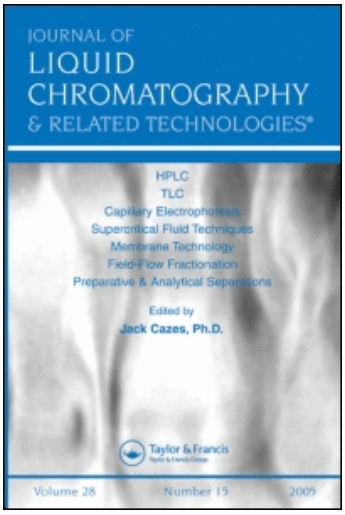

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Quantitation of Terbutaline Sulfate in Pharmaceutical Dosage Forms Using High Performance Liquid Chromatography

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QUANTITATION OF TERBUTALINE SULFATE IN PHARMACEUTICAL DOSAGE FORMS USING HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

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ABSTRACT

A stability-indicating reverse phase high-performance liquid chromatography method has been developed to quantify terbutaline sulfate in pharmaceutical dosage forms. The method is accurate and precise with percent relative standard deviations based on 6 readings of 0.6 with an internal standard (salicylic acid) and 0.8 without an internal standard. The results are in excellent agreement with the USP-NF method. A decomposed sample gave 49.4% results with the developed method versus 71.3% with the USP-NF method.

INTRODUCTION

Terbutaline sulfate (Figure 1) is extensively used against bronchial asthma. It is commercially supplied as tablets, bronchodilator aerosol for oral inhalation and injectable.

The USP-NF method (1) for analysis of terbutaline in tablets and injections is based on a colorimetric reaction with 4-aminoanti-

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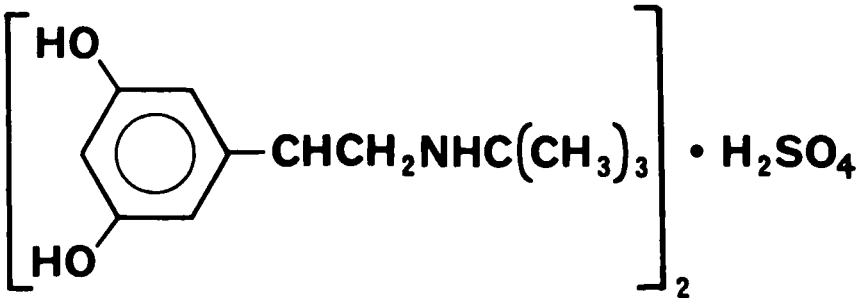

Figure 1 - Structure of terbutaline sulfate.

pyrine. Aerosol is not an official dosage form. An ion-paired high-performance liquid chromatography method (2) for the analysis of terbutaline using a spectrofluorometer as the detector has been recommended.

The purpose of these investigations was to develop a stability-indicating assay method based on reverse phase high-performance liquid chromatography (without ion-pairing) using a UV detector which is available in most of the laboratories.

MATERIALS AND METHODS

Chemicals and Reagents - All the chemicals and reagents were either USP-NF or ACS grade and used without further purification. The terbutaline sulfate (3) and salicylic acid (4) powders were used as received. All the dosage forms analyzed were from commercial lots.

Apparatus - A high-performance liquid chromatograph (5) attached to a multiple wavelength detector (6) and a recorder (7) was used. All pH values were determined using a pHmeter (8).

Columns - A microphenyl column (9), 30 cm long x 3.9 mm i.d. was used.

Chromatographic Conditions - The mobile phase contained 8% (V/V) of methanol in 0.02M KH_2PO_4 in water. The pH was adjusted to ∿3.6 with 1.7% aqueous solution of phosphoric acid. The flow rate was 2.0 ml/min. The detector was set at 278 nm (330 nm for detecting the colored products of oxidation), the sensitivity was 0.04 AUFS, the chart speed 30.5 cm/hr, and the temperature was ambient.

Stock Solutions - A 0.1% solution of salicylic acid (the internal standard) in methanol was prepared fresh every 2 weeks. A 0.1% solution of terbutaline sulfate in water was prepared fresh daily.

Standard Solutions - The standard solutions with or without the internal standard were prepared as needed by diluting the stock solution(s) with water. The most commonly used concentrations were 200 µg/ml of terbutaline sulfate and 50 µg/ml of salicylic acid.

Assay Solutions - Bronchodilator aerosol. Using the manufacturer's directions, ten metered doses (each one contained 0.2 mg of terbutaline sulfate) were collected in a 250 ml Erlenmyer flask. The internal standard (0.5 ml of the stock solution of salicylic acid) was added and the mixture brought to volume (10.0 ml) with water using a volumetric flask.

Injection - A 10.0 ml quantity of the injection (1 mg/ml) was mixed with 2.5 ml quantity of the stock solution of salicylic acid and the mixture brought to volume (50.0 ml) with water.

Tablets - Ten tablets were ground to a fine powder. A quantity of the powder representing 10.0 mg of the powder was mixed with 0.4 ml

of ~1N H_2SO_4 in a pestle mortar. The mixture was mixed thoroughly, 35 ml of water and 2.5 ml of the stock solution of salicylic acid was added. After thorough mixing, more water was added to volume (50.0 ml) and the mixture was filtered (10). First 10 ml of the filtrate was rejected and then collected for analysis. For content uniformity of 5 and 2.5 mg tablets, the quantity of ~1N H_2SO_4 was 0.2 and 0.1 ml, respectively. The internal standard was not added. The mixture was brought to volume (25.0 ml for 5 mg tablets and 12.5 ml for 2.5 mg tablets).

Assay Procedure - A 20.0 µl aliquot of the assay solution was injected into the chromatograph using the described conditions. For comparison, an identical volume of the standard solution containing 200 µg/ml of terbutaline sulfate and 50 µg/ml of the salicylic acid (where needed) was injected after the assay solution eluted.

Calculations - The results were calculated using:

$$\frac{Pha}{Phs} \times 100 = \text{Percent of the label claim found}$$

where Pha is the peak height or peak heights ratio (drug/internal standard) of the assay solution and Phs that of the standard solution. Preliminary investigations indicated that the concentrations of terbutaline sulfate versus peak heights or ratio of the peak heights were linear between 2-7 µg or 100-350 µg/ml of the drug.

Other Experiments - Solution in dextrose 5% injection. A 200.0 µg/ml solution of terbutaline sulfate in dextrose 5% injection (11) was prepared and assayed initially and after 24 and 96 hours of storage at 25° (± 1°).

Decomposition of Terbutaline Sulfate - To a 25 ml portion of the standard solution (200.0 µg/ml without an internal standard) a sodium hydroxide pellet (∿200 mg) was added. The mixture was heated on a hot plate (in a 100 ml glass beaker) until the volume remaining was approximately 5 ml. The decomposed solution was cooled, 2 ml of ∿1N H_2SO_4 added to acidify the solution, and then enough water was added to bring it to volume (25.0 ml). The solution was assayed using the described conditions and was also chromatogramed at wavelength of 330 nm. For purpose of comparison, all the solutions (except for content uniformity) were assayed using USP-NF (1) method.

RESULTS AND DISCUSSION

The results (Table 1) indicate that terbutaline sulfate can be quantified in dosage forms using the developed HPLC method. The method is precise and accurate with a percent relative standard deviations based on 6 readings of 0.6 (with an internal standard) and 0.8 (without an internal standard). The chromatograms from the standard solution and all the dosage forms were similar (Figure 2). The results are in excellent agreement (Table 1) with USP-NF method (1) which is based on a colorimetric reaction. This indicated that various excipients present in the dosage forms did not interfere with the assay procedure. Also, the simple procedure developed for the extraction of terbutaline sulfate from tablets appears to be quantitative.

When assaying the aerosol, the author also tried to collect the metered doses in a 150 ml beaker instead of 250 ml Erlenmyer flask. The results were lower by approximately 4%. Apparently, some of the spray was lost to the outside atmosphere, which was expected.

TABLE 1
Assay Results

Name of the Dosage Form/Synthetic Mixture	HCl (Terbutaline Sulfate)	Other Ingredients if any	Percent of the Label Claim Found Using HPLC	USP-NF Method
Aerosol	0.2 mg per metered dose	Excipients	102.4	102.0
Injection	1.0 mg/ml	None	100.5	100.2
Injection	1.0 mg/ml	None	100.2	100.2
Tablets	2.5 mg	Excipients	99.5	99.8
Tablets	5.0 mg	Excipients	99.2	99.2
Solution in 5% Dextrose Injection	0.02%	Dextrose	98.8[a]	98.8[a]
Synthetic Mixtures				
#1	10.0 mg per 200 mg	Dextrose	100.2	100.0
#2	20.0 mg per 200 mg	Dextrose	100.0	100.0
#3	40.0 mg per 200 mg	Dextrose	101.2	101.4
Decomposed Solution	0.02%	Products of Decomposition	49.4	71.3

[a]Initial results. Results after 24 and 96 hours of storage at room temperature were similar.

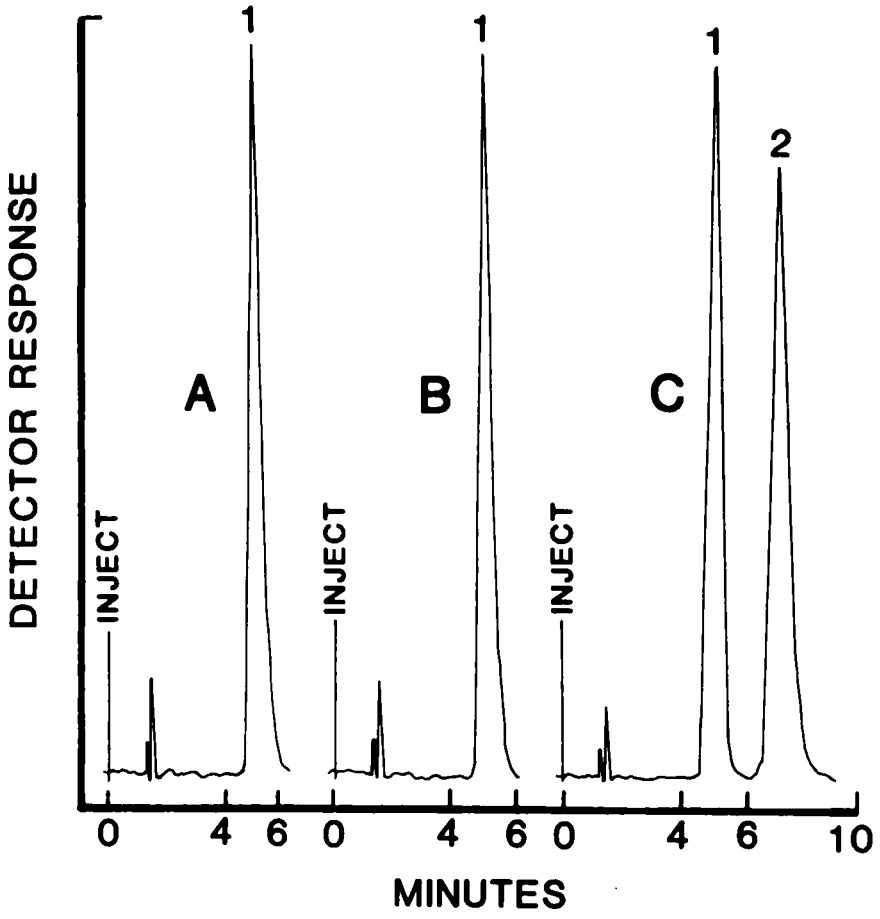

Figure 2 - Sample chromatograms. Peaks 1-2 are from terbutaline and salicylic acid (the internal standard), respectively. Chromatogram A is from a standard solution; B from 5 mg tablets and C from an injection with the internal standard. For chromatographic conditions, see text.

TABLE 2
Content Uniformity Results Using HPLC METHOD

Tablet No.	RESULTS - Percent of the Label Claim Found 5.0 mg Tablets	2.5 mg Tablets
1	97.6	102.9
2	99.2	100.0
3	97.8	99.0
4	101.7	100.0
5	99.8	97.2
6	103.0	97.7
7	102.2	98.4
8	99.4	99.0
9	96.7	103.5
10	101.1	97.2

The method can also be used to determine the content uniformity of the tablets (Table 2). The method appears to be stability-indicating since a number of new peaks from the decomposition products were present (Figure 3A) in the chromatogram. The USP-NF (1) does not appear to be stability-indicating since the results of the decomposed sample were higher (71.3%) versus 49.4% by the developed method. Furthermore, the chromatogram at 330 nm (Figure 3B) did not show any peak from the decomposition products with the same retention time as that of terbutaline sulfate. This wavelength has been recommended in the USP-NF monograph (1) to detect one of the oxidation products.

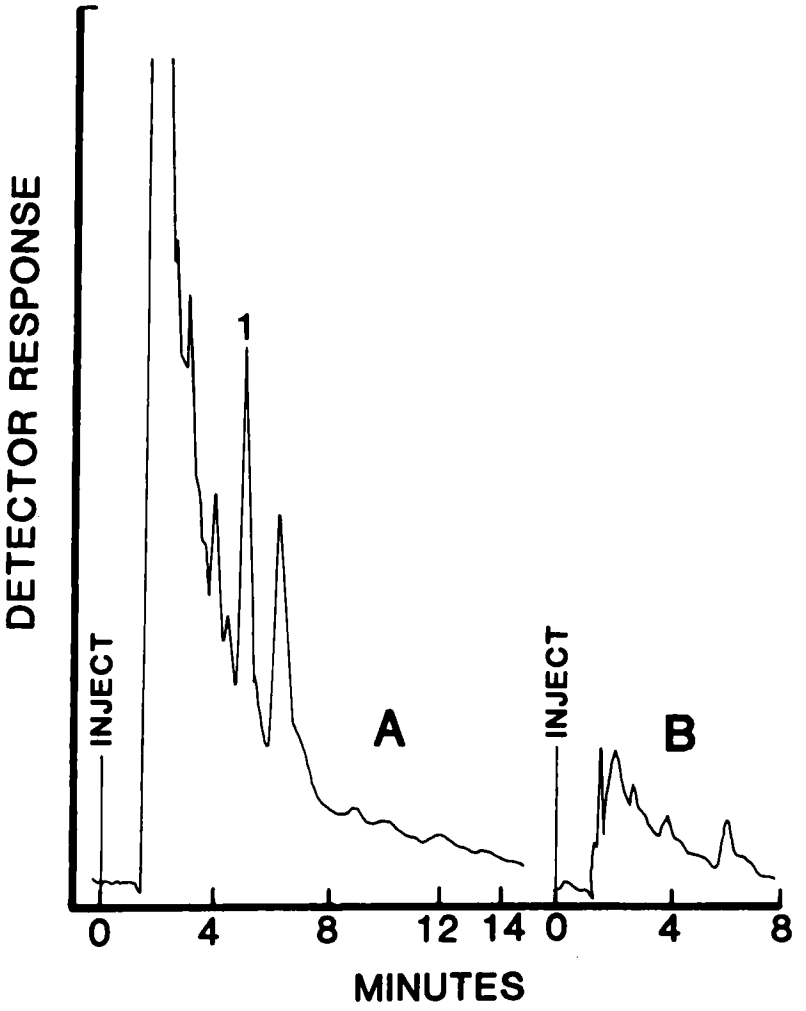

Figure 3 - Sample chromatograms. Peak 1 is from terbutaline sulfate and all others from the decomposition products. Chromatogram A is from a decomposed solution (see text) at 278 nm and B from the same solution at 330 nm. No internal standard was added. For other chromatographic conditions, see text.

The developed method did not require the use of a spectrofluorometric detector which is not very common in the laboratories. Furthermore, no ion-pairing was necessary as recommended in the literature (2). Ion-pairing usually shortens the life of the column and the cells of the UV detector.

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