KRÜSS DSA30 contact angle meter. Reported values are the average contact angle from 3 droplets. No significant change in contact angle was observed between CPEs during the short measurement time (less than 1 minute). An accuracy of 2 degrees in the angle values was considered.

In order to evaluate the real area of electrodes, CPE, CPE-CHr and CPE-Ce were used to record by cyclic voltammetry the curves of a 5 mM $[Fe(CN)_6]^{3-}$ solution in 0.1 M KNO_3 [27]. The peak intensity (I_p) of the analyte at a given electrode can be used to evaluate the real area (A) of the electrode on the basis of Randles-Sevick equation:

$$I_p = k \cdot n^{3/2} \cdot A \cdot D^{1/2} \cdot C \cdot v^{1/2},$$

where $k = 2.69 \times 10^5$; n is the number of moles of electrons transferred per mole of electroactive species (e.g., ferricyanide); A (in cm^2) is the area of the electrode; D (in $cm^2\,s^{-1}$) is the diffusion coefficient; C (in mol L^{-1}) is the solution concentration; and v (in V s^{-1}) is the potential scan rate.

The SWV curves were registered in the range of –0.2 to 0.8 V, with the following optimized parameters (determined in [27]): frequency 400 Hz, pulse height 90 mV, equilibration time 30 s, and step potential 5 mV. This sensitive electrochemical technique was used to compare the modified and unmodified CPEs tested for the determination of PCT and also for the analysis of commercialized tablets with the CPE-Ce electrode.

3 RESULTS AND DISCUSSION

3.1 Electrochemical Behavior of PCT in SWV

The SEM 2D images of surfaces of the bare CPE and modified CPEs are shown in Figure 1. The surface of unmodified CPE was compact and homogenous, whereas it was irregular for CPE-CHr and CPE-Ce in relation to the presence of treated coffee husk or cellulose powder, respectively, in the carbon paste, indicating microporosity which could facilitate the diffusion of PCT in the bulk of modified CPEs.

3.2 Electrochemical Behavior of PCT in SWV

Square wave voltammetry (SWV) was used to investigate the electrochemical behavior of PCT and to compare the individual current responses for the analyte on CPE, CPE-CHr and CPE-Ce. Figure 2 shows the square wave voltammograms of PCT recorded on the tested CPEs. An anodic peak was observed at 450 mV versus SCE.

Each peak is associated with a redox process corresponding to the oxidation of PCT in N-acetyl-parabenzoquinone imine (NAPQI) [27, 41, 42], as illustrated by Scheme 1:

The corresponding current densities were found to be 400, 800 and 1040 µA cm^{-2}, with CPE, CPE-CHr and CPE-Ce, respectively. The use of modified CPEs resulted in a more intense peak characterized by a two-fold higher current density for CPE-CHr compared to unmodified CPE and almost 30% higher for CPE-Ce vs. CPE-CHr. This could be assigned to the presence of treated coffee husk or cellulose powder on modified CPEs that improves the hydrophilicity of the surface and also increases the real area of the working electrode.

3.3 Sessile Drop Contact Angle Measurements and Sensor Sensitivity to PCT

The wettability variations of CPEs were evaluated using sessile drop contact measurements, as illustrated in Figure 3. A progressive decrease was observed in contact angle from 106° ± 1° for the bare CPE to 89° ± 1° for CPE-CHr and 75° ± 1° for CPE-Ce, along with the increase in the cellulose content in the carbon paste.

These results therefore demonstrated a decrease in the hydrophobicity of the electrode surface due to the presence of cellulose-based materials, a well-known hydrophilic matter, at the surface of modified

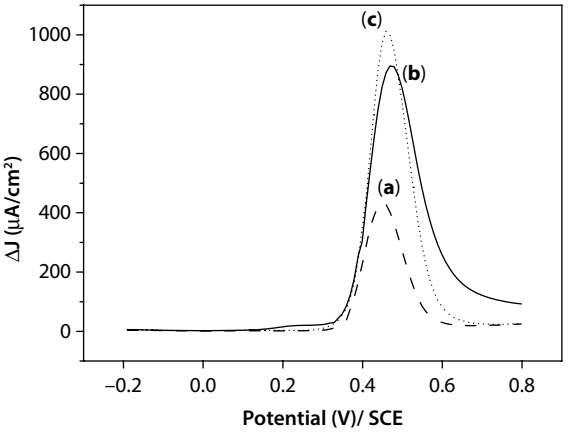
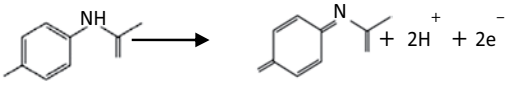
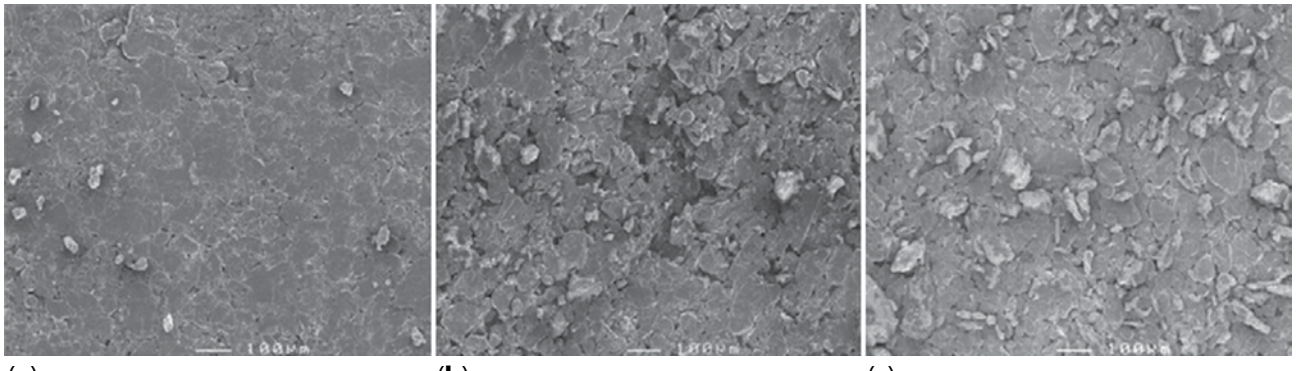


Figure 2 Square wave voltammograms of 75 mg L^{-1} PCT in 4.9410^{-4} M PBS (pH 7.4) at the (**a**) bare CPE, (**b**) CPE-CHr and (**c**) CPE-Ce. SWV was performed with a pulse high of 90 mV, frequency of 400 Hz and scan increment of 15 mV.



Scheme 1 Electrochemical oxidation of PCT.



(**a**) (**b**) (**c**)

Figure 1 2D-SEM images of bare CPE (**a**), CPE-CHr (**b**) and CPE-Ce (**c**).

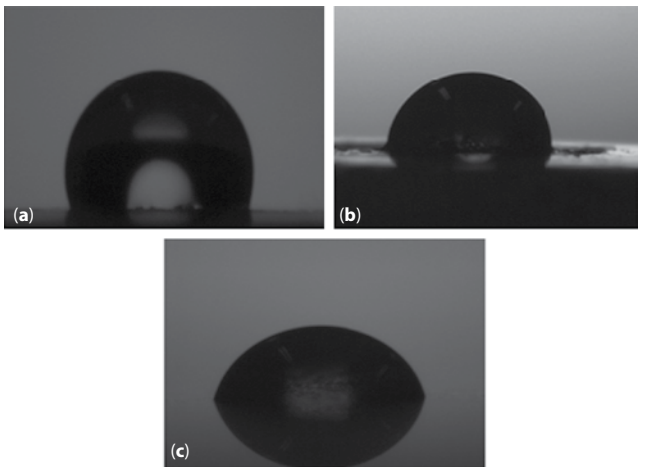


Figure 3 Wettability variations of CPEs studied determined by contact angle measurements A = CPE; B = CPE-CHr, C = CPE-Ce *(pH of the water deposited 6.5, technic: sessile drop; droplet volume 2 mL; temperature: 22 °C)*.

CPEs. This decrease was even more pronounced for CPE-Ce, which contains a high amount of cellulose (100% in theory) at its surface. From these data, one may speculate for CPE-Ce, and to a lesser extent for CPE-CHr, a higher sensitivity in the uptake of PCT compared to the unmodified electrode, since there is a relationship between sensitivity of the electrodes and the hydrophilic character of their surface [41], as observed in Figures 2 and 3.

3.4 Determination of Real Area of Unmodified CPE and Modified CPEs

The geometric surface of CPE, CPE-CHr and CPE-Ce was calculated using the following formula:

$$S_g = \pi r^2,$$

with r = 15 mm, which is the geometric radius (r) of the electrode active surface.

The geometrical area of the tested electrodes was 0.071 cm^2. By contrast, the real surface of CPE, CPE-CHr and CPE-Ce was evaluated from the anodic current intensity obtained for each electrode using cyclic voltammetry, as seen in Figure 4.

The observed peak current, given by the Randles-Sevick equation, was applied to derive the real surface of the investigated working electrodes. The obtained values showed a marked increase in the real surface from unmodified CPE to CPE-CHr and CPE-Ce (Table 1).

The three electrodes were then used to record by cyclic voltammetry the signal of a 75 mg L^{-1} of PCT solution in PBS (Figure 5).

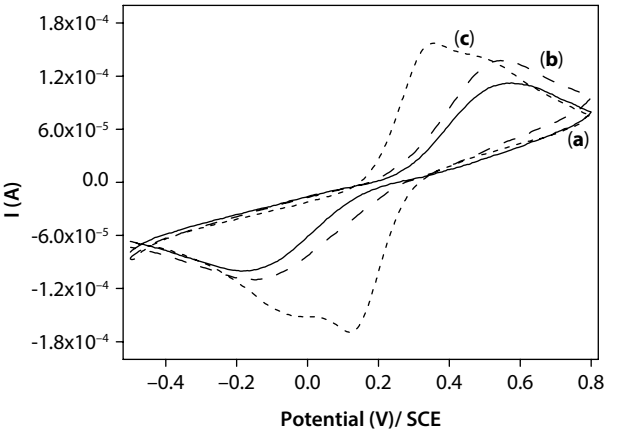


Figure 4 Cyclic voltammograms of 5 mM $[Fe(CN)_6]^{3-}$ solution in 0.1 M KNO_3 at the (**a**) bare CPE, (**b**) CPE-CHr and (**c**) CPE-Ce. Potential scan rate: 100 mV s^{-1}.

One can reasonably assign the observed differences to modifiers (treated coffee husk and cellulose powders) which have improved the organophilic character of the electrodes, thereby increasing the amount of PCT chemically transformed at the electrode.

The ratios of peak intensities and of real surface areas obtained with modified CPEs, compared to the bare CPE, are reported in Table 1.

The peak current was influenced by the percentage of cellulose in the carbon paste: the oxidation peak intensity was affected by both the increase in the real surface exposed to the solution of PCT to be analyzed and the hydrophilic character of coffee husk or cellulose powder. For CPE-CHr, the increase in hydrophilicity was largely predominant (82% of gain in sensitivity compared to a gain of 18% only in the real surface). On the contrary, the main phenomenon for CPE-Ce was a physical effect (24% only for gain in sensitivity compared to 72% of gain in the real surface).

3.5 Determination of the Limits of Saturation of Modified CPEs

The limit of saturation is the Achilles' heel of CPEs [42]. The main interest in the approach of carbon paste modifications is to change this situation. Figure 6a,b displays the oxidation current density of PCT at different concentrations on CPE-CHr and CPE-Ce respectively.

As illustrated in Figure 6, we have followed the current density of the tested modified CPEs vs. increasing PCT concentrations. CPE-CHr showed a limit of saturation of 420 mg/L, as recently reported [42]. On the contrary, and in agreement with the gain in real surface (72%, see Table 1), a limit of saturation of

Table 1 Real surface of electrodes and physical/chemical gains in sensitivity.

Electrodes	Real surface(x 10^{-6}cm^2)	Ipa (x 10^{-5} A)*	Modified electrodes *vs.* bare CPE		Gain in sensitivity (%)
			Ratio of I_p	Ratio of real surface areas (% of gain)	
CPE	0.082 ± 6.7	8.666 ± 0.675	1	1	0
CPE-CHt	0.097 ± 6.6	10.561 ± 0.680	2.000	1.182 (18)	0.820 (82)
CPE-Ce	0.141 ± 3.2	44.075 ± 0.956	2.600	1.719 (72)	0.881 (28)

**n = 1, D = 0.62 x 10^{-5} cm^2 s^{-1}, C = 5 mM with a potential scan rate of 100 mV s^{-1}.*

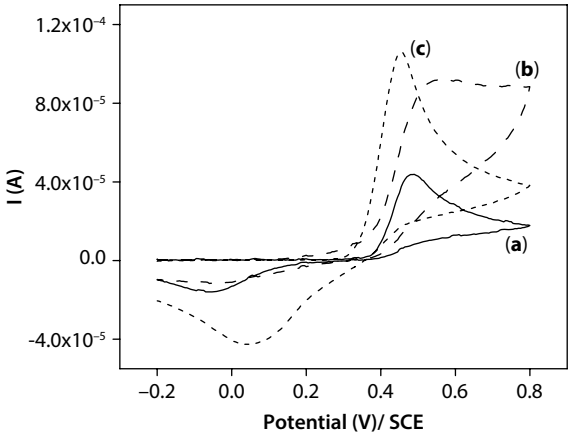


Figure 5 Cyclic voltammograms of 75 mg L^{-1} PCT in PBS at the (**a**) bare CPE, (**b**) CPE-CHr and (**c**) CPE-Ce. Potential scan rate: 100 mV s^{-1}.

950 mg/L was observed for CPE-Ce. This result illustrates the main interest in using cellulose powder in the form of fibers to increase the real surface, and thus to markedly increase the limit of saturation.

Nevertheless, as illustrated in Figure 7, some impurities can be observed when using CPE-CHr at +0.27 V/SCE.

A treatment of raw coffee husks with methanol maybe could remove extractives considered but a supplementary cost is added in the preparation of CPE-CH. Furthermore, considering the obtained results in Section 3.5 showing a limit of saturation of 420 and 950 mg/L for CPE-CHt and CPE-Ce respectively, we decided to use only CPE-Ce sensor for the following experiments.

3.6 Tablet Analysis with CPE-Ce

Current intensity of the oxidation peak of PCT was directly proportional to its concentration over the range from 0.1 µM to 0.5 mM (Figure 8). CPE-Ce was therefore applied to direct detection of PCT in commercial tablets, Doliprane 500, using the common analytical method of internal standards.

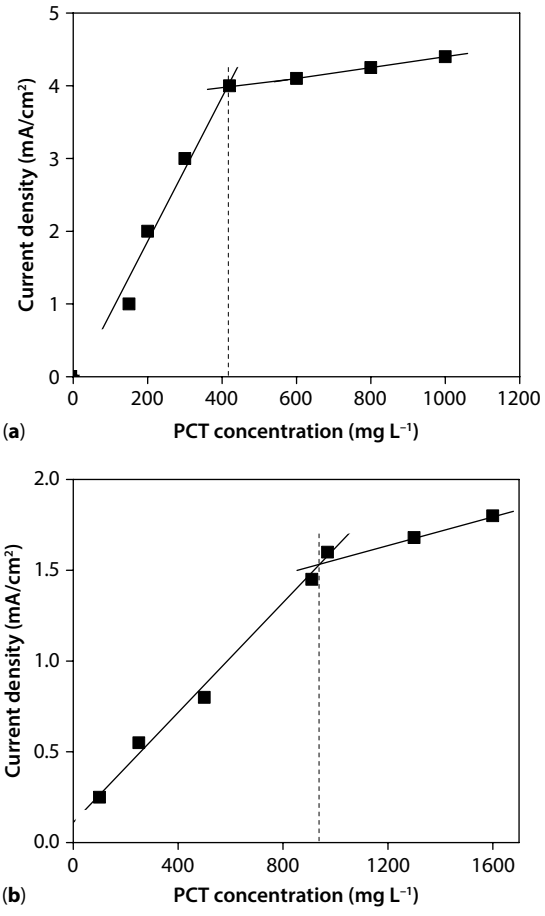


Figure 6 Evolution of peak current densities vs. PCT concentration at (**a**) CPE-CHr and (**b**) CPE-Ce.

Figure 8 shows the results of the addition of known amounts of PCT in an unknown solution prepared with a commercialized tablet of Doliprane 500.

As illustrated in Figure 8, an affine relationship was obtained between the peak intensity (observed at 0.45 V vs. SCE) and concentration of added PCT. It is expressed as I_p (µA) = 1.9 C (mg L^{-1}) + 47 (R^2 = 0.99) for Doliprane 500. The obtained results were in the range of the commercial limit of quality admitted by the European drug regulations (3%) and the obtained

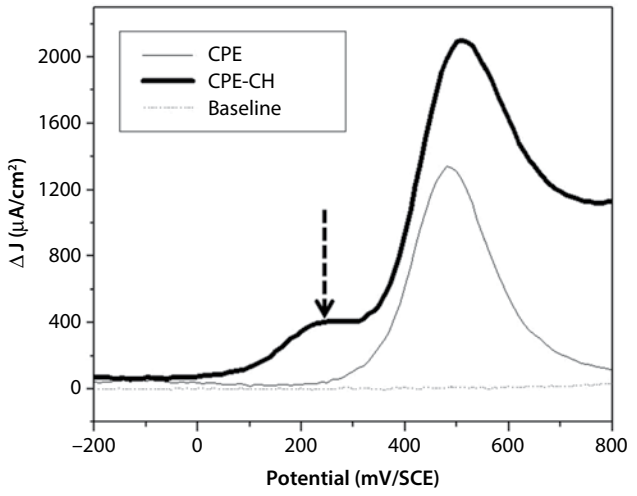


Figure 7 Square wave voltamogramms of 75 mg L^{-1} PCT at the bare CPE and CPE-CHr in PBS, with a pulse high of 90 mV, frequency of 400 Hz and scan increment of 15 mV.

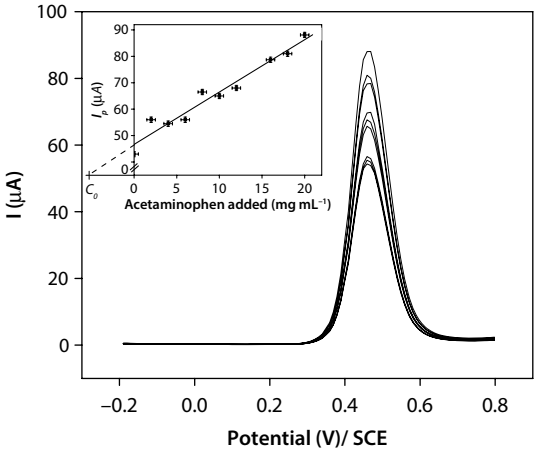


Figure 8 SWV curves recorded for the commercial tablet Doliprane 500, upon addition of known amounts of PCT in PBS. Insert displays the corresponding calibration curve.

recovery rates were 103% to 97% (Table 2). As shown in Table 2, the recovery rates of PCT in three commercial tablets were in an acceptable range, proving that the proposed sensor and the standard addition method are suitable for the determination of PCT in pharmaceutical formulations.

No excipient effects were observed in PCT determination from commercialized tablets of Doliprane 500.

Furthermore, the detection limit (DL) calculated with a signal-to-noise ratio of 3 was found to be 0.44 µM for CPE-Ce sensor. This value can be compared to the LD of 0.66 µM reported for CPE-CH [27]. Comparing these results for the voltammetric determination of PCT using other modified CPEs reported in the literature, the obtained detection limit (0.44 µM)

Table 2 Determination of PCT in commercial tablets Doliprane 500 using CPE-Ce (all values are in mg, excepted recovery rate which is in %).

**Doliprane® 500*	*Tablet initial mass*	*600 ± 1*
	Tablet mass obtained after powdering	*599 ± 1*
	Theoretical PCT mass in the weighted tablet	*494 ± 15*
	PCT mass determined with CPE-Ce	*494 ± 20*
	Recovery rate (%)	*100 ± 3*

**3% error admitted by the European drug regulations for the commercialization of PCT tablets.*

is very close to the studies of other authors [22, 42, 43] or even better than those achieved with CPEs incorporating gold nanoparticles [43], graphene oxide [44], carbon nanotubes [45] or with neviparine [28], as main modifiers. One advantage of the present work is that the electrochemical device is based on inexpensive materials (cellulose-based powders), conversely to other materials used as electrode modifiers.

4 CONCLUSIONS

This work demonstrates the interest of a cellulose-based CPE for the electrochemical determination of PCT in pharmaceutical formulations. The beneficial hydrophilization combined with increasing real surface area of cellulose based on both ligno-cellulosic materials, coffee husk and pure cellulose powders, in the bulk of the carbon paste electrode was first demonstrated through the accumulation of PCT using SWV. A detection limit of 4.4×10^{-7} M (S/N = 3) was obtained for CPE-Ce. The use of this proposed cellulose-based sensor for the determination of PCT in commercialized tablets of Doliprane 500 showed an acceptable recovery rate ranging from 97% to 103%. The simplicity and low cost of the proposed method and the performance of the sensor in terms of low detection limit suggest that carbon paste electrodes modified with lingo-cellulosic materials may be useful for quality control laboratories. Further experiments will focus on possible improvement of CPE-Ce performances in terms of sensitivity and limit of saturation by using nanofiber cellulose in order to directly analyze PCT in commercialized formulations (Doliprane 500 and 1000) without previous dilution and powdering step before analysis.

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Conflict of Interest: The authors declare that there is no conflict of interest regarding the publication of this study.

REFERENCES

1. O. Fatibello-Filho, K.O. Lupetti, and I.C. Vieira, Chronoamperometric determination of acetaminophen using an avocado tissue (*Persea americana*) biosensor. *Talanta* **55**(4), 685–692 (2001).
2. A. Afkhami, H. Khoshsafar, H. Bagheri, and T. Madrakian, Preparation of $NiFe_2O_4$/graphene nanocomposite and its application as a modifier for the fabrication of an electrochemical sensor for the simultaneous determination of tramadol and acetaminophen. *Anal. Chim. Acta* **831**, 50–59 (2014).
3. H. Beitollahi, J.B. Raoof, and R. Hosseinzadeh, Fabrication of a nanostructure-based electrochemical sensor for simultaneous determination of N-acetylcysteine and acetaminophen. *Talanta* **85**, 2128–2134 (2011).
4. F.L. Martin and A.E. MacLean, Comparison of paracetamol-induced hepatotoxicity in the rat in-vivo with progression of cell injury in-vitro in rat-liver slices. *Drug Chem. Toxicol.* **21**(4), 477–494 (1998).
5. H.M. Moghaddam, Electrocatalytic determination of carbidopa and acetaminophen using a modified carbon nanotube paste electrode. *Int. J. Electrochem. Sci.* **6**, 6557–6566 (2011).
6. H. Filik, G. Çetintas, A.A. Avan, S.N. Koçn, and I. Boz, Electrochemical sensing of acetaminophen on electrochemically reduced graphene oxide-nafion composite film modified electrode. *Int. J. Electrochem. Sci.* **8**, 5724–5737 (2013).
7. K.G. Kumar and R. Letha, Determination of paracetamol in pure form and in dosage forms using N,N-dibromodimethylhydantoin. *J. Pharm. Biomed. Anal.* **15**, 1725–1728 (1997).
8. F.A. Mohamed, M.A. Abdallah, and S.M. Shammat, Selective spectrophotometric determination of p-aminophenol and acetaminophen. *Talanta* **44**(1), 61–68 (1997).
9. M.S. Bloomfield, A sensitive and rapid assay for 4-aminophenol in paracetamol drug and tablet formulation, by flow injection analysis with spectrophotometric detection. *Talanta* **58**, 1301–1310 (2002).
10. K.A.R. Sirajuddin, A. Shah, M.I. Bhanger, A. Niaz, and S. Mahesar, Simpler spectrophotometric assay of paracetamol in tablets and urine samples. *Spectrochim. Acta Mol. Biomol. Spectrosc.* **68**(3), 747–751 (2007).
11. J.A.M. Pulgarin and L.F.G. Bermejo, Flow-injection stopped-flow spectrofluorimetric kinetic determination of paracetamol based on its oxidation reaction by hexacyanoferrate (III). *Anal. Chim. Acta* **333**, 59–69 (1996).
12. D. Easwaramoorthy, Y.C. Yu, and H-J. Huang, Chemiluminescence detection of paracetamol by a luminol-permanganate based reaction. *Anal. Chim. Acta* **439**, 95–100 (2001).
13. W. Peng, T. Li, H. Li, and E. Wang, Direct injection of urine and determination of acetaminophen by micellar liquid chromatography with wall-jet cell/carbon fiber microelectrode. *Anal. Chim. Acta* **298**, 415–421 (1994).
14. M.G. Gioia, P. Andreatta, S. Boschetti, and R. Gatti, Development and validation of a liquid chromatographic method for the determination of ascorbic acid, dehydroascorbic acid and acetaminophen in pharmaceuticals. *J. Pharm. Biomed. Anal.* **48**, 331–339 (2008).
15. J. Sun, L.K. Schnackenberg, R.D. Holland, T.C. Schmitt, G.H. Cantor, Y.P. Dragan, and R.D. Berger, Metabonomics evaluation of urine from rats given acute and chronic doses of acetaminophen using NMR and UPLC/MS. *J. Chromatogr. B* **871**, 328–340 (2008).
16. S.A. Kumar, C.F. Tang, and S.M. Chen, Electroanalytical determination of acetaminophen using nano-TiO_2/polymer coated electrode in the presence of dopamine. *Talanta* **76**(5), 997–1005 (2008).
17. M. Mazloum-Ardakani, H. Beitollahi, M.K. Amini, F. Mirkhalaf, and B.B.F. Mirjalili, A highly sensitive nanostructure-based electrochemical sensor for electrocatalytic determination of norepinephrine in the presence of acetaminophen and tryptophan. *Biosens. Bioelectron.* **26**, 2102–2106 (2011).
18. B. Habibi, M. Jahanbakhshi, and M.H. Pournaghi-Azar, Differential pulse voltammetric simultaneous determination of acetaminophen and ascorbic acid using single-walled carbon nanotube-modified carbon-ceramic electrode. *Anal. Biochem.* **411**(2), 167–175 (2011).
19. S. Cheemalapati, S. Palanisamy, V. Mani, and S.-M. Chen, Simultaneous electrochemical determination of dopamine and paracetamol on multiwalled carbon nanotubes/graphene oxide nanocomposite-modified glassy carbon electrode. *Talanta* 117, 297–304 (2013).
20. K. Tyszczuk-Rotko, I. Beczkowska, M. Wojciak-Kosior, and I. Sowa, Simultaneous voltammetric determination of paracetamol and ascorbic acid using a boron-doped diamond electrode modified with nafion and lead films. *Talanta* 129, 384–391 (2014).
21. H. Beitollahi, A. Mohadesi, S. Mohammadi, and A. Akbari, Electrochemical behavior of a carbon paste electrode modified with 5-amino-3′,4′-dimethylbiphenyl-2-ol/carbon nanotube and its application for simultaneous determination of isoproterenol, acetaminophen and N-acetylcysteine. *Electrochim. Acta* **68**, 220–226 (2012).
22. M.R. Shahmiri, A. Bahari, H. Karimi-Maleh, R. Hosseinzadeh, and N. Mirnia, Ethynylferrocene-NiO/MWCNT nanocomposite modified carbon paste electrode as a novel voltammetric sensor for simultaneous determination of glutathione and acetaminophen. *Sens. Actuators B Chem.* 177, 70–77 (2013).
23. M.H. Mashhadizadeh and F. Rasouli, Design of a new carbon paste electrode modified with TiO_2

nanoparticles to use in an electrochemical study of codeine and simultaneous determination of codeine and acetaminophen in human plasma serum samples. *Electroanalysis* **26**, 1 (2014).
24. R.N. Adams, Carbon paste electrodes. *Anal. Chem.* **30**, 1576–1576 (1958).
25. B.J. Sanghavi and A.K. Srivastava, Simultaneous voltammetry determination of acetaminophen, aspirin and caffeine using an in situ surfactant-modified multiwalled carbon nanotube paste electrode. *Electrochim. Acta* **55**, 8638–8648 (2010).
26. I.G. Svegl and B.O. Fresenius, Soil-modified carbon paste electrode: A useful tool in environmental assessment of heavy metal ion binding interactions. *J. Anal. Chem.* **367**, 701–706 (2000).
27. S.F. Mbokou, M. Pontié, J.-P. Bouchara, F.M. Melataguia Tchieno, E. Njanja, A. Mogni, P.-Y. Pontalier, and I. Kenfack Tonle, Electroanalytical performance of a carbon paste electrode modified by coffee husks for the quantification of acetaminophen in quality control of commercialized pharmaceutical tablets. *Int. J. Electrochem. Sci.* **ID 1953278**, 1 (2016).
28. S.B. Tanuja, B.E. Kumara Swamy, and K. Vasantakumar Pai, Electrochemical determination of paracetamol in presence of folic acid at nevirapine modified carbon paster electrode: A cyclic voltammetric study. *J. Electroanal. Chem.* **798**, 17–23 (2017).
29. A. Zumriye, Application of biosorption for the removal of organic pollutants. *Process Biochem.* 40, 997–1026 (2005).
30. W.S.W. Ngah and M.A.K.M. Hanafiah, Removal of heavy metal ions from wastewater by chemically modified plant wastes as adsorbents. *Bioresour. Technol.* 99, 3935–3948 (2008).
31. C.P. Nanseu-Njiki, G.D. Kenne, and E. Ngameni, Study of the removal of paraquat from aqueous solution by biosorption onto Ayous (*Triplochiton schleroxylon*) sawdust. *J. Hazard. Mater.* **179**, 63–71 (2010).
32. M. Akhtar, S.M. Hasany, M.I. Bhanger, and S. Iqbal, Low cost sorbent for the removal of methyl parathion pesticide from aqueous solution. *Chemosphere* **66**, 1829–1838 (2007).
33. A.E. Ofomaja, Kinetic study and sorption mechanism of methylene blue and methyl violet onto Mansonia (*Mansonia altissima*) wood sawdust. *Chem. Eng. J.* 143, 85–95 (2008).
34. P.S. Murthy and M.M. Naidu, Sustainable management of coffee industry by-products and value addition–A review. *Resour. Conserv. Recycl.* **6**, 45–58 (2012).
35. S.A. Bekalo and H.W. Reinhardt, Fibers of coffee husk and hulls for the production of particleboard. *Mater. Struct.* **43**, 1049–1060 (2010).
36. P.J. Van Soest and R.H. Wine, Use of detergents in the analysis of fibrous feeds. IV. Determination of plant cell wall constituents. *J. AOAC* **50**, 50–55 (1967).
37. A. Ishizu, The chemistry of paper, in *Wood and Cellulosic Chemistry*, D.N. Shon and N. Shiraishi (Eds.), pp. 757–795, Marcel Dekker, New York (1991).
38. F. Le Digabel and L. Avérous, Effect of lignins content on the properties of lignocellulose-based biocomposites. *Carbohydr. Polym.* **66**, 537–545 (2006).
39. S.I. Mussatto, L.M. Carneiro, J.P.A. Silva, I.C. Roberto, and J.A. Teixeira, A study on chemical constituents and sugars extraction from spent coffee grounds. *Carbohydr. Polym.* **83**, 368–374 (2011).
40. P.J. Van Soest and R.H. Wine, Determination of lignin and cellulose in acid detergent fiber with permanganate. *J. AOAC* **51**, 780–785 (1968).
41. M. Pontié, L. Sikpo, G. Thouand, R. Lahan, I. Tapsoba, R. Mallet, and T. Feng, Direct electroanalysis of p-nitrophenol (PNP) in estuarine and surface waters by a high sensitive type C/p-NiTSPc coating carbon fiber microelectrode (CFME). *Electroanalysis* **23**(2), 433–441 (2011).
42. S.F. Mbokou, M. Pontié, B. Razafimandimby, J.P. Bouchara, E. Njanja, and I. Kenfack Tonle, Evaluation of the degradation of acetaminophen by the filamentous fungus *Scedosporium dehoogii* using carbon-based modified electrodes. *Anal. Bioanal. Chem.* **408**, 5895–5903 (2016).
43. S. Tajik, M.A. Taher, and H. Beitollahi, Application of a new ferrocene-derivative modified-graphene paste electrode for simultaneous determination of isoproterenol, acetaminophen and theophylline. *Sens. Actuators B Chem.* **197**, 228–236 (2014).
44. L. Özcan and Y. Sahin, Determination of paracetamol based on electropolymerized-molecularly imprinted polypyrrole modified pencil graphite electrode. *Sens. Actuators B Chem.* **127**(2), 362–369 (2007).
45. I. Noviandri and R. Rakhmana, Carbon paste electrode modified with carbon nanotubes and poly(3-aminophenol) for voltammetric determination of paracetamol. *Int. J. Electrochem. Sci.* **7**, 4479–4487 (2012).