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Article

A Fast Fluorimetric Flow Injection Method to Determine Ibuprofen

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A fluorescência natural da ibuprofeína foi melhorada quando foi formado um complexo convidado-hospedeiro com a beta-ciclodextrina (beta-CD). A partir disso, foi desenvolvido um método por injeção em fluxo para a determinação de ibuprofeína em diferentes preparações farmacêuticas, com detecção fluorescente (λ_{em} 287 nm, λ_{ex} 233 nm). A curva de calibração foi linear no intervalo entre 6,00 a 60,0 mg L^{-1} de ibuprofeína, com limite de detecção (LOD para S/N=3) de 4,5 mg L^{-1}. O desvio padrão relativo foi de 1,2% e a velocidade de determinação de 240 amostras por hora. O método foi validado pela comparação do método proposto, e do usado oficialmente, em amostras comerciais preparadas.

The native fluorescence of ibuprofen was enhanced when a host-guest complex of the analyte with β cyclodextrin (β-CD) was formed. So, based on this fact, a flow injection method to determine ibuprofen in different pharmaceutical preparations with fluorescence detection (λ_{em} 287 nm, λ_{exc} 223 nm) was developed. 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 relative standard deviation was 1.2% and the sample throughput 240 h^{-1}. The method was validated by comparing the proposed and the official method to commercial preparation 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.[1] Several methods have been developed to determine ibuprofen in pharmaceutical formulations and biological fluids specially by using gas liquid or high performance liquid chromatography.[2-9]

Hergert and Escandar[10] have developed a spectrofluorimetric method for the determination of ibuprofen. This method is based on the host-guest complexation of the analyte with β ciclodextryn (β-CD). It was possible to improve the analytical parameters of the method because the fluorescent properties of the inclusion complex were better than those of the free compound.

Quality control in pharmaceutical preparations requires analytical methods for routine that should be accurate, simple, and economical in time and cost. 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.[11,12]

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. It was based on the inclusion complex formation studied by Hergert and Escandar[10] and 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.[13]

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.

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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[14] 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 recristalized 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 NH_3 (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 NH_3 (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 NH_3 (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 λ_{em}=287 nm (λ_{exc}=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

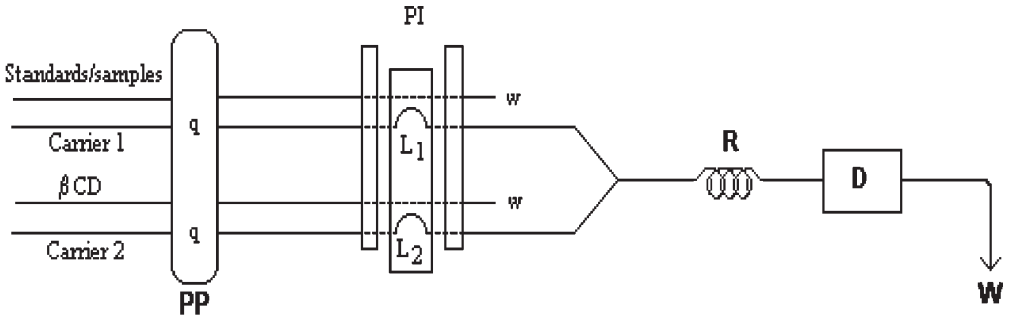

Figure 1. FIA manifold; q: flow rates; PP: peristaltic pump; PI: proportional injector; L_1 and L_2: loops, Carrier 1: ammonium hydroxide; Carrier 2: water, R: reactor, D: spectrofluorimeter, W: waste.

0.5×10^{-3} to 2.0×10^{-3} mol L^{-1} were tested. The best signal was obtained with $1x10^{-3}$ 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

Variable	Studied range	Optimum value
Reactor length / (mm)	100 – 600	300
Sample volume / (μL)	100 – 300	200
Flow rate / (mL min^{-1})	0.8 – 2.5	2.1

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.[15]

Table 2. Comparison of the slopes

Samples	Slopes of standard addition method calibration	t calculated value
A	1.699 ± 0.038	0.779
B	1.618 ± 0.060	0.530
C	1.728 ± 0.042	1.435
D	1.720 ± 0.039	1.336

Slope of the proposed method: 1.653 ± 0.030, $t_{tabulated\ (4,a=5\%)}$=2.776.

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.[13] 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.[13]

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

Sample	Amount		
	Labelled	Found	
		Proposed method	HPLC
Ibupirac 600	600 mg *per* tablet	611 (5)[a] (102%)[b]	606 (101%)
Teprix	400 mg *per* tablet	416 (8) (104%)	404 (101%)
Causalon gesic	250 mg *per* tablet	249 (4) (99.6%)	251 (100.4%)
Ibupirac syrup	2 g *per* 100mL	2.07 (0.01) (103.5%)	2.10 (105%)

[a]Standard deviations (n=5); [b]the recoveries are based on the labelled amount.

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