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QUANTITATION OF FLURBIPROFEN IN TABLETS USING HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

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ABSTRACT

A stability-indicating high-performance liquid chromatography method for the quantitation of flurbiprofen in tablets was developed. The method is accurate and precise with a percent relative standard deviation of 0.7 based on 8 readings. A number of inactive ingredients present in the tablets did not interfere with the assay procedure. The extraction procedure from the tablets is very simple. The recovery from the synthetic mixtures was quantitative. The drug appears to be very sensitive to strong acids and bases since a 5 minute boiling caused the degradation of drug (100 %) in both the solutions.

BACKGROUND

Flurbiprofen (Figure 1) is a new nonsteroidal anti-inflammatory agent which is available only in the form of tablets (50 and 100 mg). Since the tablets are not official in the USP-NF, no official method for the quantitative analysis is available. When the authors were ready to send this paper for publication, a method was published to quantify flurbiprofen in tablets based on HPLC. The recommended procedure for

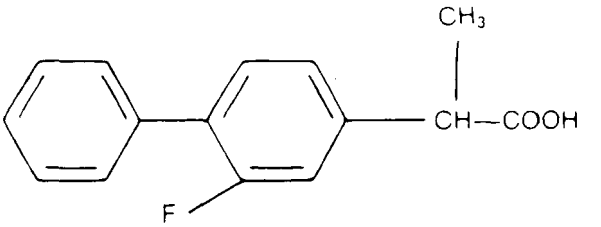

Figure 1 - Structure of Flurbiprofen.

the extraction of drug from the tablets is tedious and cumbersome (requires 30 minutes shaking and subsequent centrifugation). The purpose of these investigations was to develop a stability-indicating high performance liquid chromatography method for the quantitative determination of flurbiprofen using a very simple method for the extraction of drug from the tablets.

MATERIALS AND METHODS

Chemical Reagents: All the chemicals and reagents were USP-NF or ACS quality and were used without further purification. Ibuprofen and flurbiprofen were supplied by The Upjohn Co. and used as received.

Apparatus: A high-pressure liquid chromatograph (Waters ALC 202) equipped with a universal injector (Rheodyne Model 7125), a multiple wavelength detector (Schoeffel's SF 770, Kratos, Inc.) and a recorder (Omniscribe 5213-12, Houston Instruments, Austin) was used. A micro C_{18} column (Waters Associates, 30 cm x 3.9 mm i.d.) was the stationary phase.

Chromatographic Conditions: The mobile phase contained acetonitrile 48% (v/v) in 0.01M KH_2PO_4 aqueous buffer. The flow rate was 2.2 ml/min., the wavelength was 234 nm (sensitivity 0.1 AUFS), the chart speed was 30.5 cm/hr and the temperature was ambient.

Preparation of Stock and Standard Solutions: A stock solution of flurbiprofen was prepared fresh every day by dissolving 50.0 mg of the powder in enough methanol to make 100.0 ml of the solution. A stock solution of ibuprofen (the internal standard) was prepared by dissolving 400.0 mg of the powder in enough methanol to make 100.0 ml of the solution. A most commonly standard solution was prepared by mixing 1.8 ml of the stock solution of drug with 2.0 ml of the stock solution of the internal standard, and bringing to volume (25.0 ml) with a diluting mixture (40 % v/v of methanol in 0.02M KH_2PO_4 aqueous buffer). The solutions of other concentrations were prepared as needed.

Extraction from Tablets: Five tablets (each containing 50 or 100 mg of the drug) was mixed with 40 ml methanol, stirred occasionally for 5 minutes, then brought to volume (50.0 ml) with methanol. The mixture was filtered (Fisher's 9-803-SE filter paper), the first 10 ml of filtrate was rejected, and then collected for analysis. A 1.8 ml quantity of the clear filtrate was mixed with 2.0 ml of the stock solution of ibuprofen and brought to volume (25.0 ml) with a diluting mixture (see above).

Decomposition of Flurbiprofen: A 3.6 ml of the stock solution of flurbiprofen was mixed with 10 ml of methanol and either ~ 1 ml of ~ 1N H_2SO_4 or NaOH in a 150 ml beaker. The mixture was heated to boiling (~ 5 minutes), cooled and brought to volume (50.0 ml) with the diluting mixture (see above). The mixtures were injected without the addition of an internal standard in order to detect new peaks (if any) in the chromatogram. Also, the pH values of the solutions were adjusted to weakly acidic and then the solutions were rechromatogramed.

Assay Procedure: A 20 μl quantity of the assay solution was injected into the chromatograph using the conditions described. For comparison,

TABLE 1

ASSAY RESULTS

Name of the Sample	Percent of the Label Claim Found	Other Ingredients if any
Tablets 100 mg	98.3	100 mg tablets contained: carnauba wax, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, titanium dioxide and FD&C No. 2 dye.
Tablets 100 mg (different lot)	104.2	
Tablets 50 mg	98.8	Same as above except no dye was present.
Synthetic Mixture 1	101.3	Glucose
Synthetic Mixture 2	100.7	Lactose

an identical volume of the standard solution was injected after the sample eluted. The standard solution contained identical concentrations of the drug (based on the label claim) and the internal standard.

Calculations: Preliminary investigations indicated that the ratio of peak heights were related to the concentrations of the drug. The results were calculated using a simple equation:

$$\frac{(Rph)_a}{(Rph)_s} \times 100 = \text{percent of the label claim found,}$$

where $(Rph)_a$ is the ratio of the peak heights of drug to internal standard in the assay solution and $(Rph)_s$ that of the standard solution.

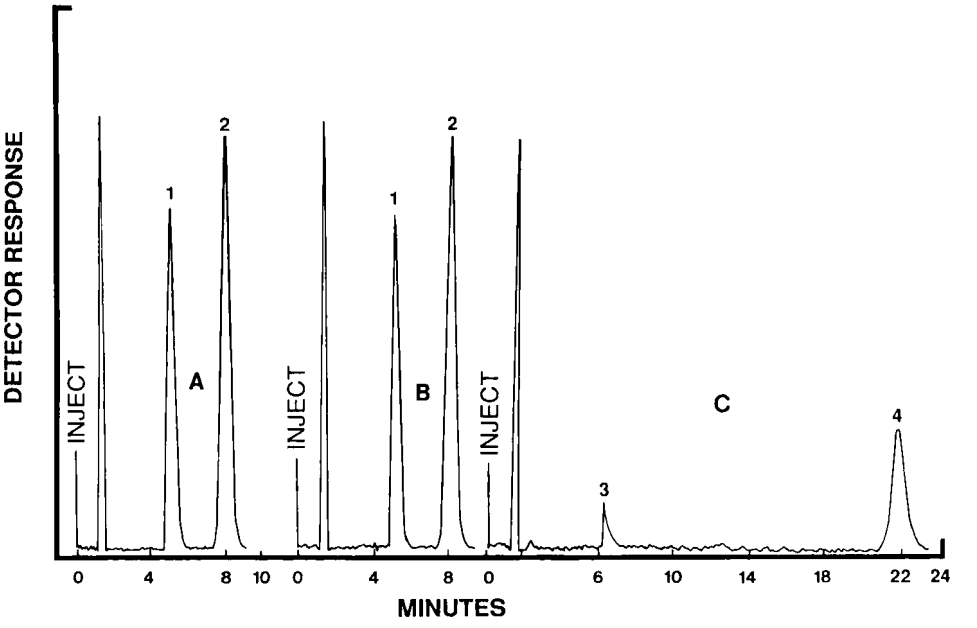

Figure 2 - Sample Chromatograms.

Peaks 1-4 are from flurbiprofen, ibuprofen and the products of decomposition (3 and 4), respectively. Chromatogram A is from a standard solution; B from 100 mg tablets (#1 in table 1) and C from a solution decomposed using sulfuric acid. For Chromatographic Conditions, see text.

RESULTS AND DISCUSSION

The results (Table 1) indicate that the developed method can be used to quantify flurbiprofen in the tablets. The method is accurate and precise with percent relative standard deviation of 0.7 based on 8 readings. Although the ratio of peak heights were related to the drug concentrations (range tested 20-44 μg/ml of flurbiprofen), the line did not pass through the origin. The authors do not understand this. The correlation factor, r was 0.997. The recovery from the synthetic

mixtures was quantitative (Table 1) and there was no interference (Figure 2) from the excipients present in tablets such as carnauba wax, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, titanium dioxide and FD&C blue No. 2 dye. The procedure for the extraction of drug from the tablets is very simple as compared with the method (1) published recently. Also, the developed method requires only 0.036 mg/ml of drug in the sample to be injected versus 0.1 mg/ml recommended in the recently published method (1). There were two new products (Figure 2C) from the solution decomposed by using acid. The first peak (peak 3, Figure 2C) will elute out between the drug and the internal standard (Figure 2A). The second peak (peak 4, Figure 2C) did not interfere in the assay procedure. On changing the pH of this solution to weakly acidic (approximately same pH as the standard solution), there was no change in retention time. On the other hand, a solution decomposed using sodium hydroxide showed only one product of decomposition whose retention time was 4 minutes versus 5 for flurbiprofen. On changing the pH of this solution to weakly acidic, the retention time of this peak was same as that of peak 3 in Figure 2C. This indicated that in the basic solution, the product of decomposition is probably a weak acid. In both the solutions, no flurbiprofen was left intact.

The wavelength of maximum absorption for flurbiprofen was 247 nm. The wavelength of 234 nm was used to increase the absorption of ibuprofen (the internal standard) in the assay procedure.

REFERENCE

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