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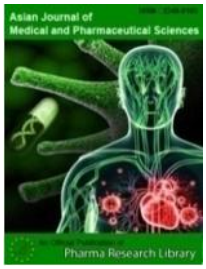

R E S E A R C H A R T I C L E

Stability indicating LC-MS/MS method for estimation of Bromocriptine mesylate in human plasma application to a bioequivalence study

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A B S T R A C T

Background: Sensitive and selective analytical method is required for the estimation of Bromocriptine in human plasma as Bromocriptine has been reported to have high intra-subject variability and is converted to its active metabolite Bromocriptine mesylate in in-vitro system and vice versa. If this inter conversion is not restricted, it could lead to pseudo estimation of Bromocriptine in human plasma. **Methods:** Aspecific, sensitive and reproducible high-performance liquid chromatography-tandem mass spectrometric (LC-MS/MS) method was developed and validated for determination of Bromocriptine in human plasma, using Quetiapineas an internal standard. Bromocriptine and Quetiapine were extracted from human plasma using solid phase extraction, separated on Luna C18 (2) 100A (100×4.6mm, 5µm) column with mobile phase consisting of acetonitrile and 2mM ammonium acetate buffer (pH3.6) in the ratio of 90:10, v/v. Quantification was achieved by monitoring transitions of m/z 422.1 → 285.4 for Bromocriptine and 425.4 → 285.4 for Quetiapine in multiple reaction monitoring, using turbo ion source in positive polarity. **Results:** No matrix effect was observed within the linearity range of 0.121–35.637ng/mL (r>0.99).The degree of matrix effect for lovastatin was determined as 2.74%, and it had no impact on incurred samples analysis with runtime of 4.5min. The intra-and inter-day precision values were within11.38and8.62 %respectively, for lovastatin at the lower limit of quantification level. **Conclusions:** Stability data indicated that Bromocriptine is stable under various handling conditions & within significant inter-conversion between Bromocriptine and Bromocriptine mesylate. The method was successfully applied for the bioequivalence study of Bromocriptine after oral administration of 20mg tablet in healthy volunteer.

Keywords: Liquid chromatography-mass spectrometry, Bromocriptinemesylate, Quetiapine Hemi fumarate Inter-conversion.

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C O N T E N T S

1. Introduction

Bromocriptine is an oral dopamine receptor agonist used predominantly in the therapy of Parkinson disease, but which has other activities including inhibition of prolactin and growth hormone release which has led to its use in acromegaly, infertility and galactorrhea. Bromocriptine therapy is associated with low rate of transient serum enzyme elevations during treatment and has been implicated in rare cases of acute liver injury.

Background

Bromocriptine (broe" moekrip' teen) is a semisynthetic ergot alkaloid derivative which acts as a dopamine receptor agonist. Bromocriptine has strong agonist activity on the D2 class of dopamine receptors and partial antagonist of the D1 receptors in central nervous system. Bromocriptine was approved for use in the United States in 1978, the first in this class of agents, and has been in wide use since. Current indications are the therapy of symptomatic Parkinson disease as well as spastic disorders and extrapyramidal disorders caused by medications. Bromocriptine also has inhibitory activity on prolactin and growth hormone release, and its indications also include treatment of amenorrhea and galactorrhea related to hyperprolactinemia, female infertility, acromegaly, Cushing syndrome and premenstrual syndrome. Bromocriptine is available in tablets of 2.5 mg and capsules of 5 mg in generic forms and under the brand name of Parlodel. The recommended dose for Parkinson disease is 10 to 40 mg daily, but it must be introduced gradually and the dose titrated based upon tolerance and effect. In Parkinson disease, it is usually used in combination with levodopa/carbidopa. Common side effects include profound hypotension (with the first dose), somnolence, fatigue, vivid dreams, anxiety, confusion, hallucinations, delusions, depression, dizziness, headache, nausea and gastrointestinal upset, symptoms common with increased dopaminergic activity.

2. Materials and Methods

Chemicals: Reference standard of Bromocriptinemesylate and Internal Standard Quetiapine Hemifumarate were received from vendor Splendid Labs which are of 99.20% and 99.56% purity respectively. Methanol, acetonitrile of HPLC grade and Ammonium Trifluoro Acetate, Formic acid, Ammonium Acetate, Ortho Phosphoric Acid, Ammonia of GR/AR grade were purchased from Merck, Schuchardt OHG, Germany. High pure water was prepared by using Millipore Milli Q purification system.

Instrumentation:

The LC-MS/MS system, used for the method development and stability experiments in method validation was SIL-HTC HPLC Shimadzu connected to Applied bio systems API 4000 of MDS Sciex model mass spectrometry. The output signal was monitored and processed using Analyst software version 1.5.1 (Applied bio systems). A high-speed desk centrifuge Sorvall Legend XTR Thermo Scientific was used to centrifuge the samples. Ultra microbalance SE2 of Sartorius and Semi Microbalance CPA225D of Sartorius was used for weighing the samples. The analyte and internal standard was extracted by solid phase extraction using Ezypress 48 of Orochem 1ml, 30mg cartridge.

3. Results and Discussion

Determination of Bromocriptine Mesylate in Human Plasma

A. Summary of Experimental Parameters

Optimization of Chromatographic conditions

Good response was observed for both analyte and ISTD when Acetonitrile: 2mM Ammonium trifluoroacetate (90:10v/v) was used as mobile phase and Gemini C18 (4.6x100mm, 5µm) as column. The retention times of Bromocriptine and Quetiapine were found to be 3.760 min and 2.762 min respectively.

B. Analytical Method Validation:

Linearity: Representative Chromatogram of Calibration curve.

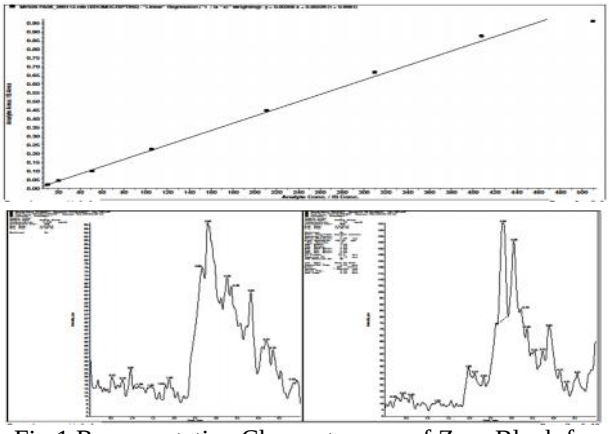

Fig.1 Representative Chromatogram of Zero Blank for Drug and ISTD

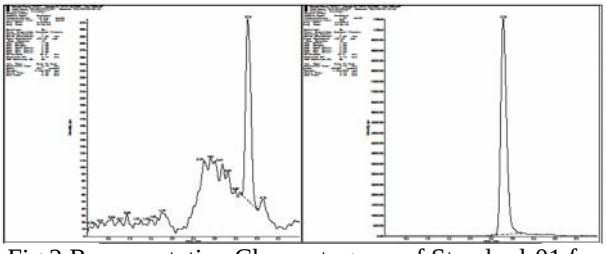

Fig.2.Representative Chromatogram of Standard-01 for Drug and ISTD

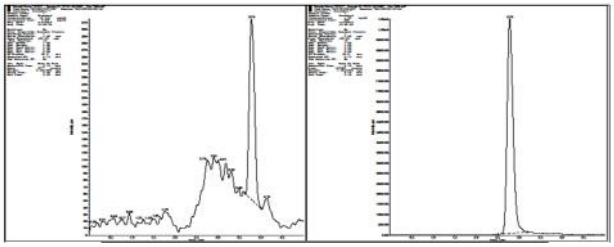

Fig.3.Representative Chromatogram of Standard-08 for Drug and ISTD

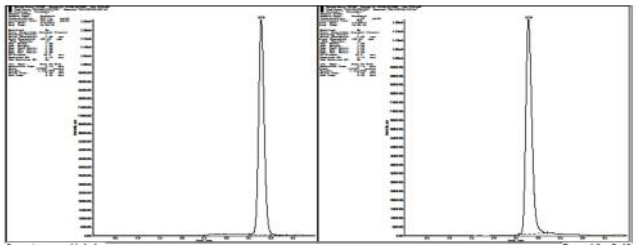

Fig.4. Representative Chromatogram of HQC for Drug and ISTD

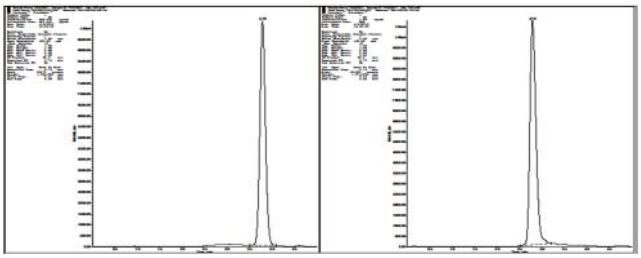

Fig.5.Representative Chromatogram of MQC for Drug and ISTD

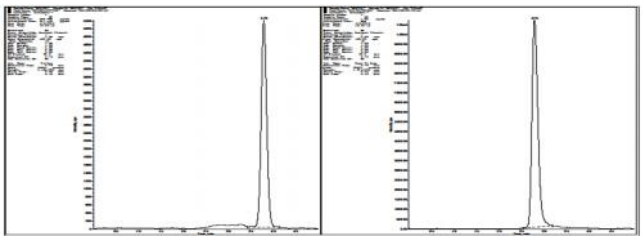

Fig.6.Representative Chromatogram of LQC for Drug and ISTD

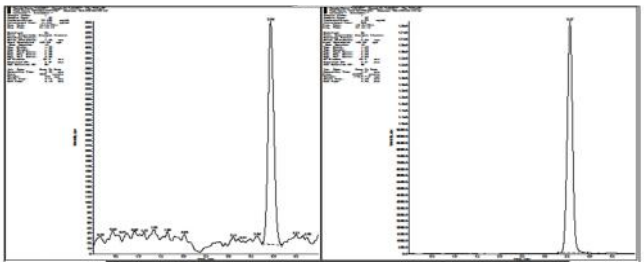

Fig.7.Representative Chromatogram of LLOQQC for Drug and ISTD

4. Conclusion

Bromocriptine (Bromocriptinemesylate) is an ergot derivative with potent dopamine receptor agonist activity. This drug was clinically used to treat Amenorrhea, female infertility, galactorrhea, hypogonadism, acromegaly, parkinsonism disease, in our experimental work we used Quetiapinehemifurate as internal standard which has structural similarity with Bromocriptine for its determination in Homogeneous K_2 EDTA human plasma. The results obtained from validation concludes that, the developed method is simple, linear, accurate, precise, less time consuming, economically useful, applicable for the routine analysis of pharmaceutical dosage forms, bioavailability- bioequivalence studies and pharmacokinetic studies to quantify Bromocriptine in human plasma by using LC-MS/MS.

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