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Voltammetric Determination of Active Pharmaceutical Ingredients Using Screen-Printed Electrodes

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Abstract: A simple, fast, sensitive and low-cost voltammetric method using a screen-printed carbon electrode (SPCE) is presented in this work for the simultaneous determination of ascorbic acid (AA), paracetamol (PA), dextromethorphan (DX) and caffeine (CF) in both pharmaceutical formulations and samples of environmental interest. The oxidative peak current displayed linear dependence on concentration within the range 1.7–60.5, 0.6–40.0, 0.9–8.4 (1st linear part) and 1.8–22.0 mg L^{-1} for AA, PA, DX and CF, respectively; and detection limits of 0.5, 0.2, 0.3 and 0.5 mg L^{-1}, respectively. The developed differential pulse voltammetric (DPV) method was validated using both a pharmaceutical product and a spiked well water sample. A very good agreement between the determined and the theoretical label drug content and recoveries in the range of 99.5–100.8% were obtained for pharmaceutical product and well water samples, respectively.

Keywords: screen-printed electrodes; voltammetry; ascorbic acid; paracetamol; dextromethorphan; caffeine

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1. Introduction

An increase of the global population, longer life expectancies and changes in clinical practices have led to increased pharmaceutical consumption worldwide [1], with over 1000 billion US dollars in global pharmaceutical sales in 2020 [2]. Moreover, pharmaceutical consumption has also diversified, mainly to cover emerging needs of strong economies while still attending "traditional" diseases that persist in less-developed areas [1]. This rise in pharmaceutical consumption is concerning from an environmental perspective because it has been accompanied by a discharge of both pharmaceutical products and their metabolites into the water cycle [3,4]. Typical concentrations in environmental waters are at the level of ng L^{-1} [5–7] and the main sources of pharmaceutical residues include industrial and hospital effluents, sewage treatment plants and septic tanks [4]. All this has led to pharmaceuticals being considered an important group of emerging contaminants that need to be monitored [6–8]. No legal limits have been established yet but a strategic approach to the risks from pharmaceuticals in the environment has already been set out in the European Union [9].

In particular, ascorbic acid (AA), better known as vitamin C, is in a class of drugs called antioxidants, which efficiently protect cells against toxic free radicals, and is typically used to prevent and cure scurvy [10]. AA is also utilized as a reagent for the preparation of fine chemicals and nanomaterials and as an enzymatic reagent. Therefore, the determination of AA in food samples and products is receiving great attention among researchers [11]. Paracetamol (PA), also denoted as acetaminophen, is a standard antipyretic and analgesic drug employed for fever reduction and for mild to moderate pain states [12]. PA is the most consumed drug in Europe, being one of the most frequent analgesics and anti-inflammatories found in aquatic environments in African and European countries [13]. Dextromethorphan (DX) is a highly effective and widely used nonopioid cough suppressant

drug that is found in many cough/cold syrups or capsules. The presence of DX and its metabolites, in higher concentrations than the parent drug DX, is reported in surface water and wastewater [14]. Caffeine (CF) is a stimulant of the central nervous system that belongs to the methylxanthine group, which is frequently used combined with other drugs to enhance their effects [12]. CF is the most extensively consumed psychoactive substance in the world, becoming the most detected drug in the surface water of Africa and Europe. Consequently, CF is a significant indicator of wastewater contamination [13].

The most leading and most used techniques for the pharmaceutical residues' analysis in samples of environmental origin are gas chromatography-mass spectrometry (GC-MS) and high-performance liquid chromatography combined with mass spectrometry (HPLC-MS) [15–17]. However, chromatographic instruments are quite expensive and can only be managed by trained personnel because of their complexity. Moreover, as compared to other analytical methods, chromatography involves a lot of waste and some instruments require high power consumption. Therefore, electroanalytical methods are postulated as an attractive option for drug residue screening in environmental samples due to their intrinsic characteristics (low-cost, simplicity, specificity, selectivity, high sensitivity, low detection limits and the possibility of real time results) that can overcome the major drawbacks of chromatographic methods [18]. Furthermore, the emergence of the screen-printing technology that produces screen-printed electrodes (SPEs) characterized by their low-cost, flexibility of their design, disposable character, great reproducibility and the wide capacity of modification of the working surface, has given rise to a powerful sensing tool for real-time monitoring in environmental, food and agricultural samples [19,20]. Thus, the combination of electroanalytical methods with the use of SPEs represents a pioneering and attractive possibility for the determination of pharmaceutical residues. It is true that electrochemical sensors based on SPEs have a limited selectivity, especially if we take into account the enormous quantity of electroactive drugs that can be detected in the same potential region. This is not a great problem in samples with a moderate number of substances (e.g., pharmaceutical formulations) but may hinder the quantitative analysis in complex matrices such as biological or environmental samples. However, even in this case, sensors can be valuable for screening, i.e., detecting the presence of groups of drugs whose identity and concentration would have to be further elucidated by HPLC-MS.

The voltammetric determination of pharmaceuticals using a wide variety of electrodes has been widely reported in the literature [18,21–23]. However, it is worth noting that the reported studies are mainly focused on the individual voltammetric determination of a single drug residue, in particular PA and dopamine, or, at most, the simultaneous determination of two or three residues. For the latter, most works are based on the dropping mercury electrode, hanging mercury drop electrode, carbon paste electrode or glassy carbon electrode by differential pulse voltammetry (DPV), cyclic voltammetry (CV) or adsorptive stripping voltammetry (AdSV). Moreover, these determinations are mostly performed in pharmaceutical formulations, human serum, human urine, and in the case of CF, in drinks. Therefore, from these works it should be remarked that the multi-compound voltammetric determination of more than three drug residues at once in pharmaceutical and human body fluids, but especially in samples of environmental interest, combined with the use of SPEs, has been scarcely studied [24,25].

In the present work, a commercial screen-printed carbon electrode (SPCE) was used for the simultaneous determination of AA (a water-soluble vitamin involved in the formation of collagen and in tissue repair), PA (analgesic and antipyretic), DX (a cough suppressant) and CF (stimulant) by DPV. The analytical performance of both individual and simultaneous determination of target drugs was assessed. Furthermore, the voltammetric determination of considered drug residues in both pharmaceutical product and spiked well water samples was successfully carried out.

2. Materials and Methods

2.1. Chemicals

L-ascorbic acid, paracetamol, caffeine and dextromethorphan hydrobromide monohydrate were provided by Sigma-Aldrich (St. Louis, MO, USA). Acetic acid 100% and sodium acetate were purchased from Merck (Darmstadt, Germany). Absolute ethanol was supplied by Panreac (Barcelona, Spain). All reagents used were of analytical grade.

Stock solutions of 1761 mg L^{-1} of AA, 1512 mg L^{-1} of PA, 2714 mg L^{-1} of DX and 1942 mg L^{-1} of CF were prepared weekly in order to prevent changes in their concentration, especially those related to AA oxidation. AA, PA and CF stock solutions were prepared in ultrapure water obtained from a Milli-Q reference A+ System (Millipore, France). DX stock solution was prepared in absolute ethanol since it is sparingly soluble in water. Stock solutions were stored in the refrigerator at 4 °C and diluted daily in ultrapure water to the corresponding working concentrations.

Frenadol® Complex (paracetamol 650 mg, caffeine citrate 30 mg, dextromethorphan hydrobromide 20 mg, ascorbic acid 250 mg and chlorphenamine maleate 4 mg, granules for oral solution from the laboratory Johnson & Johnson) was purchased from a local drug store. A drinking well water sample collected in Sant Quirze de Safaja (Spain) was also considered for analysis of target drugs.

2.2. Apparatus

Differential pulse voltammetric measurements were performed in a potentiostat Metrohm 910 PSTAT mini (Metrohm Dropsens, Oviedo, Spain), connected to a personal computer equipped with the software DropView 200 (Metrohm DropSens) and attached to a screen-printed carbon electrode (SPCE) by means of a flexible cable from Metrohm DropSens. A SPCE from Metrohm DropSens (ref. 110) was used as a sensing device. The SPCE comprises working (4 mm diameter) and auxiliary electrodes made of carbon and a reference electrode made of silver.

For DPV measurements, the solution under study was placed on a plastic vessel and the stirring was performed using a magnetic stirrer from the supplier IKA (Staufen, Germany).

A Crison micro pH 2000 (Hach Lange, Barcelona, Spain) was used for pH control.

2.3. Differential Pulse Voltammetric Measurements

DPV measurements were performed by scanning the potential from −0.5 V to 1.5 V using a step potential of 5 mV, pulse amplitudes of 0.1 V, pulse times of 50 ms and a scan rate of 0.01 V s^{-1}. If the sample under study contains CF, a conditioning potential of −0.5 V during 30 s is required to ensure the removal of the remaining adsorbed CF. Measurements were carried out without oxygen removal.

Before starting the measurements, repeated blank measurements were recorded (usually three times) in 25.0 mL of acetic/acetate buffer until a stable background current was obtained.

Individual and simultaneous calibrations of AA, PA, DX and CF were performed in 0.1 mol L^{-1} acetic/acetate buffer at pH 5.00 by adding increasing concentrations of the target compounds. Both calibrations were carried out by the external calibration method in triplicate.

For the assay of AA and PA in the pharmaceutical product Frenadol® Complex, the average mass of 3 sachets was determined. Then, 0.3 g of powder, equivalent to 8.6 mg of AA and 22.3 mg of PA, were accurately weighed, transferred into a 25.0 mL volumetric flask and made up to the mark with Milli-Q water. Frenadol® Complex is a water-soluble pharmaceutical product; all incipients were properly dissolved and, therefore, no filtration was required. For the determination of AA, PA, DX and CF in the well water, the collected water sample was spiked with 51.8 mg L^{-1} of AA, 18.8 mg L^{-1} of PA, 47.1 mg L^{-1} of DX and 14.1 mg L^{-1} of CF. For DPV measurements, 500 µL of the prepared Frenadol® Complex solution or 12.5 mL of the spiked well water sample were transferred into a plastic vessel containing 25.0 mL (Frenadol® Complex sample) or 12.5 mL (well water sample) of acetic/acetate buffer pH 5.00. Once the sample was recorded, three additions of standard solutions of AA and PA (Frenadol® Complex sample) or AA, PA, DX and CF (well water

sample) were successively added and the respective DPV curves were also recorded. Both assays were performed by the standard addition method [26] in triplicate using a new SPCE unit in each replicate.

3. Results and Discussion

3.1. Optimization

Firstly, the identification of the voltammetric peaks of the four target compounds was carried out by the successive addition of 25.0 mg L^{-1} of the individual standards in 0.1 mol L^{-1} acetic/acetate buffer pH 5.00. As it is shown in the inset of Figure 1, the oxidation peaks of AA, PA, DX and CF appear close to 0.10 V, 0.35 V, 0.85 V and 1.25 V, respectively. Oxidation reactions and acid-base distribution diagrams are depicted in Figures S1 and S2 [27–29]. Thus, a potential window from −0.5 to 1.6 V was selected.

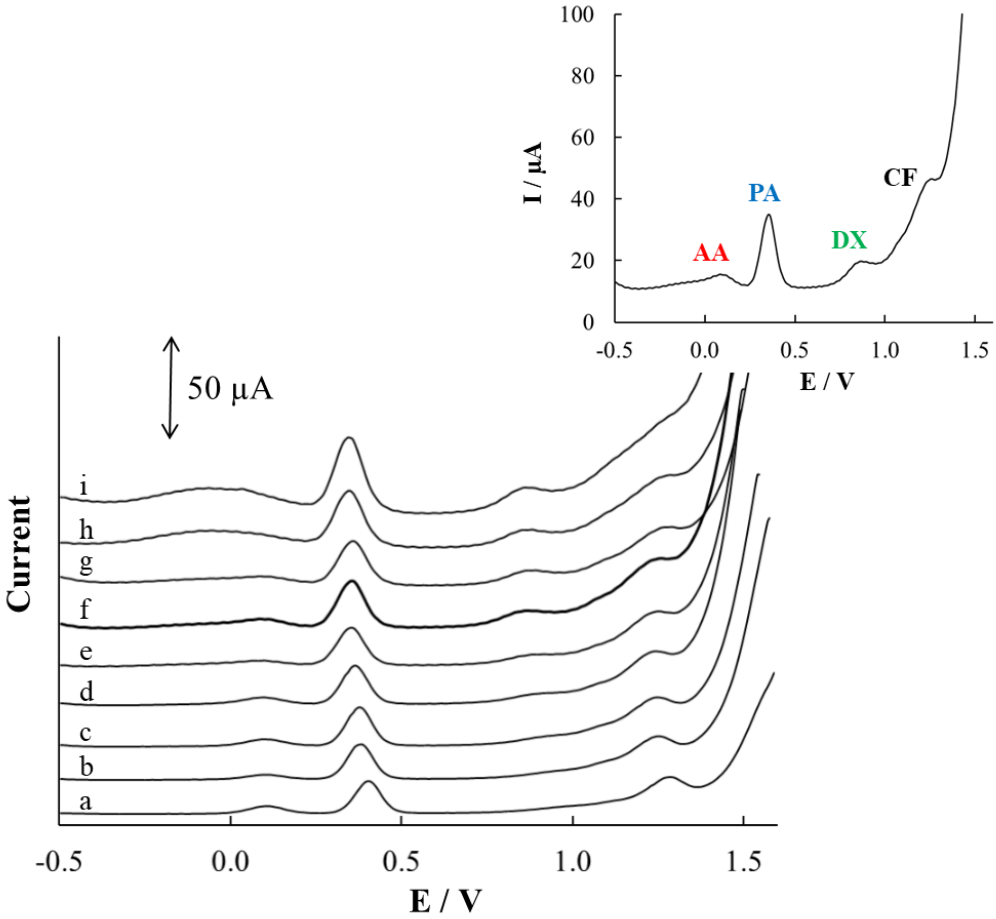

Figure 1. Differential pulse voltammetric measurements of 25 mg L^{-1} ascorbic acid, paracetamol, dextromethorphan and caffeine solutions performed in 0.1 mol L^{-1} acetic/acetate buffer at different pH values: (a) pH 3.75; (b) pH 4.00; (c) pH 4.25; (d) pH 4.50; (e) pH 4.75; (f) pH 5.00 (inset); (g) pH 5.25; (h) pH 5.50 and (i) pH 5.75.

For pH optimization, we took into account the results of previous studies with AA, PA and CF [30] and with DX [31], which are in part summarized in Table S1 of Supplementary Materials. Then, we only considered a pH range restricted to the most promising values. For this purpose, simultaneous DPV measurements of a solution containing 25.0 mg L^{-1} of AA, PA, DX and CF were carried out in 0.1 mol L^{-1} acetic/acetate buffer solutions at pH values ranging from 3.75 to 5.75 (Figure 1).

As it can be seen in Figure 1, at pH values from 3.75 to 4.25, only three voltammetric peaks corresponding to AA, PA and CF were detected. The peak associated to DX does not appear until pH 4.50. This is consistent with Figures S1c and S2c, showing that oxidation

involves the neutral form of DX, which is extensively protonated at acidic pH values. In the case of AA, PA and CF, the release of H^+-ions in the corresponding oxidation reactions (Figure S1) would suggest an enhancement of the oxidation signals as pH becomes less acidic and the released H^+-ions can be removed more effectively. This is really confirmed for PA, whose peak increases as pH goes higher. In contrast, the shapes of AA and CF peaks progressively deteriorate at increasing pH values, resulting in poorly defined, broad signals at pH values higher than 5.25. For CF peak this is clearly due to the increasing overlapping with the huge signal of the solvent oxidation, which is moved to less positive potentials as pH goes higher. As for AA, this seems a consequence of the competence between the electrochemical oxidation at the electrode and the chemical oxidation in solution, favored at increasing pH values [32]. Finally, the peak potentials moved with pH accordingly to previous results (Table S1), but they did not produce any overlapping of the peaks of the analytes inside the considered pH range.

According to the obtained results, a pH value of 5.00 (thick line in Figure 1) was selected for the following experiments as the optimal pH, since at this pH value the four considered analytes can be identified with relatively high current values.

3.2. Analytical Performance Evaluation

The sensitivity, linear range, limit of detection (LOD) and limit of quantification (LOQ) of both individual and simultaneous determinations of AA, PA, DX and CF were assessed. With this purpose, both the individual and the simultaneous calibrations of target drugs in acetic/acetate buffer (pH 5.00) using a SPCE by DPV were carried out. The performance of the individual calibration data of AA, PA, DX and CF is illustrated in Figure 2a–d, respectively, whereas Figure 3 shows the development of the simultaneous calibration of AA, PA, DX and CF (see Figure S3 for a zooming into the lower concentrations). It should be noted that well-defined oxidation peaks over the analyzed concentration intervals were obtained for all considered drugs in both individual and simultaneous calibrations. Calibration plots were achieved by recording increasing concentrations ranging from 0.02 to 100 mg L^{-1} of AA, PA and CF (inset of Figure 2a,b,d respectively for individual calibration, and Figure 3b for AA and PA and Figure 3c for CF for simultaneous calibration), and from 0.02 to 75 mg L^{-1} of DX (inset of Figure 2c for individual calibration and Figure 3c for simultaneous calibration). The analytical performance for the individual and the simultaneous calibration of AA, PA, DX and CF is shown in Table 1. Sensitivities were considered in terms of the slope of the linear relationship between current and target drug concentrations. For calculating LOD and LOQ of target drugs, the formula used is 3 and 10 times, respectively, the standard deviation of the intercept divided by the slope of the calibration curve [33]. The initial value of the linear range was established from the first analyte concentration that can be accurately determined (LOQ).

From data reported in Table 1, it can be concluded that there are no important interferences between the studied drugs since sensitivities achieved from both individual and simultaneous calibrations were similar for all considered compounds. Thus, the concurrent presence of AA, PA, DX and CF does not influence their determination. Good correlation coefficients were obtained in all studied cases. However, with regard to the linear ranges, it can be seen that wider linear ranges up to a concentration level of 100 mg L^{-1} for AA, PA and CF, and 75 mg L^{-1} for DX were obtained in separate calibrations. The linear ranges are narrowed when the compounds were simultaneously determined, especially for CF. This fact can be attributed to the competition among analytes for the working electrode surface. In the case of DX, it should be mentioned that two well-defined linear ranges were observed when it is determined jointly with the other studied drugs. At this point, it is worth noting that to the best of our knowledge, no previous studies related to the simultaneous voltammetric determination of AA, PA, DX and CF using SPEs or more classical electrodes are available in the literature. As compared to previous studies reported in the literature using SPEs, the linear ranges obtained in this study for the simultaneous determination of PA and CF are in general terms much wider than those achieved by DPV

using both a carbon nanofibers modified screen-printed electrode (up to 0.8 mg L^{-1} for PA and up to 1.1 mg L^{-1} for CF) [25] and a graphite polyurethane screen-printed composite electrode (up to 6.0 mg L^{-1} for PA and up to 38.8 mg L^{-1} for CF) [34]. In contrast, the linear ranges achieved in this work for the determination of AA and DX are narrower than those found using a screen-printed graphene electrode by cyclic voltammetry (up to 792.5 mg L^{-1}) [35] and using unmodified SPE by potentiometry (up to 2714 mg L^{-1}) [36], respectively.

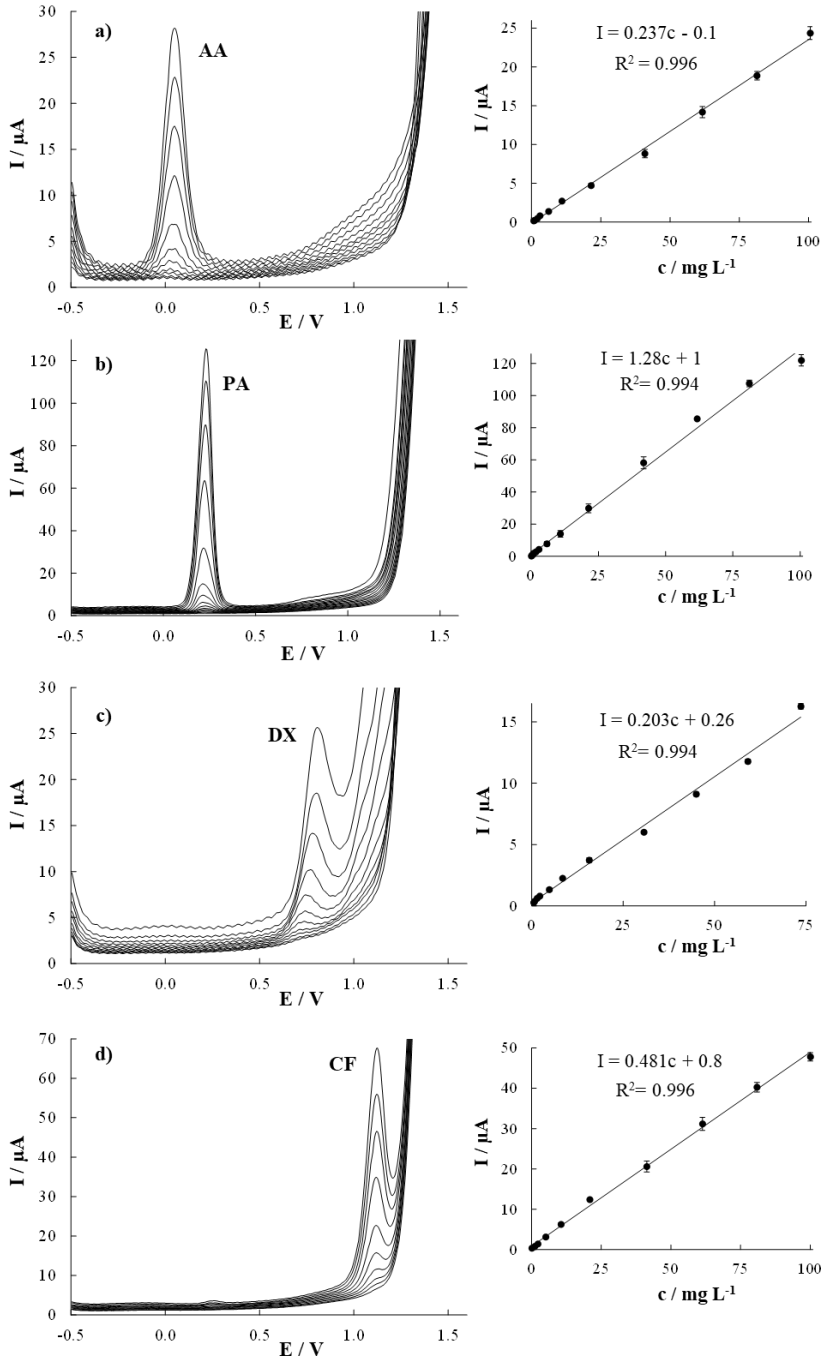

Figure 2. Individual DP voltammograms of ascorbic acid (**a**), paracetamol (**b**), dextromethorphan (**c**) and caffeine (**d**); and their respective calibration plots (insets) in 0.1 mol L^{-1} acetic/acetate buffer pH 5.00 on SPCE. Error bars in the calibration plots represent the standard deviations from replicate calibration curves carried out with three different electrodes.

LODs and LOQs obtained in separate calibrations were practically the same as those provided by the joint calibration for all considered drugs, ranging from 0.1 to 0.5 mg L^{-1} and from 0.5 to 1.8 mg L^{-1}, respectively, depending on the compound considered. In comparison with early published works related to the one-compound determination or the study of two of them at the same time using SPEs, the LODs obtained in this work for the determination of PA and CF using a bare SPCE are slightly higher than those achieved by using carbon-nanotube-modified SPE by cyclic voltammetry/FIA amperometry (0.02 mg L^{-1} for PA) [37] and graphite polyurethane screen-printed composite electrode by DPV (0.02 mg L^{-1} for PA and 0.03 mg L^{-1} for CF) [34]. However, as compared to the LODs provided for the individual calibration of PA and CF in a preliminary study by DPV using different carbon-based modified SPEs (ranging from 0.1 to 0.6 mg L^{-1} for PA, and 0.9 to 1.4 mg L^{-1} for CF, depending on the considered SPE), the LODs achieved in the present work are similar or even somewhat better for PA and considerably much better for CF [25]. Moreover, bare SPCEs have the additional advantage of being commercially available with a relatively high reproducibility and a price significantly lower than that of SPEs based on carbon nanoallotropes. Concerning the AA determination, the LODs provided in this work are of the same order of magnitude of that reported using a screen-printed graphene electrode by cyclic voltammetry [35], being 0.2 mg L^{-1}. In contrast, the LOD provided in this work for the determination of DX is considerably lower than that achieved by potentiometry using unmodified SPE (1.6 mg L^{-1}), drug–ion pair complex-modified SPE (1.6 mg L^{-1}), or in situ-modified SPE with ion-pairing agents (2.7 mg L^{-1}) [36].

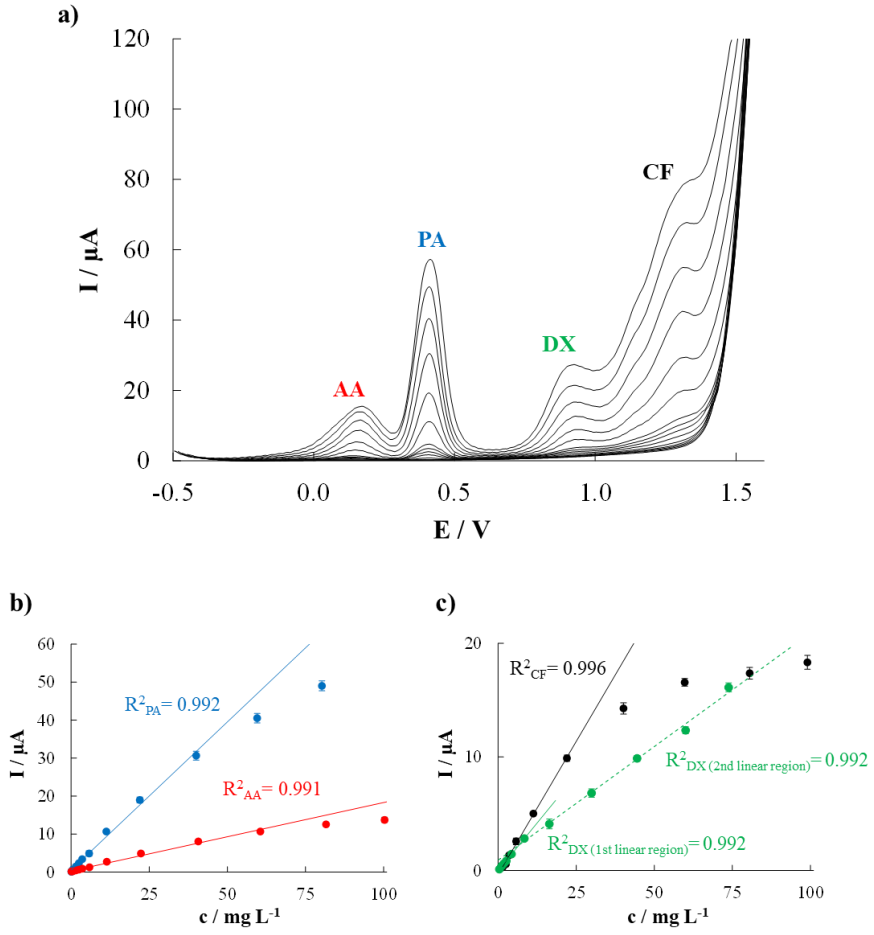

Figure 3. (**a**) Simultaneous DP voltammograms of ascorbic acid, paracetamol, dextromethorphan and caffeine; and the calibration plots of ascorbic acid and paracetamol (**b**) and dextromethorphan and caffeine (**c**) in 0.1 mol L^{-1} acetic/acetate buffer pH 5.00 on SPCE. Error bars in the calibration plots represent the standard deviations from replicate calibration curves carried out with three different electrodes.

Table 1. Calibration data for the individual and simultaneous determination of target analytes on SPCE at acetate buffer at pH 5.0. The standard deviations are denoted by parenthesis.

	Ascorbic Acid		**Paracetamol**		**Dextromethorphan**		**Caffeine**	
	Individual Determination	**Simultaneous Determination**	**Individual Determination**	**Simultaneous Determination**	**Individual Determination**	**Simultaneous Determination**	**Individual Determination**	**Simultaneous Determination**
Sensitivity ($\mu A\ mg^{-1}\ L$)	0.237 (0.003)	0.180 (0.003)	1.28 (0.02)	0.78 (0.02)	0.203 (0.003)	*1st linear part* 0.335 (0.007) *2nd linear part* 0.198 (0.005)	0.481 (0.006)	0.466 (0.008)
Linear range [a] ($mg\ L^{-1}$)	1.3–100.6	1.7–60.5	0.5–100.5	0.6–40.0	1.1–73.6	*1st linear part* 0.9–8.4 *2nd linear part* 8.4–73.8	1.2–100.0	1.8–22.0
R^2	0.996	0.991	0.994	0.992	0.994	*1st linear part* 0.992 *2nd linear part* 0.992	0.996	0.996
LOD ($mg\ L^{-1}$)	0.4	0.5	0.1	0.2	0.3	0.3	0.4	0.5

[a] The lowest value of the linear range was the LOQ.

With the purpose of assessing the repeatability and reproducibility of the SPCE for the determination of target compounds, DPV measurements in a solution containing 25.0 mg L^{-1} of AA, PA, DX, and CF in 0.1 mol L^{-1} acetic/acetate buffer were carried out following the above-mentioned conditions. Table 2 reports the repeatability and reproducibility values computed for the simultaneous determination of AA, PA, DX and CF. The repeatability was established from the relative standard deviation (RSD, %) of 5 consecutive DPV measurements using the same SPCE device, whereas the reproducibility was estimated from the RSD of the slope corresponding to the linear range of three independent calibration curves performed using three different sensor units: from 0.1 to 60.5 mg L^{-1}, from 0.07 to 40.0 mg L^{-1}, from 0.4 to 8.4 mg L^{-1} and from 1.5 to 22.0 mg L^{-1} for AA, PA, DX and CF, respectively. RSD values ranging from 1.8 to 8.1 %, and from 0.7 to 5.5 % were achieved by repeatability and reproducibility, respectively, depending on the tested drug. These values are in the same order of magnitude as those obtained in previous works for the voltammetric determination of drug residues [25] and for the determination of polyphenols by HPLC with electrochemical detection (HPLC-EC) [38].

Table 2. Repeatability and reproducibility values for the simultaneous determination of ascorbic acid, paracetamol, dextromethorphan and caffeine by differential pulse voltammetry using a SPCE in 0.1 mol L^{-1} acetic/acetate buffer pH 5.00.

	Ascorbic Acid	Paracetamol	Dextromethorphan	Caffeine
Repeatability (RSD, %)	8.1	1.8	4.7	3.2
Reproducibility (RSD, %)	0.7	3.2	5.5	3.1

Thus, the presented results allow us to conclude that the use of unmodified SPCE at the above-stated conditions is fully suitable for both the individual and the simultaneous determination of AA, PA, DX and CF in pharmaceutical products with the plus that SPEs can be easily coupled to hand-held potentiostats, enabling on-site determination. In addition, it should be noted that this voltammetric method could also be extended to the screening of environmental water samples with very low concentrations of the considered analytes (low µg L^{-1} or ng L^{-1}) by prior preconcentration of analytes from large sample volume of water by solid phase extraction.

3.3. Application to Real Samples

The developed DPV method was first applied to the simultaneous determination of AA and PA concentration in a Frenadol® Complex drug sample prepared as described in Section 2.3 (Figure S4). The determined AA and PA content as well as the relative error to the theoretical label (which is a rough estimate of the accuracy) are summarized in Table 3. Results show an excellent concordance between the determined and the theoretical label content of AA and PA as it can be inferred by relative error (%) values below 3%. This, coupled to the low RSD (%) values of 4.2% at most demonstrated the accuracy and precision of the developed method. It should be noted that although Frenadol® Complex also contains DX and CF, the simultaneous determination of the four analytes was not possible due to large differences in relative concentrations (increasing the amount of the sample to detect DX and CX resulted in too high concentrations of AA and PA which were also oxidated and saturated the electrode). It is expected that the proposed method could simultaneously determine all four analytes in samples with more similar concentration levels.

Table 3. Determination of target analytes in Frenadol® Complex drug and in spiked well water by DPV on SPCE by standard addition calibration method.

Sample	Analyte	$C_{determined}$	RSD (%)	Relative Error (%)	Recovery (%)
Frenadol® Complex	AA	260 (10) mg per sachet	4.2	2.9	N/A
	PA	644 (3) mg per sachet	0.5	1.0	N/A
Spiked well water	AA	51 (1) mg L^{-1}	2.1	N/A	99.5
	PA	19.0 (0.4) mg L^{-1}	2.2	N/A	100.8
	DX	47.1 (0.5) mg L^{-1}	1.0	N/A	100.1
	CF	14.1 (0.3) mg L^{-1}	2.0	N/A	100.0

To further validate the applicability of the developed method, the simultaneous determination of AA, PA, DX and CF in a drinking well water sample spiked with 51.8, 18.8, 47.1 and 14.1 mg L^{-1} of AA, PA, DX and CF, respectively (see Section 2.3 for more experimental details) using a SPCE was performed. As it can be seen from Figure 4a, voltammograms with well-defined peaks and with similar performance to those obtained for simultaneous calibration of considered drugs were attained. It should be mentioned that DPV measurements of non-spiked well water samples did not exhibit any AA, PA, DX and CF signals. The AA, PA, DX and CF calibration curves (Figure 4b,c) showed in all cases a good correlation. Excellent recoveries of the spiked well water sample (Table 3) in the range of 99.5–100.8% were obtained, and the very low RSD (%) values of 2.2% at most revealed that the agreement between AA, PA, DX and CF concentration from the three analyzed well water samples was very good.

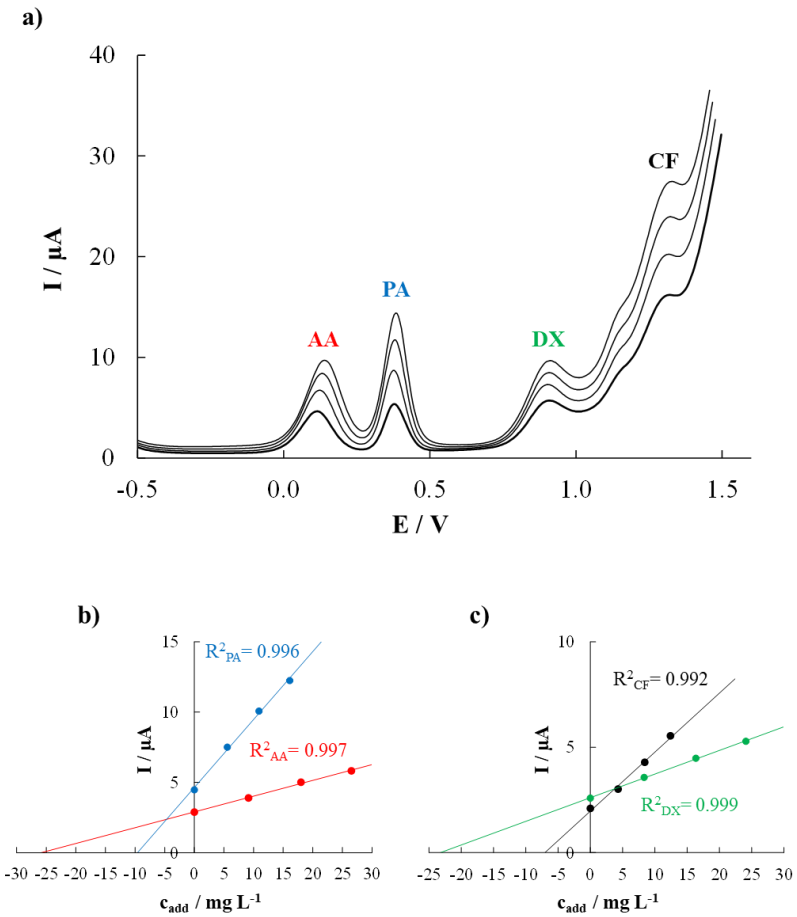

Figure 4. (**a**) DPV measurements in a well water sample in 0.1 mol L^{-1} acetic/acetate buffer pH 5.00 on SPCE; (**b**) ascorbic acid and paracetamol standard addition plots and (**c**) dextromethorphan and caffeine standard addition plots.

Thus, the successful results obtained validate the applicability of the proposed DPV method using a SPCE for the determination of considered drugs in pharmaceutics and water samples. Furthermore, it should be considered that this method could be applied for the determination of target drugs in environmental water samples with a very low content by previous preconcentration of the considered analytes from large sample volumes, for example, by solid phase extraction.

4. Conclusions

Differential pulse voltammetry coupled to a screen-printed carbon electrode was used for the simultaneous determination of ascorbic acid, paracetamol, dextromethorphan and caffeine. pH was firstly optimized obtaining the best DPV response in 0.1 mol L^{-1} acetic/acetate buffer at pH 5.00. As a next step, the analytical performance of both individual and simultaneous determination of considered drugs was evaluated, concluding that: (i) the coexistence of AA, PA, DX and CF at similar concentration levels does not present important interferences, allowing their simultaneous determination with a similar sensitivity; (ii) linear ranges obtained for the simultaneous determination of target compounds were slightly narrower than those achieved by individual drug determinations; and (iii) LODs and LOQs obtained in both individual and simultaneous calibrations were in all cases almost the same, ranging from 0.1 to 0.5 mg L^{-1} and from 0.5 to 1.8 mg L^{-1}, respectively, depending on the compound considered. Thus, these results combined with the benefits of using SPCE, i.e., low-cost, reproducible and disposable devices that can be easily coupled to portable potentiostats, demonstrated the goodness of the developed method for the simultaneous screening and/or determination of AA, PA, DX and CF in both pharmaceutical formulations and water samples of environmental interest. The applicability to biological samples such as blood or urine should also be investigated, but in this case a careful evaluation of matrix effects and interferences should be carried out, which exceeds the purpose of the present work. Moreover, the developed method was validated by: i) the determination of AA and PA in a pharmaceutical product with an exceptional agreement between the determined and the theoretical label content of considered drugs (relative error (%) values below 3%) and good reproducibility (RSD (%) values of 4.2% at most); and ii) the simultaneous determination of AA, PA, DX and CF in a spiked drinking well water sample with excellent recoveries (99.5, 100.8, 100.1 and 100.0% for AA, PA, DX and CF, respectively) and reproducibility (RSD (%) values of 2.2% at most). Finally, it should be pointed out that if ultra-trace analysis (low µg L^{-1} or ng L^{-1}) was demanded, the developed voltammetric method could be extended by the previous preconcentration of analytes, for example by solid phase extraction.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/chemosensors10030095/s1, Figure S1: Oxidation reactions for studied compounds; Figure S2: Species distribution diagram as a function of pH for studied compounds; Figure S3: DP voltammograms for low concentrations of studied compounds; Figure S4: DP voltammograms for the simultaneous determination of ascorbic acid and paracetamol in Frenadol® Complex. Table S1: Summary of E vs. pH plots obtained from literature. (References [27–30] are cited in the Supplementary Materials).

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