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HIGH-PERFORMANCE LIQUID CHROMATOGRAPHIC DETERMINATION OF IBUPROFEN IN BULK DRUG AND TABLETS

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ABSTRACT

A simple and rapid HPLC procedure is described for the assay of ibuprofen in bulk drug and tablets and for dosage uniformity testing. HPLC was carried out on a stainless steel octadecylsilane (5 um) column (150 X 4.6 mm) using 25% 0.25M glacial acetic acid in acetonitrile as the mobile phase, with UV detection at 254 nm. Results obtained with this procedure compared favorably with those obtained using the USP procedures.

INTRODUCTION

Ibuprofen [(±)-2-(p-isobutylphenyl)propionic acid] is a non-steriodal drug possessing anti-inflammatory, analgesic and anti-pyretic activities. It has been indicated for the symptomatic treatment of rheumatoid arthritis and osteoarthritis (1,2,3).

The USP XX monograph (4) describes a GC method for the analysis of ibuprofen in bulk drug and tablets. These procedures in-

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volve an extraction of the drug substance into chloroform and the subsequent derivatization of ibuprofen. While this GC assay utilizes silylation as the derivatization procedure, the purity test by GC for ibuprofen bulk drug employs a methylation procedure which requires the synthesis and use of a highly toxic and potentially hazardous compound (diazomethane). Several other analytical methods including HPLC procedures have been developed. However, most are for the detection of ibuprofen levels in biological fluids (5,6,7). Recently, a microbore HPLC procedure was published for pharmaceutical compounds including ibuprofen, but no detailed analytical data were presented (8).

This report describes an HPLC procedure for the assay of ibuprofen bulk drug and ibuprofen tablets. This method is simple, accurate, and rapid, and compares favorably with the USP method.

EXPERIMENTAL

Materials - The ibuprofen reference standard was obtained from the U.S. Pharmacopeial Convention. Ibuprofen bulk drug and tablets were provided by the manufacturers. All chemicals were either reagent or spectrophotometric grade and used without further purification. Membrane filters[1] were used for filtration of the HPLC mobile phase and sample solutions.

High-Performance Liquid Chromatography - The liquid chromatographic system consisted of the following components: pump[2], injector valve with 20-uL sample loop[3], fixed wavelength UV detector (254 nm)[4], and integrator.[5] A stainless steel column, 150 X 4.6 mm packed with 5-um octadecylsilane[6] was used. Acetonitrile-0.25 M acetic acid (75:25 v/v) was used as the mobile phase and was filtered and deaerated prior to use. Flow rate was 1.2 mL/min at room temperature.

Standard Solution Preparation - 5 mg of p-phenylphenol, the internal standard, was dissolved in 100 mL of mobile phase.

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Approx. 5 mg ibuprofen standard, accurately weighed, was transferred to a 10 mL volumetric flask. 1.0 mL internal standard solution was added. Mobile phase was added to volume and the solution was mixed and filtered.

Sample Preparation - Bulk drug: a solution containing the bulk drug ibuprofen was prepared according to the procedure as described above for the standard solution. Tablets: twenty tablets were placed in a 1-liter volumetric flask containing 100 mL of 0.25 M acetic acid. Upon complete disintegration, 300 mL acetonitrile were added. Mobile phase was added to volume and mixed. 10 mL of the solution was filtered, discarding the first 2 mL of filtrate. An aliquot of the filtrate was diluted with mobile phase to obtain a solution containing approximately 5 mg/mL of ibuprofen. 1.0 mL of this solution was transferred into a 10-mL volumetric flask containing 1.0 mL of the internal standard solution and diluted to volume with mobile phase.

Single-Tablet Assay for Dosage Uniformity - One tablet was placed in a 250-mL volumetric flask containing 50 mL 0.25 M acetic acid. The flask was shaken gently until the tablet had disintegrated. 150 mL acetonitrile was added, followed by the addition of mobile phase to volume. 10 mL of the mixture was filtered, discarding the first 2 mL of the filtrate. An aliquot equivalent to about 5 mg of ibuprofen was transferred into a 10-mL volumetric flask containing 1.0 mL internal standard, and diluted to volume with mobile phase.

Chromatographic Purity - A test solution containing 500 ug of bulk drug substance per ml of mobile phase was prepared. This solution and a mobile phase blank were chromatographed using increased detector sensitivity to ensure the detection of any peaks. The ratio of the sum of impurity peak areas was determined for all peaks excluding any from the blank relative to the peak area of ibuprofen.

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Assay Procedure - Five replicate injections of the standard solution were made. The response ratio of the ibuprofen and p-phenylphenol peak areas was determined. When the reproducibility was such that the relative standard deviation of the five response ratios was not greater than 2%, duplicate injections of the sample solution were made. The average peak area ratio of ibuprofen relative to p-phenylphenol was determined.

Calculation - The quantity of ibuprofen (mg) in the portion of bulk drug taken was

$$(R_u/R_s) \times W_s$$

where R_u and R_s were the peak area ratios obtained from the sample and the standard solution, respectively, and W_s was the weight (mg) of ibuprofen taken.

The quantity of ibuprofen (mg) per tablet was

$$C(R_u/R_s) \times VD/N$$

where C was the concentration of the standard solution (mg per mL), V was the volume (mL) of the tablet sample solution, D was the sample dilution factor, and N was the number of tablets taken.

RESULTS AND DISCUSSION

While the official assay of ibuprofen drug substance is adequate, the tablet assay procedure is tedious and time consuming. The method involves a lengthy shake-out technique by separatory funnel followed by derivatization for GC analysis. This process is especially inefficient for large numbers of tablets as required by the current compendial dosage uniformity test. The official chromatographic purity test requires preparation of diazomethane by distillation. This procedure presents a risk of explosion and a potential health hazard. With the described HPLC procedure, the

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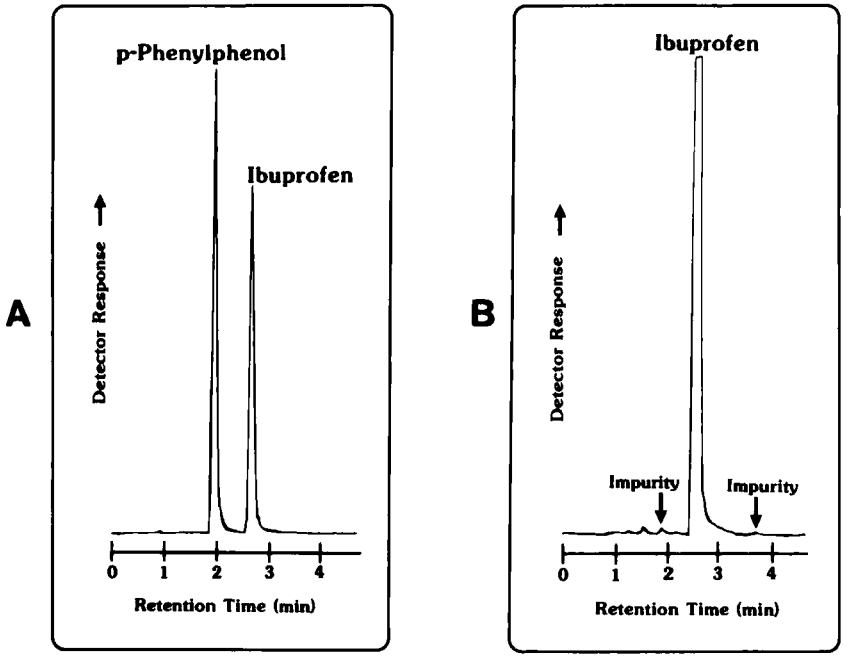

FIGURE 1

(A) sample chromatogram of ibuprofen and p-phenylphenol, the internal standard. (B) chromatogram of HPLC impurities. See text for chromatographic conditions.

simplified sample preparation avoids laborious extraction and derivatization and eliminates the need for the hazardous diazomethane.

In this procedure, the mobile phase used was acidified with acetic acid to pH 3.7 to suppress the ionization of ibuprofen and reduce peak tailing. As shown in Fig. 1A, ibuprofen and the internal standard were well resolved. The retention times were approximately 2.5 min and 1.9 min, respectively. The resolution (R) and tailing factor (T), calculated according to USP XX, were 3.3 and 1.2 respectively. The peak area ratio response was shown

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TABLE 1

Analysis of Ibuprofen Bulk Drug and Tablet Composites

Mfr.	Bulk Drug Found, (%)		Composited Tablets		
			Labeled, (mg/tab)	Found, (% Lbld.)	
	HPLC	USP[a]		HPLC	USP[b]
A	100.0	103.3	300	102.0	100.2
			400	101.4	98.3
			600	102.9	101.7
B	100.6	101.8	400	99.5	100.3

[a] USP XX limits are between 97.0-103.0%

[b] USP XX limits are between 90.0-110.0%

to be linear throughout the ibuprofen concentration range of 62.8 ug/mL to 2.01 mg/mL with a correlation coefficient of 0.999. Precision was demonstrated by a relative standard deviation of 0.5% for 14 replicate standard injections. No significant interference from impurities was detected under the chromatographic conditions described.

Samples of two bulk drug substances and four commercial tablet formulations were assayed by both the current USP GC method and the proposed HPLC procedure. Good agreement between the two methods was obtained. An average of 100.3% of the bulk drug and 101.5% of the declared potency in tablets were found by HPLC procedure as compared to 102.6% and 100.1%, respectively, obtained by the USP method. The assay data are presented in Table 1. For the chromatographic purity test the impurites found in the two bulk drug samples, as measured in ibuprofen equivalents, were 0.3% and 1.2% as compared to 1.1% found in the standard. The GC results of all three samples showed 0.3% to 0.4% impurities which was calculated using the total of all peak areas (Fig. 1B).

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TABLE 2
Single-Tablet Analysis for Dosage Uniformity

Mfr	Lbld (mg/tab)	Mean[a] (% of Label Claim)		RSD (%)	
		HPLC	USP XX[b]	HPLC	USP XX[c]
A	300	99.0	102.6	1.3	1.9
	400	99.2	97.2	1.2	2.3
B	600	101.6	102.0	1.2	1.0
	400	99.6	104.3	0.6	2.8

[a] Mean of ten single-tablet assays.
[b] USP XX limits are 85–115%.
[c] USP XX limit is 6.0%.

TABLE 3
Recovery of Ibuprofen in Synthetic Mixtures

Synthetic Mixture	Ibuprofen (mg)		Recovery (%)
	added	recovered	
1	306.7	309.8	101.0
2	297.6	301.5	101.3
3	399.5	401.0	100.4
4	401.5	402.4	100.2
5	596.6	597.4	100.1
6	595.2	595.4	100.0
	Average		100.5
	SD		0.53
	%RSD		0.5

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The HPLC technique greatly simplifies the dosage uniformiity test. Assays by both methods were performed on ten single tablets of each of the four formulations. The HPLC analyses showed that the average percentage of declared potency ranged from 99% to 102% with a relative standard deviation (RSD) of approximately 1%, compared to a range of 97% to 104% with a RSD of 1 to 3% found by the GC method. The accuracy of the assay represented by these results is illustrated in Table 2. In addition, six synthetic mixtures containing tablet excipients and ibuprofen in amounts similar to the tablet formulations[7] were prepared. Each mixture was carried through the described HPLC procedure. The average recovery was 100.5% (Table 3). In conclusion, the described HPLC procedure is an effective and practical alternative to the official GC method for routine analysis of ibuprofen bulk drug and tablets.

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FOOTNOTES

[1]0.45 um Regenerated Cellulose; Micro Filtration Systems, Dublin, CA

[2]Model 100; Altex Scientific, Berkeley, CA

[3]Model 7125; Rheodyne, Berkeley, CA

[4]Model SP 8200; Spectra-Physics, Santa Clara, CA

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[5]Model 5660; Hewlett-Packard, Avondale, PA

[6]Ultrasphere ODS, 5 um; Altex Scientific, Berkeley, CA

[7]The identities of tablet excipients are not revealed to protect manufacturer confidentiality.

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