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 \(3 \times 10^{-6} - 3 \times 10^{-3}\) 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, anti-inflammatory 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

Reagents 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 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.

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 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
DETERMINATION OF NOVALGIN BY A FI METHOD

1.0
0.8
0.6
0.4
0.2
0.0

E(V)

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).

1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0

Time ----->

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 in-
creased 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:

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

As was to be expected, owing to the inherent
sensitivity of the flow-through amperometric
detector, which is a function of the hydro-
dynamic conditions at the electrode surface
[15], a high slope was obtained for the cali-
bration 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 devi-
ations (RSD) were 0.35 and 0.26%, respect-
ively (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 sub-
stance 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 re-
action conditions followed most of these sub-
stances did not interfere.

Analytical applications
The proposed methods were satisfactorily
applied to the determination of Novalgin in a
number of commercial pharmaceutical pre-
parations. 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

<table>
<thead>
<tr>
<th>Substance</th>
<th>Tolerable molar ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine</td>
<td>100</td>
</tr>
<tr>
<td>Lactic acid, acetylsalicylic acid</td>
<td>50</td>
</tr>
<tr>
<td>Diazepam</td>
<td>30</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>Interference</td>
</tr>
</tbody>
</table>

*Mean of three determinations.

Table 2
Determination of Novalgin in pharmaceutical preparations

<table>
<thead>
<tr>
<th>Sample</th>
<th>Source</th>
<th>Nominal value (g)</th>
<th>FL method found† (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buscapina Compositum</td>
<td>Boehringer Ingelheim</td>
<td>2.50</td>
<td>2.53 ± 0.06</td>
</tr>
<tr>
<td>Baralgin</td>
<td>Hoechst</td>
<td>2.50</td>
<td>2.44 ± 0.07</td>
</tr>
<tr>
<td>Nolotil Compositum</td>
<td>Europharme</td>
<td>2.00</td>
<td>1.94 ± 0.10</td>
</tr>
<tr>
<td>Neomelubrina</td>
<td>Hoechst</td>
<td>2.50</td>
<td>2.45 ± 0.08</td>
</tr>
<tr>
<td>Nolotil</td>
<td>Europharme</td>
<td>2.00</td>
<td>1.93 ± 0.07</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Sample*</th>
<th>Added (µg ml⁻¹)</th>
<th>Found† (µg ml⁻¹)</th>
<th>Recovery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buscapina Compositum</td>
<td>1.00</td>
<td>1.03 ± 0.07</td>
<td>103.0</td>
</tr>
<tr>
<td>Baralgin</td>
<td>2.00</td>
<td>1.96 ± 0.08</td>
<td>96.0</td>
</tr>
<tr>
<td>Nolotil Compositum</td>
<td>1.00</td>
<td>0.99 ± 0.10</td>
<td>99.0</td>
</tr>
<tr>
<td>Neomelubrina</td>
<td>2.00</td>
<td>1.95 ± 0.09</td>
<td>97.5</td>
</tr>
<tr>
<td>Nolotil</td>
<td>1.00</td>
<td>1.03 ± 0.09</td>
<td>103.0</td>
</tr>
<tr>
<td></td>
<td>2.00</td>
<td>1.97 ± 0.06</td>
<td>98.5</td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>1.00 ± 0.08</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td>2.00</td>
<td>2.04 ± 0.07</td>
<td>102.0</td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>0.97 ± 0.10</td>
<td>97.0</td>
</tr>
<tr>
<td></td>
<td>2.00</td>
<td>2.03 ± 0.08</td>
<td>101.5</td>
</tr>
</tbody>
</table>

*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

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