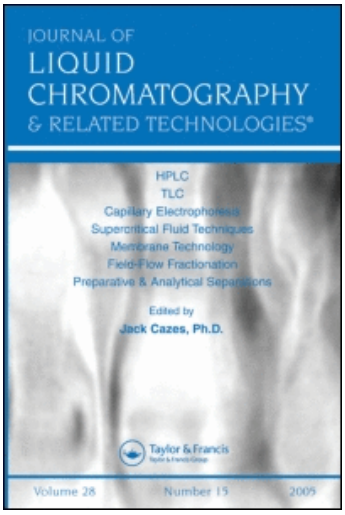

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Quantitation of Baclofen in Tablets Using High-Performance Liquid Chromatography

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QUANTITATION OF BACLOFEN IN TABLETS USING HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY

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ABSTRACT

A reverse phase high-performance liquid chromatography method has been developed to quantify baclofen in tablets. The method is accurate and precise with a percent relative standard deviation of 0.52 based on 5 readings. The recovery from the synthetic mixtures was quantitative. The results were in excellent agreement with the USP-NF colorimetric method. The method can be used to test the content uniformity of the tablets. Samples which were treated with either sulfuric acid or sodium hydroxide and boiled for 10 minutes did not show new peaks in the chromatogram. Baclofen appears to be a very stable compound.

INTRODUCTION

Baclofen (Figure 1) is used to alleviate the signs and symptoms of spasticity resulting from multiple sclerosis and muscular rigidity, etc. It is a relatively new drug and is official only in the USP-NF 1985, first supplement. Recently, FDA has approved its use on trial basis for treating spinal cord injuries. A local

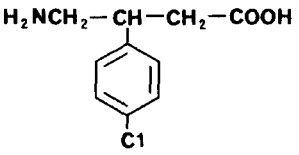

Figure 1 - Structure of baclofen.

hospital is in the process of compounding an injectable liquid dosage form for this purpose. The USP-NF method (1) for the quantitation of baclofen in tablets requires a tedious extraction procedure and subsequent time consuming colorimetric method. The purpose of these investigations was to develop a high-performance liquid chromatography method for the quantitation of baclofen in tablets, the only dosage form available commercially. No such method has been reported in the literature.

MATERIALS AND METHODS

Chemicals and Reagents - All the chemical and reagents were either USP-NF or ACS grade and used without further purification. The baclofen powder was used as received from Geigy Pharmaceuticals. The tablets were of commercial lots.

Apparatus - A high-performance liquid chromatograph (2) attached to a multiple wavelength detector (3) and a recorder (4) was used.

Column - A microbondapak C_{18} column (5), 30 cm long x 3.9 mm i.d. was used.

Chromatographic Conditions - The mobile phase contained 0.02M KH_2PO_4, 12% V/V methanol and 2% V/V acetonitrile in water. The flow rate was 2.0 ml/min, the detector was set 266 nm and the sensitivity was 0.04

(0.02 for content uniformity test). The chart speed was 30.5 cm/hr and the temperature was ambient.

Stock Solution - A 0.5 mg/ml solution of sulfamerazine (the internal standard) in methanol was prepared using a simple solution method.

Standard Solution - A 120.0 mg quantity of the baclofen powder was mixed with 2 ml of dilute sulfuric acid and 2 ml of water. After the powder dissolved, a 4.0 ml quantity of the stock solution of sulfamerazine was added and the mixture brought to volume (100.0 ml) with water. The solutions of other baclofen concentrations were prepared as needed.

Assay Solutions - Six 20 mg tablets or twelve 10 mg tablets were ground to a fine powder. A 2 ml quantity of dilute sulfuric acid and 2 ml of water was added. The mixture was stirred for about 3-5 minutes using a pestle mortar and 4.0 ml quantity of the stock solution of sulfamerazine was added. The mixture was brought to volume (100.0 ml) with water, shaken and filtered (6). First 15 ml of the filtrate was rejected and then some collected for HPLC analysis.

Assay Solution for Content Uniformity - One 10 mg tablet was ground to a fine powder and mixed with 0.5 ml each of dilute sulfuric acid and water. The rest of the procedure was same as given above except that only 1.0 ml of the stock solution of sulfamerazine was added and the final volume was 25.0 ml. For the analysis of this solution, the sensitivity of the detector was set at 0.02 and the standard solution contained 400 µg/ml of baclofen and 20 µg/ml of sulfamerazine.

HPLC Assay Procedure - A 20 µl of the assay solution was injected into the chromatograph using the described conditions. For comparison, a similar volume of the standard solution containing identical concen-

trations of baclofen and the internal standard (based on the label claim) was injected after the assay solution eluted.

Calculations - Since preliminary investigations indicated that the ratio of the peak heights (drug/internal standard) were directly related to the concentrations of baclofen (range tested ± 30% of the standard concentration), the results were calculated using the 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 the assay solution and $(RPh)_s$ that of the standard solution.

Decomposition of Baclofen - With 30.0 mg of baclofen powder, either one ml of dilute sulfuric acid or one ml of 1N NaOH was mixed in a 150 ml beaker. Ten ml of water was then added and the mixture heated on a hot plate to boiling for approximately 10 minutes. During heating, more water was added as needed. The mixture was cooled and brought to volume (25.0 ml) with water. Before bringing to volume, to the mixture which was treated with sodium hydroxide, 1.5 ml of dilute sulfuric acid was added to acidify it. The mixtures were assayed using the described conditions except that no internal standard was added in order to identify any new peaks in the chromatogram.

RESULTS AND DISCUSSION

The results indicate (Table 1) that baclofen can be quantified in tablets using the developed HPLC procedure. The method is precise and accurate with percent relative standard deviation based on 5 readings of 0.52. The recovery from the synthetic mixtures was quantitative

TABLE 1

ASSAY RESULTS

Dosage Form[a] or Synthetic Mixture	Percent of the Label Claim Found HPLC Method	USP-NF Method
Tablets 10 mg	99.7	99.4
Tablets 10 mg (different lot)	99.5	99.4
Tablets 30 mg	99.2	99.1
Tablets 10 mg (different lot)	99.9	99.4
Synthetic Mixture #1 120 mg of baclofen + 500 mg of lactose	100.2	99.8
Synthetic Mixture #2 240 mg of baclofen + 750 mg of lactose	99.0	100.2
Content Uniformity Test Results (10 mg Tablets)		
Tablet		
1	100.4	-[b]
2	97.6	-[b]
3	95.8	-[b]
4	99.1	-[b]
5	99.9	-[b]
6	100.3	-[b]
7	100.7	-[b]
8	99.9	-[b]
9	99.2	-[b]
10	99.0	-[b]

[a]Only tablets are available commercially.
[b]Not determined using USP-NF method.

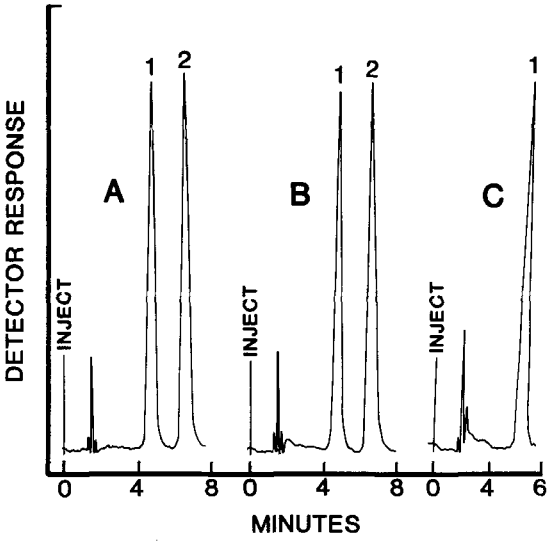

Figure 2 - Sample chromatograms. Peaks 1-2 are from baclofen and sulfamerazine, respectively. Chromatogram A is from a standard solution, B from 20 mg tablets and C from a solution which was boiled for 10 minutes with dilute sulfuric acid (see text).

(Table 1). The results were in excellent agreement (Table 1) with the USP-NF colorimetric method (1).

The extraction procedure for baclofen from tablets is very simple versus a very tedious and time consuming extraction procedure of USP-NF (1). Moreover, it was very difficult to dissolve baclofen powder in 90% aqueous methanol as recommended by the USP-NF (1).

The separation of internal standard from the drug was complete (Figure 2). The method can also be used to test the content uniformity of the tablets. In these studies, 10 mg tablets were tested for content uniformity with excellent results (Table 1). In order to adopt

the method for content uniformity test, the sensitivity of detector was increased from 0.04 to 0.02 AUFS.

It appears that baclofen (Figure 1) is a very stable compound since heating with sulfuric acid or sodium hydroxide hardly caused any decomposition. The results were very close to 100% intact with no change in the shape of the peak (Figure 2C). The decomposed solutions could not be assayed using USP-NF procedure (1) since it requires the use of 90% aqueous methanol as the solvent. The reagent salicylaldehyde is not even soluble in aqueous systems. From the structure (Figure 1), also, it does not appear to be sensitive to hydrolysis or oxidation, the two most common pathways of degradation.

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