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Flow-injection determination of Novalgin using amperometric detection at a glassy carbon electrode

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Abstract: An electroanalytical study of the oxidation of Novalgin (dipyrone) at a glassy carbon electrode in aqueous solution has been carried out. A flow-injection method with amperometric detection based on this oxidation process is also described. The influence of flow rate, coil length and injection volume on the sensitivity of the method was established. The calibration graph was linear within the range 3×10^{-6}–3×10^{-5} M in an ammonia buffer solution (pH 9) at a potential of 0.4 V versus an Ag/AgCl reference electrode. The sampling rate was 54 samples h^{-1}. The applicability of the method to the determination of Novalgin in pharmaceutical preparations was demonstrated by investigating the effect of potential sources of interference and by analysing commercial preparations.

Keywords: *Novalgin; dipyrone; flow-injection; amperometry; pharmaceuticals.*

Introduction

Novalgin (dipyrone, analgin, metamizole), a therapeutic agent used commonly as an analgesic, antipyretic and antispasmodic, is the sodium salt of [2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H(-pyrazol-4-yl) methylamino] methanesulphonic acid. Novalgin forms the active constituent of several pharmaceutical preparations and its determination in these formulations is therefore very important. This compound has been determined in pharmaceuticals by spectrophotometry after reaction with sodium nitrite [1], 4-dimethylaminobenzaldehyde [2], cerium (IV) [3], N-bromosuccinimide [4], potassium iodate [5], 3-methyl-2-benzo-thiazolinone hydrazone hydrochloride [6] and iron(III)-1,10-phenanthroline [7]. Other methods include titrimetry with N-bromosuccinimide [8], coulometry [9] and high-performance liquid chromatography [10–12]. However, flow-injection analysis has rarely been applied to the determination of Novalgin and only two flow-injection methods have been described. One is based on the oxidation of the drug using cerium (IV) and monitoring the fluorescence of cerium (III) formed [13]; the other makes use of coulometric detection with a porous platinum electrode [14].

Electrochemical detection is being explored as a means of carrying out assays without reagents in optically opaque solutions with equipment at a fraction of the cost of most other detectors. The increasing demand for the analytical control of pharmaceuticals necessitates the development of rapid, precise and selective methods of analysis. Flow-injection analysis has inherent advantages for drug analysis. A flow-injection (FI) procedure is described in this paper for the determination of Novalgin in multi-component pharmaceutical formulations, the method is based on the oxidation of the drug at a glassy carbon electrode.

Experimental

Reagent and solutions

All reagents were of analytical reagent grade and were used as received. Double-distilled water was used throughout the work. An aqueous 10^{-2} M Novalgin stock solution was prepared from the pure product (Sigma) and kept in a refrigerator. Working solutions were prepared daily by suitable dilutions.

Solutions of drugs were prepared by dissolving 100 mg of the compound in 100 ml of distilled water with further dilutions as required.

Britton–Robinson buffer solutions of different pH values were prepared by the addition

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of 1 M sodium hydroxide solution to a 0.2 M solution in respect of phosphoric, boric and acetic acids. The final pH was checked with a glass electrode. A 0.2 M ammonia buffer solution (pH 9) was also prepared.

All the buffers were used as the supporting electrolyte in voltammetric studies.

Apparatus and manifold

A Metrohm-505 polarograph and a Metrohm E-28911 glassy carbon rotating electrode were used for voltammetric studies. The flow-injection equipment comprised a Gilson Minipuls peristaltic pump and an Omnifit injection valve with variable injection volumes. The detector was a Metrohm E-656 Herisau, equipped with a Metrohm EA-1096 wall-jet cell. Electrode potentials were controlled by means of a Metrohm 641 VA potentiostat and the signals were registered on a Linseis L 6512 recorder. A Metrohm 6.0905.010 glassy carbon electrode, an Ag/AgCl–KCl(3M) reference electrode and a gold counter electrode were used.

Procedure

A single-line manifold was used. A 85-μl aliquot of 1–10 μg ml^{-1} Novalgin solution was injected into the selected carrier solution (0.2 M ammonia buffer, pH 9) at a flow rate of 1.5 ml min^{-1} using a 50-cm delay coil (0.5 mm i.d.). The detection potential was 0.4 V versus an Ag/AgCl–KCl (3M) reference electrode.

Pre-treatment of the glassy carbon electrode

The glassy carbon electrode was pre-treated daily prior to measurement in order to maintain the solid electrode surface in a reproducible active state. The pre-treatment process involved a mechanical polishing with alumina, anodization of the polished electrode for 1 min at 1 V versus Ag/AgCl followed by cathodization for 1 min at −0.6 V. This step was performed in the buffer used as carrier in the flow system and was repeated three times. After about 60 injections the electrode was again submitted to the pre-treated process.

Results and Discussion

Linear sweep voltammetric experiments demonstrated that Novalgin at pH values between 3 and 10 in Britton–Robinson buffer shows a well-defined oxidation wave (Fig. 1). The half-wave potential decreased with increasing pH over the range studied. The slope of $E_{1/2}$ versus pH was −0.056 V.

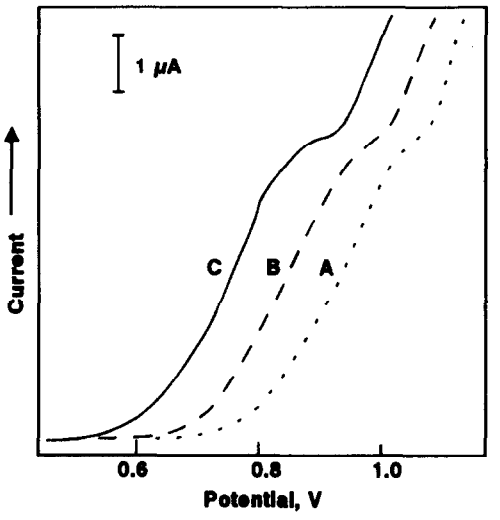

Figure 1
Linear sweep voltammograms of Novalgin (5×10^{-5} M) at a rotary glassy carbon electrode (2000 rev min^{-1}) in 0.2 M Britton–Robinson buffer. Curves A–C: pH 9, 7 and 5, respectively.

A typical hydrodynamic voltammogram, obtained by injecting Novalgin solution into 0.2 M ammonia buffer (pH 9) and measuring the signals at various potentials, is shown in Fig. 2. Potential-independent limiting-current regions are obtainable at applied potentials higher than 0.3 V. A potential of 0.4 V was chosen for further experiments.

The buffer constituents (carbonate, borate, phosphate, ammonia) had little influence on the peak height. Ammonia buffer (pH 9) provided the lowest background current level and this was therefore used in all subsequent experiments.

The pre-treated electrode maintained its stability with repeated exposure to Novalgin. Up to 60 injections of a test solution containing 2 μg ml^{-1} of Novalgin presented a stable response (only 13 injections are presented in Fig. 3) with a relative standard deviation of 0.19%.

The effect of flow-rate on signal size was studied in the range 0.5–3.5 ml min^{-1}. An increase in peak height was observed when the flow rate was increased up to 1 ml min^{-1}, above which it remained virtually constant. A flow rate of 1.5 min^{-1} was chosen as the most suitable and was used in all subsequent experiments with this system.

The peak height increased with increasing volumes of sample injected up to 85 μl, but

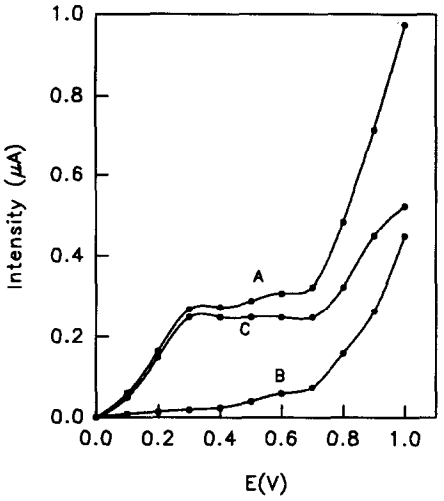

Figure 2
(A) Hydrodynamic voltammogram at a glassy carbon electrode obtained by injecting 85 μl of 5×10^{-6} M Novalgin into 0.2 M ammonia buffer (pH 9); (B) blank hydrodynamic voltammogram; and (C) difference between (A) and (B).

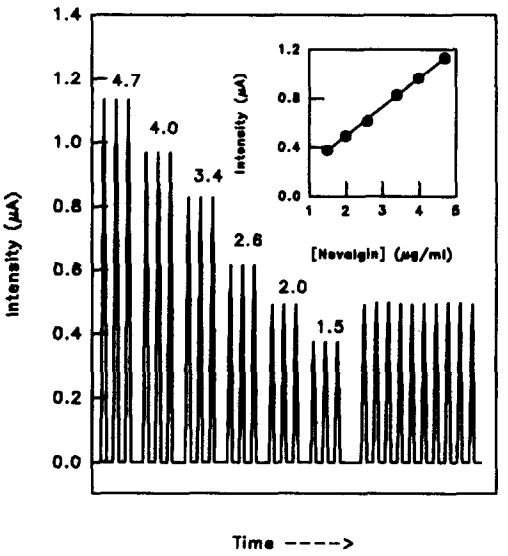

Figure 3
Calibration of the FI system for triplicate injections. The values above the peaks are μg ml^{-1} concentrations of Novalgin.

levelled off at higher volumes. A sample-loop volume of 85 μl was chosen in order to obtain the greatest sampling rate.

The peak height and its repeatability increased when a delay coil of 50 cm (i.d. 0.5 mm) was used. Under these recommended experimental conditions, about 60 samples h^{-1} of Novalgin can be analysed.

Determination of Novalgin

A series of standard solutions of Novalgin was pumped in triplicate to test the linearity of the calibration graph (Fig. 3). A plot of the current intensity vs concentration of Novalgin in the sample injected was linear over the range 1–10 μg ml^{-1} (3×10^{-6}–3×10^{-5} M), in accordance with the following equation:

$$i\,(\text{nA}) = (19.2 \pm 1.7) + (238 \pm 0.5)\,C\,(\mu\text{g ml}^{-1});$$
$$(r = 0.9987,\ n = 11).$$

As was to be expected, owing to the inherent sensitivity of the flow-through amperometric detector, which is a function of the hydrodynamic conditions at the electrode surface [15], a high slope was obtained for the calibration graph.

The precision of the results was estimated by 10 repeated injections of 2.0 and 4.0 μg ml^{-1} Novalgin solutions. The relative standard deviations (RSD) were 0.35 and 0.26%, respectively ($P = 0.05$).

The reproducibility was calculated from the results obtained for the determination of 10 different samples of Novalgin containing 4.0 μg ml^{-1}. The mean peak current found was 981 nA with a range of 1016–945 nA and an RSD of 0.53%.

Interferences

An interference study for the determination of Novalgin in pharmaceutical preparations was performed. Samples containing a fixed concentration of Novalgin (6×10^{-6} M) and various concentrations of foreign substances were injected into the FIA system. A substance was considered not to interfere if the variation in the peak height of the Novalgin was less than ±3% in its presence. The results are shown in Table 1.

The foreign substances tested were other analgesics and excipients generally used in pharmaceutical preparations. Under the reaction conditions followed most of these substances did not interfere.

Analytical applications

The proposed methods were satisfactorily applied to the determination of Novalgin in a number of commercial pharmaceutical preparations. Table 2 summarizes the data obtained. The recovery was determined by adding various amounts of Novalgin to each

Table 1
Tolerance of the proposed procedure to other substances

Substance	Tolerable molar ratio* (foreign substance)/(Novalgin)
Caffeine	100
Lactic acid, acetylsalicylic acid	50
Diazepam	30
Paracetamol	Interference

*Mean of three determinations.

Table 2
Determination of Novalgin in pharmaceutical preparations*

Sample	Source	Nominal value (g)	Fl method found† (g)
Buscapina Compositum	Boehringer Ingelheim	2.50	2.53 ± 0.06
Baralgin	Hoechst	2.50	2.44 ± 0.07
Nolotil Compositum	Europharme	2.00	1.94 ± 0.10
Neomelubrina	Hoechst	2.50	2.45 ± 0.08
Nolotil	Europharme	2.00	1.93 ± 0.07

*Composition of samples. Buscapina Compositum: hyoscine-N-butyl bromide 20 mg, Novalgin 2.50 g, water 5 g. Baralgin: sodium metamizole 2.50 g, pitophenone hydrochloride 10 mg, fenpipramide methobromide 0.1 mg, water 5 g. Nolotil Compositum: magnesium metamizole 2.00 g, hyoscine-N-butyl bromide 0.02 g, water 5 g. Neomelubrina: sodium metamizole 2.50 g, water 5 g.
†Mean of three determinations ± SD.

Table 3
Recovery of Novalgin from pharmaceutical preparation

Sample*	Added ($\mu g\ ml^{-1}$)	Found† ($\mu g\ ml^{-1}$)	Recovery (%)
Buscapina Compositum	1.00	1.03 ± 0.07	103.0
	2.00	1.96 ± 0.08	96.0
Baralgin	1.00	0.99 ± 0.10	99.0
	2.00	1.95 ± 0.09	97.5
Nolotil Compositum	1.00	1.03 ± 0.09	103.0
	2.00	1.97 ± 0.06	98.5
Neomelubrina	1.00	1.00 ± 0.08	100.0
	2.00	2.04 ± 0.07	102.0
Nolotil	1.00	0.97 ± 0.10	97.0
	2.00	2.03 ± 0.08	101.5

*For composition, see Table 2.
†Mean of three determinations ±SD.

pharmaceutical preparation and subtracting the results obtained for pharmaceuticals prepared in a similar manner but to which no Novalgin had been added. The results are presented in Table 3.

In conclusion, the flow-injection method described is rapid and sensitive, and is suitable for the routine determination of Novalgin in pharmaceuticals.

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References

[1] H. Abdine, S.A. Soliman and G.I. Morcos Magoli, *J. Pharm. Sci.* **62**, 1834–1836 (1973).
[2] R. Bontemps, J. Parmentier and M. Duesse, *J. Pharm. Belg.* **23**, 222–232 (1968).
[3] F. Buhl and U. Hachula, *Chem. Anal. Warsaw* **26**, 395–400 (1981).
[4] N.V. Pathak and I.C. Shukla, *J. Indian Chem. Soc.* **60**, 206–207 (1983).
[5] S.Z. Qureshi, A. Saeed and T. Hasan, *Talanta* **36**, 869–871 (1989).
[6] C.S.P. Sastry and A.R. Rao, *Mikrochim. Acta* **1**, 273–274 (1989).
[7] S.Z. Qureshi, A. Saeed and S. Hague, *Microchem. J.* **41**, 362–365 (1990).

[8] M.M. Amer, B.A. El-Zeany, A.M. Taha and O.A. El-Sawy, *Analyst* **107**, 1272–1278 (1982).
[9] N. Kosta, V. Ksenija and M. Mirjana, *Acta Pharm. Jugost.* **34**, 177–182 (1984).
[10] N.H. Eddine, F. Bressolle, B. Mandrou and H. Fabre, *Analyst* **107**, 67–70 (1982).
[11] F. Buhl, U. Hachula and M. Chwistek, *J. Chromatogr.* **219**, 189–191 (1981).
[12] H.L. Ran, A.R. Aroor and P. Gundu Rao, *Indian Drugs* **29**, 94–96, 97–99 (1991).
[13] T. Pérez-Ruiz, C. Martinez-Lozano, V. Tomás and J. Carpena, *Microchem. J.* **47**, 296–301 (1993).
[14] A. Daskashev, L. Ilcheva and P. Dzambazova, *Izv. Khim.* **24**, 118–123 (1991).
[15] S.G. Weber, *J. Electroanal. Chem.* **145**, 1–7 (1983).

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