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COMMUNICATION

QUANTITATION OF 4-(4-CHLOROPHENYL)-2-PYRROLIDINONE IN BACLOFEN POWDER AND TABLETS

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ABSTRACT

A high-pressure liquid chromatography method to quantify 4-(4-chlorophenyl)-2-pyrrolidinone which is present as an impurity in baclofen powder and its dosage forms has been developed. The USP-NF method for the determination of 4-(4-chlorophenyl)-2-pyrrolidinone in powder is based on TLC and is only qualitative. The developed method was successfully used to quantify 4-(4-chlorophenyl)-2-pyrrolidinone in powder (USP-NF limit 1%) and in tablets (USP-NF limit 5%). The method is accurate and reproducible with a percent error of 4% for powder and 3% for tablets.

INTRODUCTION

Baclofen is extensively used in medicine to relieve the spasticity resulting from multiple sclerosis and muscular rigidity. Gupta reported (1) the quantitation of baclofen in tablets using HPLC. However, baclofen powder contains an impurity, 4-(4-chlorophenyl)-2-pyrrolidinone (I) which tends to increase on storage, especially

in liquid dosage forms. The limit for I in powder is 1% and 5% in tablets (2). The USP-NF method (2) for the determination of I in powder is based on the comparison of the intensity of the spots from the standard and assay solutions using TLC. This method is very tedious and time consuming. In tablets, the quantitation of I is based on HPLC using a strong cation exchange resin column (2). The purpose of these investigations was (i) to prove that 4-(4-chlorophenyl)-2-pyrrolidinone does not interfere in the assay method previously reported (1), and (ii) to quantify I in powder and tablets using the same column (MicroC18) as for the analysis of baclofen in tablets.

MATERIALS AND METHODS

Reagents and Chemicals - All the chemicals and reagents were USP-NF or ACS grade and used without further purification. The baclofen powder and 4-(4-chlorophenyl)-2-pyrrolidinone were used as received from Ciba-Geigy Pharmaceuticals. The tablets were obtained from the commercial lots.

Apparatus and Column - A high-pressure liquid chromatograph (Waters ALC 202) attached to a multiple wavelength detector (Schoeffel's 770) and a recorder (Omniscribe 5312-12) was used. A Micro/C18 column (Waters, 30 cm x 3.9 mm i.d. with 10 micron size particles) was the stationary phase.

Other Chromatographic Conditions - The mobile phase contained 26% (V/V) of acetonitrile in 0.01M aqueous KH_2PO_4 buffer. The sensitivity was 0.04 AUFS (at 268 nm) and the flow rate was 2.0 ml/min. The chart speed was 30.5 cm/hr and the temperature was ambient.

Solutions - A 4.0 mg/ml solution of I in methanol was prepared and diluted further with 50% methanol in water as needed. A 150.0 mg quantity of the powder was dissolved in 1 ml of dilute sulfuric acid and brought to volume (10.0 ml) with 50% methanol in water. Ten tablets were ground to a fine powder and a quantity of the powder representing 100.0 mg of baclofen was mixed with 2 ml of dilute sulfuric acid and stirred for 3 minutes and brought to volume (20.0 ml) with 50% methanol in water. The mixture was filtered through a filter paper (Curtin Scientific, Cat. #263-798), first few ml of filtrate was rejected and then collected for analysis.

Assay Procedure - A 20.0 µl of the assay sample was injected into chromatograph using the described conditions. For comparison purpose, an identical volume of the standard solution was injected after the assay sample eluted.

Calculations - Since preliminary investigations indicated the peak heights were directly related to the concentrations of I (range tested 1.28 to 5.12 µg), the results were calculated using a standard curve.

RESULTS AND DISCUSSION

Interference from 4-(4-chlorophenyl)-2-pyrrolidinone (I) with the Baclofen Assay Method - A 1.2 mg/ml solution of I in methanol was analyzed using the conditions described in the baclofen assay method (1). While the peaks from baclofen and sulfamerazine in the standard solution were recorded in less than 10 minutes, no peak was obtained from I even in 12 minutes. Hence 4-(4-chlorophenyl)-2-pyrrolidinone did not interfere with the assay procedure for baclofen.

Quantitation of I in Powder and Tablets - To quantify I, the chromatographic conditions were changed as follows: (i) to elute I faster (about 8 minutes), the mobile phase containing 26% acetonitrile was used, and (ii) to increase the sensitivity of the assay method, the wavelength of maximum absorption for I (268 nm) was used. Using these conditions, I was quantified in powder and the tablets. They were found to contain 0.3% (USP-NF limit 1%) and 0.9% for 10 mg tablets (USP-NF limit 5%), respectively.

In Figure 1, in Chromatogram A, peak 1 is from 5.0 µg of 4-(4-chlorophenyl)-2-pyrrolidinone. In Chromatogram B (from 10 mg tablets), peak 1 is from I. If the tablets had more than 5% of I (the USP-NF limits), the height of peak 1 in chromatogram B should have been higher than the peak 1 in Chromatogram A. The comparison clearly indicated that the quantity of I in tablets was lot less than the official limit.

Later on, all the solutions for analysis (see text) were prepared in and diluted with methanol to determine if methanol would be a better solvent. While 4-(4-chlorophenyl)-2-pyrrolidinone was freely soluble in methanol, baclofen had very poor solubility. The assay solutions of baclofen from both powder and tablets had to be filtered through Fisher's (Cat. #9-801E) filter paper to obtain a clear solution for analysis. In our experience, when pure methanol is used for both stock and assay solutions, the results were not reproducible. Hence the authors do not recommend its use.

The developed method can be used to quantify I in both the powder and tablets (Table 1) of baclofen versus two different

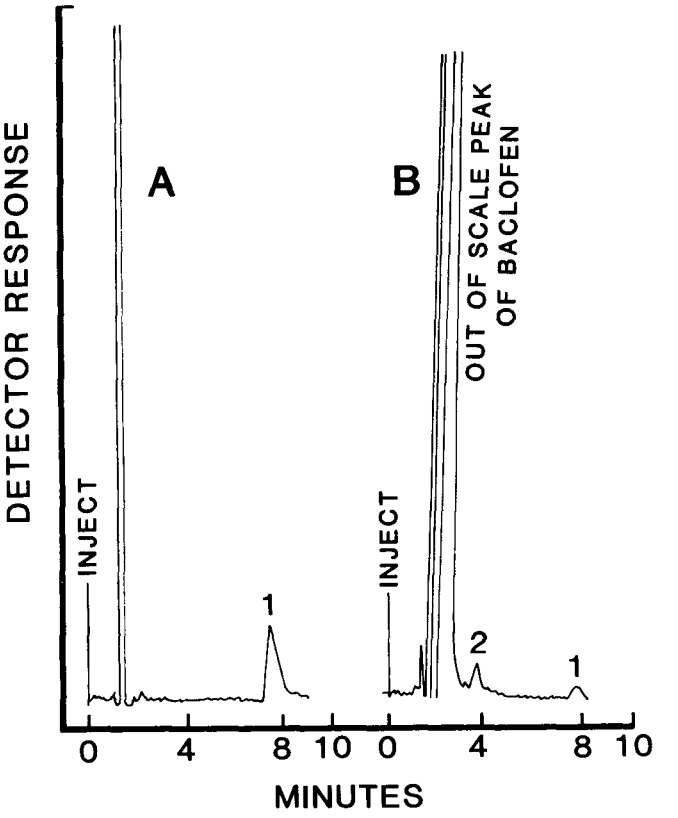

FIGURE 1

Sample Chromatograms. Peak 1 is from 4-(4-chlorophenyl)-2-pyrrolidinone and peak 2 from one of the excipients present in the tablet. Chromatogram A is from a standard solution containing 250 μg/ml of 4-(4-chlorophenyl)-2-pyrrolidinone and B from 10 mg tablets (baclofen concentration 5 mg/ml). For chromatographic conditions, see text.

methods as recommended by the USP-NF (2). The percent error was approximately 4% for the powder and 3% for the tablets. The developed method for the powder is quantitative versus the USP-NF method (2) which is qualitative. Also, when assaying baclofen I can also be assayed by using the same column and only a differrent mobile phase.

TABLE 1

Assay Results of 4-(4-chlorophenyl)-2-pyrrolidinone

Product	Percent of I Found	USP-NF Limits
Powder	0.3 ± 0.012	1.0%
Tablets - 10 mg	0.9 ± 0.027	5.0%
Tablets - 20 mg	0.6 ± 0.018	5.0%
Powder (different lot)	0.3 ± 0.012	1.0%
Tablets - 10 mg (different lot)	1.0 ± 0.030	5.0%
Tablets - 20 mg (different log)	0.7 ± 0.021	5.0%

REFERENCES

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