Article

A Fast Fluorimetric Flow Injection Method to Determine Ibuprofen

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Abstract

A fast fluorimetric flow injection method is described to determine ibuprofen in pharmaceutical formulations. The fluorescence of ibuprofen is increased upon formation of a host-guest complex with β-cyclodextrin (β-CD). This method was validated by comparing the proposed and the official method in commercial samples.

Keywords: ibuprofen, FIA, spectrofluorimetry, pharmaceutical preparation

Introduction

Ibuprofen (2-(4-isobutyl)-propionic acid) is a non-steroidal anti-inflammatory drug that is available in a variety of preparations. Usually, it is used in treatment of pain and inflammation for rheumatoid arthritis and other musculoskeletal disorders. Several methods have been developed to determine ibuprofen in pharmaceutical preparations such as gas chromatography or high performance liquid chromatography.

Hergert and Escandar have developed a spectrofluorimetric method for the determination of ibuprofen in tablets and syrups. The method is based on the formation of a host-guest complex with β-cyclodextrin (β-CD). The fluorescence of the inclusion complex is improved compared to the free compound.

Quality control in pharmaceutical preparations requires accurate, simple, and economical methods. Moreover, they should be capable to monitor a large number of samples and to detect the analyte over the established range. The automation of the laboratory process allows to attain these objectives. Flow injection analysis (FIA) is an appropriate methodology to automate analytical methods due to its extreme versatility, simplicity and inexpensive lab ware.

In order to contribute to the quality control of pharmaceutical preparations, an automated spectrofluorimetric FIA method to determine ibuprofen in tablets and syrups was developed. The method is based on the formation of a host-guest complex with β-cyclodextrin (β-CD). The measurements were done at λ_em 287 nm (λ_exc 223 nm).

The method was validated by comparing the obtained results with those obtained by official British Pharmacopoeia method.

Experimental

Instrumentation

An Aminco Bowman Serie 2 luminescence spectrophotometer controlled by a computer and equipped with a Hellma 176752 – QS flow cell with an inner volume of 25 μL was used.
All the reaction coils were made of PTFE tubing (i.d. 0.5 mm).

A Gilson Minipuls 3 peristaltic pump and a home made proportional double injection valve were used.

Reagents and solutions

Analytical grade reagent and ultra pure water (18MΩ cm⁻¹) were always used. Ibuprofen (99.9%) was obtained from Marsing & Co (Denmark).

β-CD (Aldrich, Milwaukee, WI, USA) was doubly recrystalized from water and an aqueous 1 × 10⁻³ mol L⁻¹ solution was prepared.

An alkaline stock solution of Ibuprofen was prepared by weighing 0.0375 g and diluting to 25 mL with NH₃ (Merck) 0.05 mol L⁻¹ approximately. Standard solutions were daily prepared by appropriate dilution of the stock solution.

The pharmaceutical samples were Teprix (Gramon), Ibupirac 600 (Sintyal), Ibupirac syrup (Monsanto Argentina SAIC) and Causalon gesic (Phoenix).

Sample preparation

Twenty tablets were weighed to calculate the average tablet weight. They were finely powdered and homogenised. In order to obtain approximately 20 mg of ibuprofen in 25 mL of NH₃ (0.05 mol L⁻¹), a suitable amount of the powder was accurately weighed. To obtain the same concentration of ibuprofen when Ibupirac syrup was prepared, 1 mL of the syrup was diluted to 25 mL with NH₃ (0.05 mol L⁻¹).

Appropriated dilutions of these solutions were made to determine the ibuprofen concentration.

Procedure

The double injection FIA manifold used for the determination of ibuprofen in pharmaceutical preparations is depicted in Figure 1. The same volume (200 µL) of sample and β-CD was simultaneously injected by using a proportional injector, in an ammonium hydroxide solution (0.05 mol L⁻¹) and water streams respectively. Both carriers were flowing at the same flow rate (2.1 mL min⁻¹), and they went across an equal distance from the injection point up to the confluence point, where both streams were mixed in the R reactor (300 mm). The increased fluorescence signal was measured at λₑm=287 nm (λₑx=223 nm).

Results and Discussion

Selection of FIA manifold

Two configurations for FIA system were proved. In the first one, a sample volume of ibuprofen was injected in an ammonium hydroxide carrier solution. Then, this solution merged with a stream of β-CD solution in a reactor, and the inclusion complex was formed.

In the other one, a double injection was used. The same volume of ibuprofen and β-CD was inserted simultaneously in ammonium hydroxide and water carrier solutions respectively.

A best reproducibility and enhance signal intensity were attained with the last configuration (Figure 1).

Influence of chemical and FIA variables

The variables influencing the performance of the method were optimised by the univariant method. By considering the reproducibility of the signal, and the shape and height of the peak, the optimum values were selected.

Different concentrations of the ammonium hydroxide carrier solution were tested between 0.02 and 0.08 mol L⁻¹. When 0.02 mol L⁻¹ concentration was used it was observed the formation of a precipitate into the reactor. At higher concentrations than 0.05 mol L⁻¹, signals were not increased. Thus, 0.05 mol L⁻¹ was used.

The β-CD concentration influence on fluorescent signal was studied. For that purpose concentrations from

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**Figure 1.** FIA manifold; q: flow rates; PP: peristaltic pump; PI: proportional injector; L₁ and L₂: loops, Carrier 1: ammonium hydroxide; Carrier 2: water, R: reactor, D: spectrofluorimeter, W: waste.
0.5×10⁻³ to 2.0×10⁻³ mol L⁻¹ were tested. The best signal was obtained with 1×10⁻³ mol L⁻¹.

The range of the FIA variables studied and their optimum values are listed in Table 1.

### Table 1. Optimization of FIA variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Studied range</th>
<th>Optimum value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactor length (mm)</td>
<td>100 – 600</td>
<td>300</td>
</tr>
<tr>
<td>Sample volume (μL)</td>
<td>100 – 300</td>
<td>200</td>
</tr>
<tr>
<td>Flow rate (mL min⁻¹)</td>
<td>0.8 – 2.5</td>
<td>2.1</td>
</tr>
</tbody>
</table>

**Analytical parameters**

With selecting experimental conditions above described, the calibration curve was linear over the range 6.00 – 60.0 mg L⁻¹ of ibuprofen and the detection limit (LOD) for S/N=3 was 4.5 mg L⁻¹. The calibration line was y = (1.653 ± 0.030) x + (2.294 ± 1.126) (where y is the fluorescence signal and x the concentration of ibuprofen in mg L⁻¹), with a correlation coefficient of 0.9993. The reproducibility was 1.2% (n=11 duplicates of 18 mg L⁻¹) and the sample throughput 240 h⁻¹.

**Applications to real samples**

In order to detect the absence of interference from the matrix, the standard addition calibration method was applied to different real samples. The relative systematic errors can be evaluated by comparing the slopes of the standard addition lines and an aqueous calibration line. If the matrix does not interfere, both lines must have the same slope. Table 2 shows the slopes of calibration lines obtained with the proposed method and with the standard addition method applied to different pharmaceutical samples. The slopes comparison was done by applying the “t” test. As can be seen, the slopes were not significantly different.

In order to validate the proposed method, the samples were also analyzed by using the official British Pharmacopoeia method. Table 3 shows the obtained results by both methods. The proposed method agrees with the standard method, and there are very good recovery values, all in the range recommended by Pharmacopoeias for this kind of analyses.

**Conclusions**

The proposed method is an excellent alternative to determine ibuprofen mainly in routine tasks, due to the highlight feature that is the high sample throughput. Moreover, the good reproducibility, low cost and easy implementation makes it an outstanding method for quality control. It is a simple method and free of interferents, as was showed in the analysis of different medicaments.

The advantages above mentioned and considering that the official method is more complicated, requires a technique more expensive and spent too much time for the analysis, the proposed method could be adapted easily in the pharmaceutical laboratory.

The method was validated by using real samples and the official method.

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### Table 2. Comparison of the slopes

<table>
<thead>
<tr>
<th>Samples</th>
<th>Slopes of standard addition method calibration</th>
<th>t calculated value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1.699 ± 0.038</td>
<td>0.779</td>
</tr>
<tr>
<td>B</td>
<td>1.618 ± 0.060</td>
<td>0.530</td>
</tr>
<tr>
<td>C</td>
<td>1.728 ± 0.042</td>
<td>1.435</td>
</tr>
<tr>
<td>D</td>
<td>1.720 ± 0.039</td>
<td>1.336</td>
</tr>
</tbody>
</table>

Slope of the proposed method: 1.653 ± 0.030, t<sub>tabulated</sub> (4,α=5%)=2.776.

### Table 3. Determination of ibuprofen in pharmaceutical preparations (tablets)

<table>
<thead>
<tr>
<th>Sample</th>
<th>Amount</th>
<th>Labelled</th>
<th>Found</th>
<th>Proposed method</th>
<th>HPLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibupirac 600</td>
<td>600 mg per tablet</td>
<td>611 (5%) (102%)</td>
<td>606 (101%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teprix</td>
<td>400 mg per tablet</td>
<td>416 (8) (104%)</td>
<td>404 (101%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Causalon gesic</td>
<td>250 mg per tablet</td>
<td>249 (4) (99.6%)</td>
<td>251 (100.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibupirac syrup</td>
<td>2 g per 100mL</td>
<td>2.07 (0.01) (103.5%)</td>
<td>2.10 (105%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\*Standard deviations (n=5); \*the recoveries are based on the labelled amount.
References


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