Scientific paper

Development and Validation of Voltammetric Techniques for Nabumetone in Pharmaceutical Dosage Form, Human Serum and Urine

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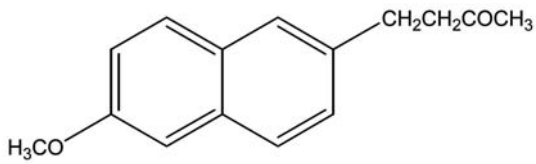
Abstract

The electrochemical behavior and determination of nabumetone, nonsteroidal anti-inflammatory drug, were studied in aqueous alcohol medium at a glassy carbon electrode using cyclic, differential pulse (DP) and osteryoung square wave (OSW) voltammetric techniques. In pH 3.7 acetate buffer, nabumetone solution presents a well-defined anodic response at 1.2 V as shown by the proposed methods. The anodic peak was characterized as being irreversible and diffusion-controlled. The slope of the log ip – log v linear plot was 0.52 indicating the diffusion control for pH 3.7 acetate buffer solution. Under optimal conditions, a detection limit of 7.65×10^{-8} M for DPV and 3.60×10^{-8} M for OSW, and a linear calibration graph in the range from 1×10^{-6} M to 8×10^{-5} M were obtained for both methods. The procedure was successfully applied to the determination of the drug in tablets, spiked human serum and spiked human urine with good recoveries. The detection limits were 2.31×10^{-7} M and 2.53×10^{-7} M in human serum and 2.68×10^{-7} M and 2.51×10^{-7} M in human urine for DPV and OSWV method, respectively.

Keywords: Nabumetone, voltammetry, determination, pharmaceutical dosage form, serum, urine.

1. Introduction

Nabumetone, naphthylalkanone designated chemically as 4-(6-methoxy-2-naphthyl) – butan-2-one (Scheme 1), is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic and antipyretic properties in pharmacologic studies.[1] As with other nonsteroidal anti-inflammatory agents, its mode of action is not known. However, the ability to inhibit prostaglandin synthesis may be involved in the anti-inflammatory effect. After oral administration, approximately 80% of a radio labeled dose of nabumetone is found in the urine, indicating that nabumetone is well absorbed from the gastrointestinal tract. Nabumetone itself is not detected in the plasma due to rapid biotransformation after absorption to the principal active metabolite, 6-methoxy-2-naphthylacetic acid .[2, 3]



Scheme 1. Chemical structure of nabumetone.

Only a few analytical methods for the determination of nabumetone are described, including phosphorescence,[4–6] high-performance liquid chromatography[7–11] and flow injection analysis.[12]

Electrochemical methods have proved to be very sensitive for the determination of organic molecules that undergo oxidation or reduction reactions, including drugs and related molecules in pharmaceutical dosage form and biological fluids.[13–17] The advance in experimental electrochemical techniques in the field of analysis of drugs is due to their simplicity, low cost and relatively short analysis time when compared with other techniques.

Practical application of electrochemistry include the determination of electrode oxidation mechanism. Due to the existing resemblance between electrochemical and biological reactions it can be assumed that the oxidation mechanism taking place at the electrode and in the body share similar principles.[18,19]

The nabumetone molecule has electroactive groups. To the best our knowledge, however, its electrochemical redox properties have not been studied earlier. This led us to study its voltammetric behavior in an attempt to develop a simple, sensitive, rapid and reliable differential pulse and square-wave method for its quantitative determination in pharmaceutical dosage form and biological fluids.

This work provides a better understanding on the the electrochemical behavior and elucidation of the electrode reaction pathway of nabumetone at glassy carbon electrode. Validated voltammetric procedures were also described for the trace determination of the nabumetone in bulk form , pharmaceutical dosage form, human serum and urine, without the need for sample pretreatment or time-consuming extraction or evaporation steps prior to the drug analysis.

2. Experimental

2.1. Reagents and Drugs

Nabumetone was supplied by GlaxoSmithKline (İstanbul, Turkey). Commercial tablets Relifex® (500 mg nabumetone) were also kindly supplied from GlaxoSmithKline (Istanbul, Turkey). Nabumetone stock solutions were prepared daily by direct dissolution in selected supporting electrolytes, namely sulphuric acid (0.1M; 0.5 M; 1M), phosphate buffer (pH 1.5–12.0, 0.2 M), acetate buffer (pH 3.0–5.70, 0.2 M), borate buffer (pH 9.3–10, 0.2 M) and Britton-Robinson buffer (pH 2.00–12.01, 0.04 M) that were prepared with distilled water. All experiments were performed with analytical reagent-grade chemicals without further purification.

Inactive ingredients consist of hydroxyl propyl methyl cellulose, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium lauryl sulfate, sodium starch glycolate and titanium dioxide.[2]

All stock solutions were protected from light and were used within several hours to avoid decompositions.

2.2. Apparatus

Voltammetric measurements were performed on a BAS 100W electrochemical analyzer (Bioanalytical System, USA). A three-electrode cell system was used with a glassy carbon electrode (ø = 3 mm, BAS) as working electrode, a platinum wire electrode as the counter-electrode and an Ag/AgCl (3 mol.L^{-1} KCL, BAS) electrode as the reference electrode. The glassy carbon working electrode was polished to a mirror finish using a BAS polishing kit with ø = 0.01 m alumina paste and thoroughly washed with purified water between measurements. All measurements were carried out at ambient temperature of the laboratory (23–27 °C).

2.3. Experimental Conditions

For the analytical application, the following parameters were employed. DP voltammetry: Pulse amplitude, 50 mV; pulse width, 0.05 s; scan rate, 20 mV.s^{-1}; SW voltammetry, pulse amplitude, 25 mV; frequency, 15 Hz; scan increment, 4 mV.

2.4. Analysis of Tablets

Ten tablets were weighed and then crushed into a fine powder in a mortar. A suitable amount of this powder corresponding to the 28.79 mg 100 mL^{-1} of nabumetone was accurately weighed and transferred into a 50 mL flask, completed to volume with methanol and sonicated for 10 min. The working solutions for the voltammetric investigations were prepared by dilution of the stock solution with the selected supporting electrolyte so that in most instances (if not stated otherwise) the final solution contained 20% methanol.

To study the accuracy of the proposed method and check the possible interferences from common excipients, recovery studies were carried out. For these experiments, known amounts of the pure drug were added to the earlier analysed tablet formulation of nabumetone. The recovery of the drug was calculated using the corresponding regression equations of the previously plotted calibration plots.

2.5. Determination of Nabumetone in Spiked Human Serum and Human Urine Samples

Drug-free human blood, obtained from healthy volunteers (after obtaining their written consent) was centrifuged (5000 rpm) for 30 min at room temperature, and separated serum samples were stored frozen until assay. An aliquot of serum sample was fortified with nabumetone dissolved in bidistilled water to achieve a final concentration of 10^{-3} M. Acetonitrile removes serum proteins effectively; the appropriate relationship of volumes to eliminate the protein was 1 to 1.5. After vortexing for 30s, the mixture was then centrifuged for 10 min at 5000 rpm in order to eliminate serum protein residues, and supernatant was taken carefully. Appropriate volumes of this supernatant were transferred into the volumetric flask and diluted up to the volume with acetate buffer at pH 3.7. An aliquot of human urine sample was collected and analysed in the same way as the serum samples.

Quantifications were performed by means of the calibration curve method from the related calibration equation.

3. Results and Discussion

The nature of nabumetone oxidation process was studied cyclic, linear-sweep (LS), differential pulse (DP)

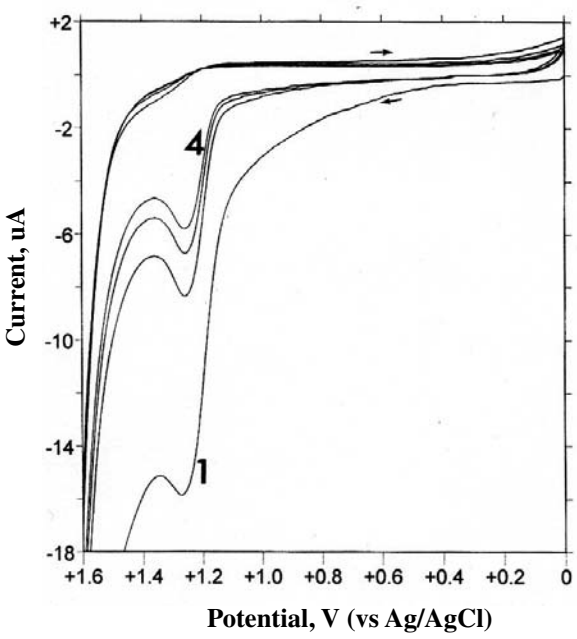


Fig.1. Repetitive cyclic voltammograms of 1×10^{-4} M nabumetone in acetate buffer at pH 3.70. Scan rate 100 mVs^{-1}. The number indicates the number of scans.

and square wave (SW) voltammetry. Nabumetone was oxidized on glassy carbon electrode producing only one anodic peak in pH 3.7 acetate buffer at +1.20 V (Fig. 1). In the forward scan, one well-defined anodic peak owing to the oxidation of methoxy group was observed and no peak was noticed in the reverse direction.

The variation of peak intensity and peak potential with for a 2×10^{-5} M nabumetone was studied by cyclic, DP and SW voltammetric techniques between pH 1.50–12.01. Fig. 2 shows the linear-sweep voltammograms where the effect of pH, both on the peak potential and on the peak current is clearly seen and agrees with the expected behavior for proton-dependent process coupled to a final irreversible chemical reaction. This chemical irreversibility leads to the absence of any oxidation peak in the reverse scan, even if the rate (ν) is increased to 750 m-Vs^{-1}. Linear Randles-Sevcik plot (plot of Ip against $\sqrt{\nu}$, correlation coefficient 0.996) was obtained indicating that diffusion is the means of mass transport.[20]

This finding was further confirmed by plotting log Ip against log ν; a straight line was obtained (correlation coefficient 0.991) with a slope of 0.52 (slopes of 0.50 and 1.0 are expected for ideal reactions of solution and surface species, respectively).[20] The peak potential was shifted to less positive values on increasing scan rate, which confirms the irreversible nature of the oxidation process. The relation between Ep and ν can be expressed by the equations.

$Ep(mV) = 0.67\nu + 1195.01$ (for 5–100 mVs^{-1}, r = 0.983)

$Ep(mV) = 0.15\nu + 1253.44$ (for 100–750 mVs^{-1}, r = 0.990)

The peak current decreases with succeeding potential scans suggesting an adsorbed species formation on the electrode surface. Therefore, the oxidation of nabumetone at the glassy carbon electrode is an irreversible diffusion-controlled process.

The Tafel plots (logi versus E) were obtained with a scan rate of 5 mVs^{-1} beginning from a steady-state potential in acetate buffer at pH 3.7. The αn value of anodic reaction from the slope of the linear part of the Tafel plot was 0.087. The exchange current density (I_o) is 0.457 $A.cm^{-2}$ for this system. These values indicated the irreversibility of the oxidation reaction. When the logarithm of the current at a potential of about +1.20 V obtained in pH 3.7 acetate buffer was plotted against the logarithm of the nabumetone in the range of $8 \times 10^{-7} - 1 \times 10^{-5}$ M, a linear relationship was obtained.

$$\text{logi}\ (\mu_A) = 0.314\text{logC(M)} + 0.251 \qquad (r = 0.993)$$

The slope of this equation gives the reaction order. These kinetic parameters and the reaction order showed that there was a mechanism related to the surface events, and the reaction seems to be of first order.

The dependence of E and Ip on pH are shown in Fig. 2 (a and b), respectively. The peak potential remains prac-

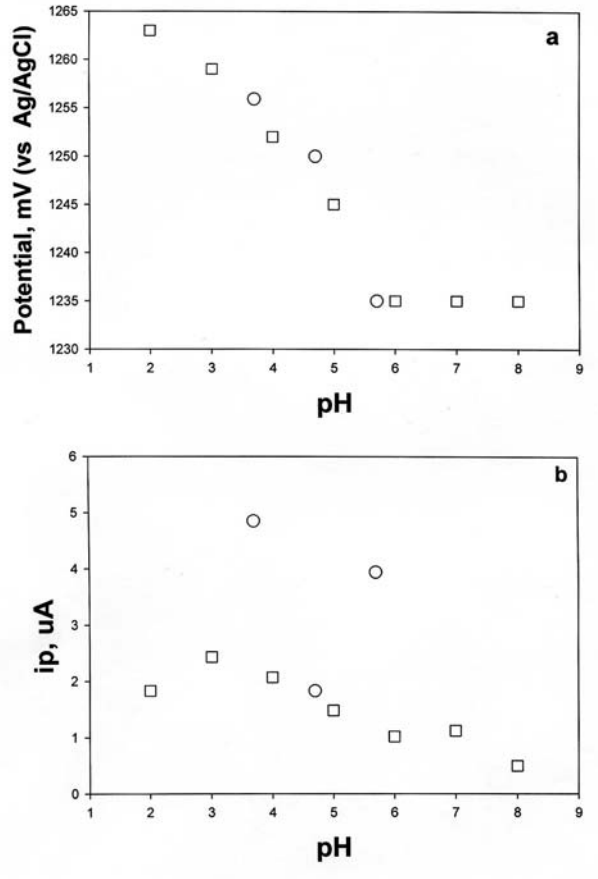


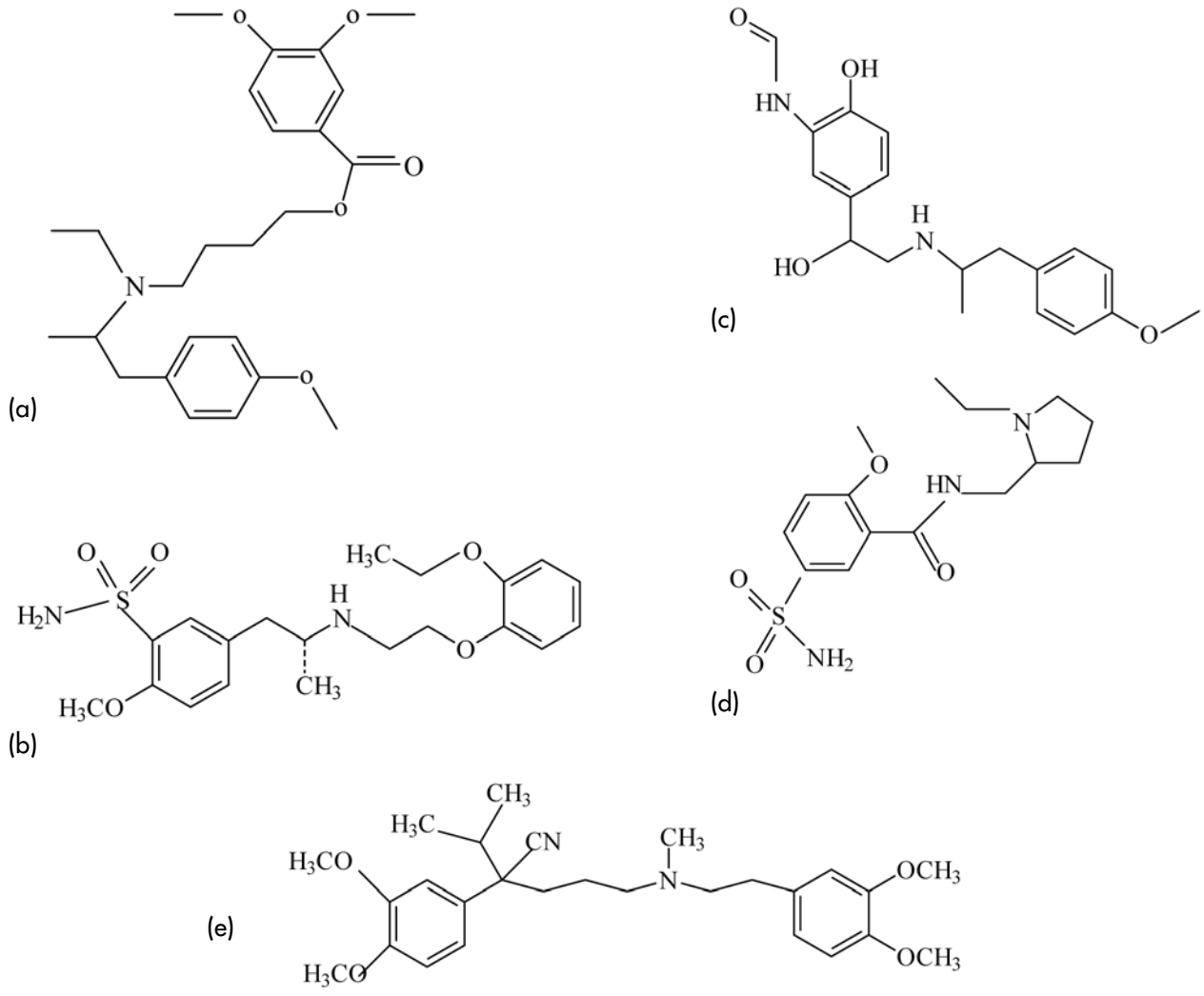
Fig.2. Effect of pH on (a) nabumetone peak potential ; and (b) peak current; ()Britton-Robinson buffer, (o) Acetate buffer solutions. DPV techniques scan rate, 20 mVs^{-1}; pulse amplitude, 50 mV and pulse width 50 ms.

tically pH-independent at pH higher than about 5.7. The observed pH-dependence indicates that the electroactive grouping responsible for the oxidation process in acid-base equilibrium with pK_a about 4.7. At pH > pK_a the conjugate base predominates in the bulk of the solution. At pH < pK_a, the conjugate base must be formed by a rapid dissociation of the protonated form. The cross section point obtained at pH value being ~4.7, corresponds to the pK_a value of nabumetone and its active acidic metabolite 6-methoxy-2-naphthylacetic acid (6-MNA; pK_a = 4.5).[21] The first part of the curve shows a slope (ΔE/Δ pH) of –5.02 mV (between pH 2.0–4.7), and the second part of –14.87 mV (between 4.7–5.7) indicating processes involving the protons in the electrode reaction.

The influence of pH on nabumetone current at glassy carbon electrode was also studied. The ip versus pH plot (Fig. 2b) shows that peak current is maximum in pH 3.7 acetate buffer.

For this reason acetate buffer at pH 3.7 was chosen for the determination of nabumetone from the pharmaceutical dosage form, serum and urine samples as the supporting electrolyte. The anodic current of an oxidation accompanied by an antecedent acid-base equilibrium therefore always increases with increasing pH. However the decrease of the anodic current with increasing pH can not be attributed to an acid-base reaction that occurs before the electron uptake.

To identify the oxidation process of nabumetone, the study on some selected model compound (Scheme 2) were performed by cyclic voltammetry at the glassy carbon electrode as a function of pH. Tamsulosin, Formoterol, Mebeverin HCl, Sulpiride, Verapamil and two model compounds 4-methoxyphenol and anisole were used as model substances for oxidation of methoxybenzene moiety. Comparative study of these substances was performed by cyclic, linear sweep, differential pulse and square wave voltammetric techniques at the glassy carbon electrode, as function of pH. Taking into account all studies performed, we suggest that the oxidation processes may be occurring on the methoxy groups on the benzen ring of



Scheme 2. The structures of Mebeverin fumarate (a); Tamsulosin (b); Formoterol (c); Sulpiride (d); Verapamil (e).

the molecule, which is electroactive in both acidic and less basic media.

The electrooxidation of the methoxybenzene of Tamsulosin and Formoterol have already been reported to our previous studies.[22, 23] Tamsulosin, Mebeverin HCl and Verapamil are oxidized over a wide pH range in a single peak at nearly similar potentials to the main peak of nabumetone. Mebeverin and Verapamil are oxidized over most of pH range, producing one well-defined, mainly irreversible oxidation peak by cyclic voltammetry in different pH's solutions. The peak potentials are shifted with increasing pH to less positive potentials similarly as Ep of nabumetone.

The anodic behavior of nabumetone is comparable to methoxybenzene oxidation also, which was reported in our previous study.[22, 23] As a comparative study anisole and 4-methoxyphenol were performed by cyclic voltammetry at the glassy carbon electrode, as a function of pH in order to identify the oxidation process of nabumetone (not shown). The results revealed a good agreement with the redox mechanism postulated for similar compounds such as formoterol fumarate, tamsulosin, mebeverin HCl, sulpiride, verapamil and model compounds such as anisole and 4-methoxyphenol and suggested that nabumetone can be determined electrochemically by oxidation of methoxybenzene group.

3.1. Validation of the Analytical Procedure

The applicability of the optimized DP and OSW voltammetric techniques for the quantification of nabumeton were tested. Under the chosen experimental parameters described in the Experimental section, the variation of the peak current with the increasing nabumeton concentration was studied by means of DPV and OSWV. Linear calibration graph was obtained within the concentration range 1×10^{-6}–8×10^{-5} M. The characteristics of these graphs are reported in Table 1. Limits of detection (LOD) and quantification (LOQ) of nabumeton were calculated using the following equations:[24, 25]

$$\text{LOD} = 3.3\ s/m;\ \text{LOQ} = 10\ s/m,$$

Where s is the standard deviation of the peak currents (three runs) and m is the calibration graph. The results of LOD=2.55×10^{-7}M and LOQ=8.50×10^{-7} M for DPV, LOD=2.85×10^{-7} M and LOQ=9.50×10^{-7} M for OSWV indicated the reliability of the proposed voltammetric procedure for the trace assay of nabumeton (Table 1).

Table 1: Regression data of the calibration lines for quantitative determination of nabumetone by DPV and OSWV in supporting electrolyte, human serum and urine samples.

	DPV			OSWV		
	Supporting Electrolyte	**Serum**	**Urine**	**Supporting Electrolyte**	**Serum**	**Urine**
Measured potential (V)	1.19	1.19	1.19	1.23	1.24	1.24
Linearity range (M)	1×10^{-6}–8×10^{-5}	1×10^{-6}–8×10^{-5}	1×10^{-6}–8×10^{-5}	1×10^{-6}–8×10^{-5}	2×10^{-6}–8×10^{-5}	1×10^{-6}–6×10^{-5}
Slope (μA/M)	7.44×10^{4}	8.21×10^{4}	8.65×10^{4}	9.05×10^{4}	9.85×10^{4}	9.52×10^{4}
Intercept (μA)	0.0813	0.1896	0.0579	–0.0858	0.0060	0.0621
Correlation coefficient	0.999	0.999	0.999	0.999	0.999	0.999
SE of slope	1.26×10^{3}	1.59×10^{3}	8.69×10^{2}	7.45×10^{2}	1.66×10^{3}	1.91×10^{3}
SE of intercept	0.044	0.056	0.027	0.026	0.061	0.048
The standard error of regression (SE)	0.10423	0.13210	0.0637	0.06185	0.13217	0.10924
Variance ratio (F)	3508.388	2659.207	9906.9	14730.967	3522.945	2498.0
LOD (M)	2.55×10^{-7}	2.31×10^{-7}	2.68×10^{-7}	2.85×10^{-7}	2.53×10^{-7}	2.51×10^{-7}
LOQ (M)	8.50×10^{-7}	7.69×10^{-7}	8.94×10^{-7}	9.50×10^{-7}	8.43×10^{-7}	8.36×10^{-7}
Repeatability of peak current (RSD%)	0.69	0.38	0.72	0.44	0.71	0.33
Repeatability of peak potential (RSD%)	0.37	0.15	0.28	0.14	0.18	0.18
Reproducibility of peak current (RSD%)	0.80	0.53	0.85	0.87	0.57	0.73
Reproducibility of peak potential (RSD%)	0.37	0.19	0.18	0.27	0.18	0.18

Five experiments on 2×10^{-5} M nabumeton were repeated using both techniques to test the repeatability and reproducibility of peak current and peak potentials. The results are shown in Table 1. Repetition of sample analysis after 72-h period did not show any significance change in results of analysis. Since the analytical response was almost the same in the pH of the medium (pH 3.7 ± 0.5) and in a temperature range from 20 to 25 °C, it can be concluded that the robustness of the proposed method with respect to these factors is quite satisfactory. In order to detect interactions of excipients (Part 2 Reagent and Drugs) in this method, the standard addition technique was applied to the same preparations which were analyzed by the calibration curve. The mean percentage recovery based on the average of five replicate measurements were 100.04 ± 0.31 for DPV and 100.04 ± 0.09 for OSW technique showed no significant interference from excipients in the analysis of nabumeton (Table 2) and indicated high precision of the proposed methods.

Table 2: Assay results from nabumetone (Relifex®) and mean recoveries in spiked tablets.

	DPV	OSWV
Labeled claim (mg)	500	500
Amount found (mg)[a]	500.91	501.0
RSD %	0.97	0.37
Bias %	–0.18	–0.20
Added (mg)	20	20
Found (mg)[a]	20.08	20.08
Recovery %	100.04	100.04
RSD % of recovery	0.31	0.09
Bias %	–0.04	–0.04

[a] Each value is the mean of 5 experiments.

3.2. Assay of Nabumetone in Tablets

The proposed DP and OSW voltammetric techniques were successfully applied for the direct determination of nabumetone in pharmaceutical dosage form (Relifex® tablet) and the validity was assessed by applying both the calibration curve and the standard additions methods. The amounts of nabumetone in tablet dosage forms are fairly close to the labeled amounts for both techniques. The results of the determination of the drug in tablet dosage forms are presented in Table 2 and were in good agreement with. The accuracy of the method was determined by its recovery during spiked experiments. Recovery studies were carried out after the addition of known amounts of the pure drug to various pre-analyzed formulation of nabumetone.

3.3. Assay of Nabumetone in Human Serum and Urine

The optimized procedure was successfully applied for the determination of nabumetone in protein-free spiked human serum samples. Acetonitrile and methanol were tried as the serum precipitating agents. The best results were obtained with acetonitrile. Hence, acetonitrile was used for the following studies.

The measurements of nabumetone in serum samples were performed as described in Section 2. The applicability of the proposed methods to the human serum, the calibration equations were obtained in spiked human serum. Calibration equation parameters and validation data are shown in Table 1. Obtained recovery results of spike human serum samples are given in Table 3. Typical DPV and OSW curves of nabumetone examined in serum samples are shown in Figure 3a and 3b, respectively. Using both proposed methods, no sample pretreatment was required other than precipitation and dilution steps. The recovery results of nabumetone (Table 3) in serum samples were calculated from the related linear regression equations, which are given in Table 1. Good recoveries of nabumetone were achieved from this type of matrix.

The optimized DPV and OSWV procedures were also successfully applied to the determination of nabumetone spiked to human urine samples. Typical DPV and OSWV curves are shown in Fig. 3c and 3d, respectively. No extraction or pretreatment steps other than centrifugal separation were required prior to assay of the drug. The calibration method was applied to determination of nabumetone in urine samples (Table 1). The analytical results obtained for nabumetone in human urine samples are also presented in Table 3. The results are satisfactorily accurate and precise.

4. Conclusions

The electrochemical behavior of nabumetone on glassy carbon electrode was established and studied for the first time. Nabumetone is irreversibly oxidized at high potentials on glassy carbon electrodes.

Table 3: Application of the DPV and OSWV methods to the determination of nabumetone in spiked human serum and urine samples.

Technique	Medium	Nabumetone added (M)	n	Nabumetone found (M)	Average recovery %	RSD %	Bias %
DPV	Serum	4×10^{-5}	5	4.014×10^{-5}	100.35	0.41	–0.35
DPV	Urine	4×10^{-5}	5	4.015×10^{-5}	100.38	0.36	–0.38
OSWV	Serum	4×10^{-5}	5	4.026×10^{-5}	100.65	0.66	–0.65
OSWV	Urine	4×10^{-5}	5	4.024×10^{-5}	100.59	0.67	–0.59

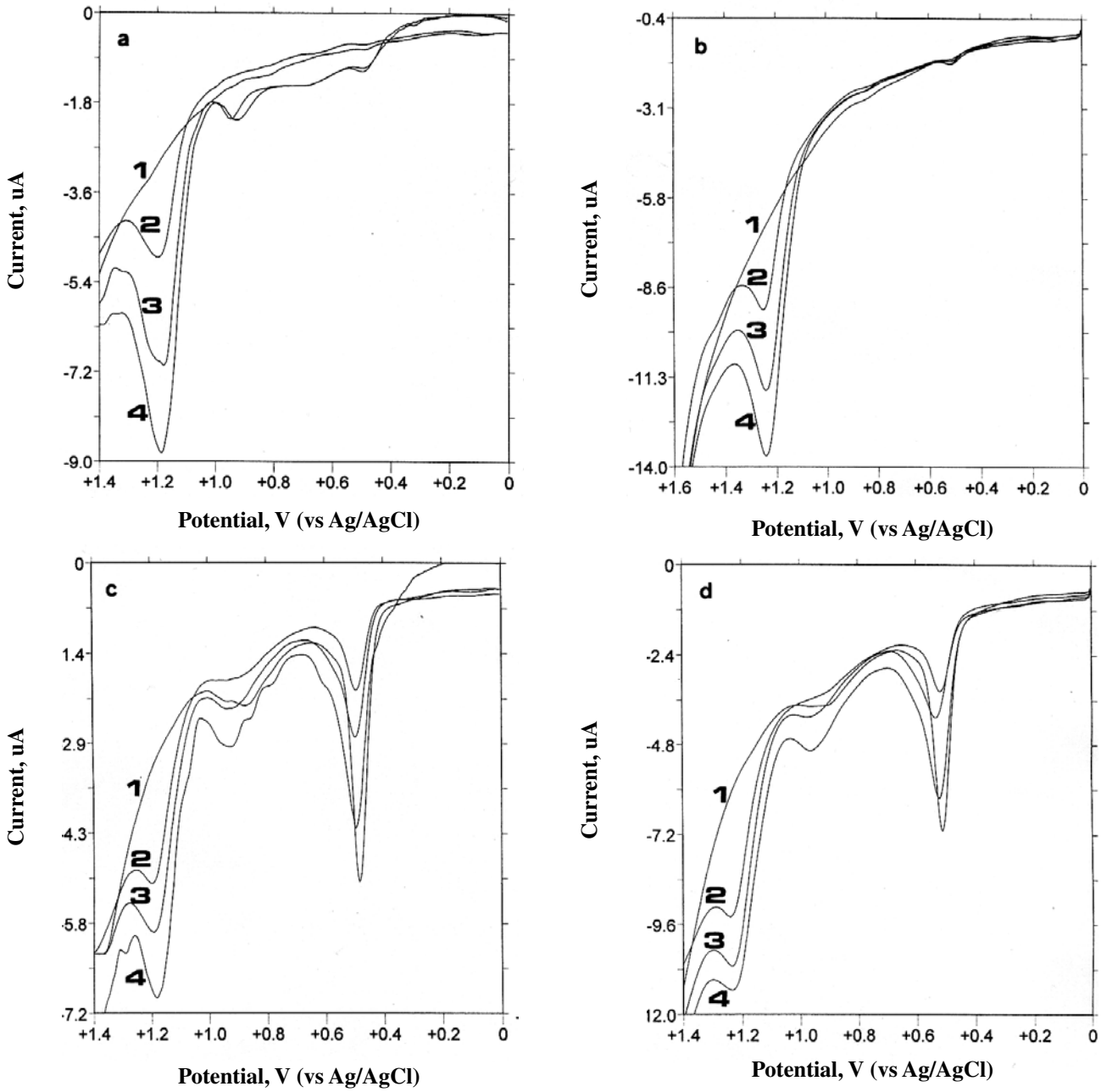


Fig.3. Differential pulse (a,c) and square wave (b,d) voltammograms in acetate buffer pH 3.70 obtained for the determination of nabumetone in spiked serum (a,b) and spiked urine (c,d) samples. (1) Blank; (2)2 × 10^{-5} M; (3) 4 × 10^{-5} M; (4) 6 × 10^{-5} M nabumetone in acetate buffer at pH 3.70.

The developed determination methods of nabumetone are based on voltammetric oxidation of methoxybenzene group.

The analytical procedure has been fully validated. The data obtained from pharmaceutical dosage form gave an average nabumetone content of 500.91 ± 0.97 for DPV and 501.00 ± 0.37 for OSWV techniques, which is in close agreement with the 500 mg/tablet quoted by the manufacturer.

The developed methods provide a sensitive and simple approach to the determination of nabumetone in tablet dosage forms, spiked human serum and spiked urine samples. The proposed method can be considered as an alternative substitute to HPLC methods. Furthermore, the present methods could possibly be adopted for the pharmacokinetic studies as well as clinical and quality control laboratories. Also this paper is not intended to be a study of the farmacokinetic and pharmacodynamic properties of nabumetone, since only healthy voluenteers were used for the sample collection and results may be of no significance. This work throws a more deep light upon the farmacoki-

netic and pharmacodynamic properties of nabumetone. It only shows that the possibility of monitoring nabumetone makes the method useful for the detection and determination of nabumetone (and all active metabolites together).

As applied to serum and urine samples, the proposed methods have advantage that no prior extractions procedure is required. Furthermore, the voltammetric analyses were not time-consuming and the excipients did not interfere in the analyses, avoiding a separation step.

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Povzetek

Elektrokemijske lastnosti in določanje nabumetona, nesteroidne protivnetne učinkovine, smo preučevali v alkoholno–vodni raztopini na steklasti ogljikovi elektrodi z uporabo voltametričnih tehnik. V acetatnem pufru pri pH 3,7 daje nabumeton dobro definiran anodni vrh pri 1,2 V. Proces je ireverzibilen in difuzijsko kontroliran. Pri optimalnih pogojih je meja zaznave $7{,}65 \cdot 10^{-8}$ M pri diferencialni pulzni voltametriji in $3{,}60 \cdot 10^{-8}$ M pri osteryoung tehniki, linearnost pa smo ugotovili v intervalu $110^{-6} – 8 \cdot 10^{-5}$ M. Postopek smo uporabili za določitev nabumetona v farmacevtskih izdelkih ter humanem serumu in urinu z dodatkom nabumetona, z dobrimi izkoristki.