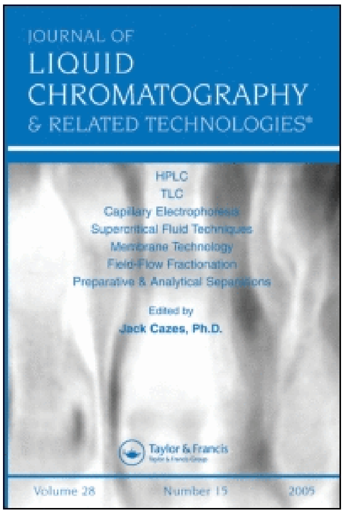

Journal of Liquid Chromatography & Related Technologies
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597273

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To cite this Article Foda, Nagwa H. and Shafie, Faiza El(1996) 'Quantitative Analysis of Bromocriptine Mesylate in Tablet Formulations by HPLC', Journal of Liquid Chromatography & Related Technologies, 19: 19, 3201 — 3209
To link to this Article: DOI: 10.1080/10826079608015818
URL: http://dx.doi.org/10.1080/10826079608015818

J. LIQ. CHROM. & REL. TECHNOL., 19(19), 3201-3209 (1996)

QUANTITATIVE ANALYSIS OF BROMOCRIPTINE MESYLATE IN TABLET FORMULATIONS BY HPLC

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ABSTRACT

A rapid, specific and reliable high performance liquid chromatographic assay of bromocriptine mesylate in tablets has been developed. Reverse phase chromatography was conducted using a mobile phase of 0.05 M ammonium acetate and acetonitrile, (40% v/v) pH 5.6 and detection at 240 nm. The % recovery and coefficient of variation from six placebo tablets containing 2.5 mg of bromocriptine mesylate were 100.65 and 0.456 respectively. Replicate regression analyses of three standard plots in the concentration range 0.5 - 10 mcg/mL obtained on three different days gave a correlation coefficient >0.9997 and the coefficient of variation of the slopes <0.1%. The assay was precise within day and between days as indicated by ANOVA test. The percentage recoveries from 10 replicate tablets of two commercial brands was 99.4 and 102.8% of the label amount and their coefficients of variation were 1.51 and 1.07%.

INTRODUCTION

Bromocriptine mesylate is 2-Bromo-12'-hydroxy-5'a-isobutyl-2'-isopropylergotaman-3',5',18-tione, a dopamine receptor against and a prolactin inhibitor.[1]

Few methods have been developed for the determination of bromocriptine in pharmaceutical dosage forms, using liquid chromatography-mass spectrometry[2,3] and HPLC method.[4,5]

The purpose of this study was to develop a simple, direct, precise and convenient HPLC assay for the quantitation of bromocriptine mesylate in tablet formulation, by passing several tedious steps involved in other assay methods.

EXPERIMENTAL

Chemical and Reagents

Bromocriptine mesylate[6] and propyl paraben[7] were used without further purifications. Acetonitrile,[8] methanol[8] and water were HPLC grade. All other chemicals and reagents were U.S.P. or A.C.S. quality and were used as received.

Instrumentation

A water HPLC systems[9] was used consisting of the following components: Model 45 pump, the WISP model 710 B autosampler, the model 481 UV detector set at 240 nm at 0.02 AUFS, the model 730 data system. Chromatographic separation was accomplished using C_{18} column, 8 mm i.d. x 10cm μBonda pack C_{18} column with 10μm packing.

Chromatographic Conditions

The eluting medium consisting of 40% v/v of 0.05 M ammonium acetate and acetonitrile pH 5.6 with glacial acetic acid, was prepared and degassed by bubbling helium gas for 5 min. prior to use. Column equilibrium with the eluting solvent was established by pumping the mobile phase at a rate of 0.2 mL/min. overnight. The flow rate was set at 0.8 mL/min. during analysis. The chromatogram was recorded and integrated at a speed of 0.2 cm/min.

Internal Standard

A stock solution of propyl paraben containing 10 mg in 100 mL methanol was prepared weekly and stored at 4°C.

Standard Solution of Bromocriptine Mesylate

A stock solution of bromocriptine mesylate was prepared by dissolving 2.5 mg of bromocriptine mesylate in 25 mL methanol (protected from light) water. Nine aliquots equivalent to 0.5, 1, 2, 3, 4, 6, 8, 9, and 10 mcg of bromocriptine were added to 1 mL volumetric flask. After the aliquot of the internal standard equivalent to 4 mcg was added, the flasks were brought to volume by acetonitrile and thoroughly mixed. Twenty μL of the standard solutions was injected onto the column for analysis. The peak area ratio of the drug: internal standard were plotted against the standard bromocriptine concentrations. Least square linear regression analysis was performed to determine the slope, y-intercept, and the correlation coefficients of the standard plots.

Sample Preparation

Individual tablets were pulverized using a mortar and pestle, and completely transferred to 25 mL volumetric flask (protected from light). The volume was adjusted with methanol and the flask was mechanically shaken for five min. Five mL of the solution was removed into a centrifuge tube and centrifuged at 3000 r.p.m. for 5 min. Eighty μL was transferred to a one mL volumetric flask containing 40 μL of propyl paraben stock solution, and diluted to the volume with acetonitrile. Twenty μL was loaded into the sample loop for chromatography. Ten replicate commercial tablets of bromocriptine mesylate were analyzed for statistical evaluation of the assay.

Quantitation

The amount of bromocriptine per tablet was determined from the following equation:

$$Q = [R/A + B] \times \text{dilution factor}$$

where Q is the mg bromocriptine per tablet, R is the peak area ratio (drug/internal standard), A is the slope of the calibration curve and B is the y-intercept.

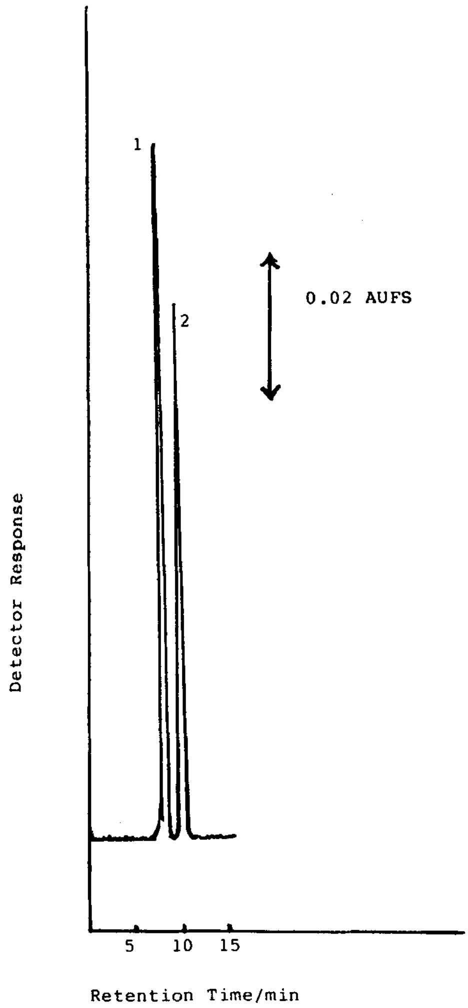

Figure 1. Chromatogram of Bromocriptine mesylate tablet.
Key: 1. Propylparaben, 2. Bromocriptine mesylate

Recovery of Bromocriptine Mesylate from the Fabricated Placebo Tablets

The reference tablets containing 2.5 mg of bromocriptine and 50 mg each of starch and lactose were prepared and subjected to the described HPLC assay to measure the accuracy and precision.

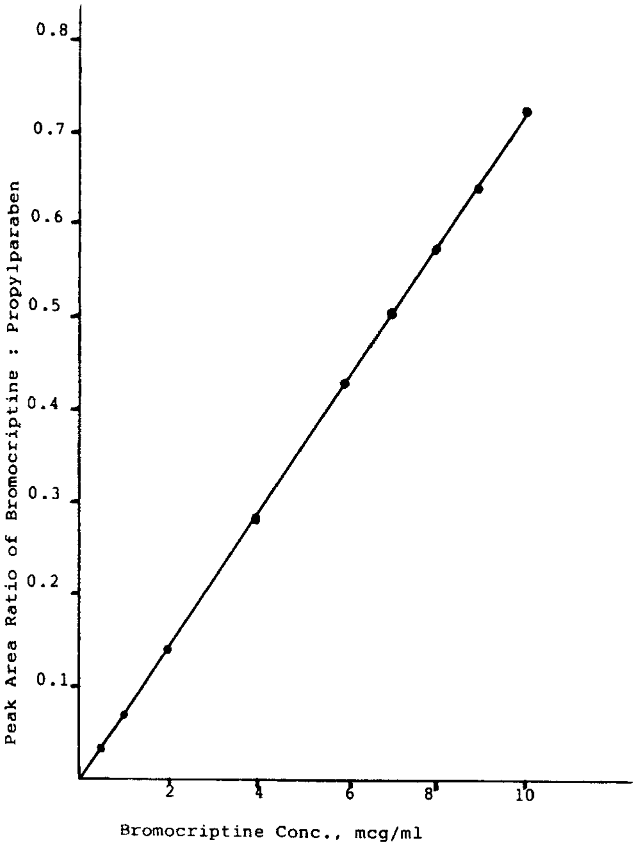

Figure 2. Standard Calibration Plot of Bromocriptine

RESULTS AND DISCUSSION

Figure 1 shows typical chromatograms obtained following analysis of bromocriptine mesylate in tablets. Using the chromatographic conditions described, bromocriptine mesylate and propyl paraben were well separated and their retention times were 9.73 and 7.9 min., respectively. For both compounds, sharp and symmetrical peaks were obtained with good baseline resolution and minimal tailing, thus, facilitating the accurate measurement of the peak area ratio. No interfering peaks were found in the chromatogram due to tablet excipients. Figure 2 shows a calibration plot for the peak area ratio

Table 1

Regression Analyses of the Three Standard Plots of Bromocriptine

Standard[a]	Slope[b]	Intercept[b]	Correlation[b] Coefficient
1	0.072778	-0.0004	0.99981
2	0.070020	-0.0013	0.99890
3	0.077200	-0.0006	0.99900

a) obtained in 3 different days

b) the mean of 3 determinations at each drug concentration

of varying amounts of bromocriptine (0.5-10 mg/mL) to a constant amount of propyl paraben (4 mcg/mL). The plots were linear (r=0.9998) and the regression analysis of the data gave the slope and intercept as:

$$Y = 0.0727\,x - 0.0004$$

where Y and X are the peak area ratio and bromocriptine concentration, respectively. Three replicate analyses of bromocriptine at concentration of 0.5 - 10 mcg/mL were performed at three different days over one week period. The results of this evaluation are summarized in Table 1. The average correlation was higher than 0.9990 and the coefficient of variation of the slopes of the three lines was <0.1%. Analysis of variance of the data showed no detectable difference in the slopes of the three standard plots ($F=4.09$, $P > 0.01$). The similarities in the slopes and the high correlation coefficients indicate that the assay possesses excellent reproducibility and linearity. Thus, the method should be accurate and precise within the assay day as well as between assay days.

Precision and Accuracy

Six placebo tablets containing 50 mg each of lactose and starch and 2.5 mg bromocriptine were assayed for four consecutive days for intra and interday precision studies. The average recovery shown in Table 2 was (2.504 mg) with the coefficient of variation 1.49%. Estimation of day to day and within day precision were calculated by ANOVA test. The calculated F values, $F_{0.05}$ (5, 15) = 0.5637 and $F_{0.05}$ (3, 15) = 1.0257 were smaller than the table values $F_{0.05}$

Table 2

Analysis of Variance for Intra- and Inter Day Precision

Day/Assay	1	2	3	4	5	6
1	2.555	2.457	2.570	2.52	2.482	2.515
2	2.510	2.455	2.495	2.542	2.477	2.517
3	2.540	2.523	2.477	2.567	2.442	2.512
4	2.465	2.547	2.522	2.507	2.462	

Mean = 2.504 mg SD = 0.0374 CV% - 1.49

Anova Test

Source of Variation	DF	Sum of Squares	Mean of Squares	F Ratio	P
Within day	5	0.0025796	0.0005159	0.56368	0.05
Between day	3	0.007824	0.0015648	1.02570	0.05
Error	15	0.022882	0.00152548		
Total	23	0.0335856			

(5, 15) = 2.44 and $F_{0.05}$ (3, 15) = 2.24, respectively. Thus, it was concluded, that there was no significant difference for the assay which was tested within day and between days.

Recovery

Table 3 shows the average recovery by the placebo tables containing 2.5 mg bromocriptine and 50 mg each of lactose and starch. The average recovery was % 100.56 and its relative standard deviation was 0.456.

Analysis of Bromocriptine Tablets

Table 4 presents the results obtained from the analysis of bromocriptine mesylate commercially available. The mean percent recoveries were 99.4, 102.8.

Table 3

Recoveries From Spiked Placebo Tablets

Bromocriptine, mg added	mg Recovered	% Recovery
2.5	2.524	100.80
2.5	2.505	100.20
2.5	2.497	99.88
2.5	2.530	101.20
2.5	2.525	101.00
2.5	2.520	100.80
Mean	2.5160	100.65
SD	0.0115	0.459
CV	0.456	0.456

Table 4

Analysis of Dosage Form of Bromocriptine

Sample	n[a]	Mean % Recovery	SD	%CV
A	10	99.4	1.5	1.518
B	10	102.8	1.1	1.070

The stability indicating nature of the assay has not been demonstrated in this study, since no sign of degradation was observed by TLC after subjecting the drug solution (pH 3 and 9) at 70°C for 2 hr which, was also evident, from the absence of any additional peaks in the chromatograms.

CONCLUSION

The HPLC method developed in this study has the advantages of simplicity, precision and convenience. It also allows for the direct determination of bromocriptine. Therefore, the method should be useful for routine analytical and quality control assay of bromocriptine in dosage forms.

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Received January 14, 1996
Accepted Feburary 10, 1996
Manuscript 4073