IJBPAS, October, 2022, 11(10): 4512-4522

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

MULTIVARIATE CALIBRATION TECHNIQUE AIDED UV SPECTROPHOTOMETRIC METHOD FOR THE ESTIMATION OF BROMOCRIPTINE MESYLATE IN PHARMACEUTICAL DOSAGE FORMS

THANGADURAI S, SEETHARAMAN R *, KAVITHA J, JAYASEELAN K AND LAKSHMI K S

Department of Pharmaceutical Analysis, SRM College of Pharmacy, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu District, Tamil Nadu - 603203, India

***Corresponding Author: Seetharaman Rathinam: E Mail: seerampharm@gmail.com**

Received 17th Nov. 2021; Revised 24th Dec. 2021; Accepted 10th Feb. 2022; Available online 1st Oct. 2022

https://doi.org/10.31032/IJBPAS/2021/11.10.6451

ABSTRACT

The current work focuses on the creation and validation of a quick, sensitive, and accurate mulitivariate calibration approach utilizing UV spectrophotometric techniques for the assessment of Bromocriptine mesylate. The λmax of Bromocriptine mesylate is at 303 nm. The multivariate calibration technique applies the linear regression equation by evaluating the link between concentration and absorbance at five distinct wavelength. The findings were processed statistically. The devised approach was verified as per the ICH criteria. The approach is accurate, precise, and linearity within the range of 7-13 µg mL^{-1}. This statistical technique delivers optimal findings by reducing the variation arising from the instrumental or experimental circumstances.

Keywords: Bromocriptine mesylate, Multivariate Calibration, Parkinson's disease, UV Spectrophotometric

INTRODUCTION

Bromocriptine mesylate (BRM) is a semisynthetic ergot alkaloid derivative that has strong dopaminergic properties **[1]**. Molecular formula of BRM is $C_{33}H_{44}BrN_5O_8S$. Molecular Weight is the 750.7 g mol^{-1}. The nomenclature is (6*aR*,9*R*)-5-bromo-*N*-[(1*S*,2*S*,4*R*,7*S*)-2-hydroxy-7-(2-methylpropyl)-5,8-dioxo-4-

propan-2-yl-3-oxa-6,9-diazatricyclo [7.3.0.0] dodecan-4-yl]-7-methyl-6,6*a*,8,9-tetrahydro-4*H*-indolo[4,3-fg] quinoline-9-carboxamide; methane sulfonic acid **[2]** Half-life is 2 to 8 hours. It is available under brand names Cycloset, Parlodel **[3]**

Bromocriptine is a brominated derivative of ergocriptine, an ergot alkaloid. A dopamine agonist, the drug is used to treat hyperprolactinemic diseases, acromegaly, and Parkinson's disease **[4]**. Bromocriptine is a selective dopamine receptor agonist that also acts as a partial antagonist for D1 dopamine receptors. Dopamine agonism has diverse effects depending on the target tissue. Bromocriptine stimulates locomotion and reduces bradykinetic symptoms induced by the degradation of dopaminergic nigrostriatal neurons in Parkinson's disease by binding directly to striatal dopamine D2 receptors. This similar D2 agonistic impact on anterior pituitary lactotrophic cells' D2 receptors limits prolactin exocytosis and gene expression, minimising the deleterious effects of hyperprolactinemia in the case of a pituitary prolactinoma **[5]**.

Literature survey reveals that bromocriptine is official in USP **[6]** and BP **[7]** which describe potentiometric titration method for the estimation of bromocriptine Bromocriptine can be determined using a limited number of analytical procedures by HPLC with UV Dr. Ashour and Kattan 2 detection **[8]**, Energy dispersive X-ray fluorescence spectroscopy **[9]** and differential pulse polarography (DPP) **[10]** in pharmaceutical preparations. Bromocriptine has been estimated by radioimmunoassay with iodine label **[11]**, HPLC with fluorescence **[12]** detection by UV and LC-TMS **[13, 14]**. Multi-variate calibration technique is used to determine BRM in pharmaceutical dosage forms and API. The instruments used to determine bromocriptin was depicted in **Table 1**.

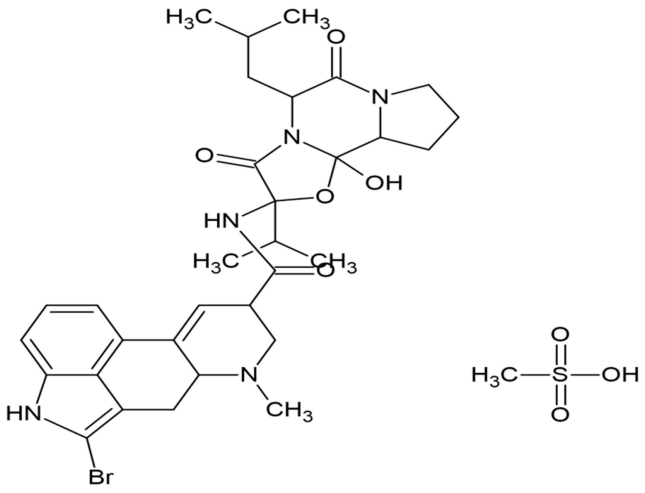


Figure 1: Chemical Structure of BRM

If the absorbance of a test solution (X) is studied at five different wavelengths, the following equation might be expressed for each wavelength (λ- 283, 293, 303, 313, and 323 nm).

$A_{\lambda 283} = a \text{ X } C_x + k_1$ ..... (1)

$A_{\lambda 293} = b \text{ X } C_x + k_2$ ..... (2)

$A_{\lambda 303} = c \text{ X } C_x + k_3$ ..... (3)

$A_{\lambda 313} = d \text{ X } C_x + k_4$ ..... (4)

$A_{\lambda 323} = e \text{ X } C_x + k_5$ ..... (5)

where A_λ is the analyte's absorbance; The slopes of the analyte's linear regression functions are denoted by a, b, c, d, and e; The intercepts of the linear regression functions for the five wavelengths selected are denoted by k1, k2, k3, k4, and k5 and the analyte's concentration is depicted by C_x.

The five equation systems (1–5) presented above may be summarised as follows:

$A_T = a \text{ x } C_x + b \text{ x } C_x + c \text{ x } C_x + d \text{ x } C_x + e \text{ x } C_x + K_T$…… (6)

The above equation can be reduced much more to

$A_T = C_x (a+b+c+d+e) + K_T$ …… (7),

The sum of the intercepts of regression equations at five different wavelengths were represented by A_T and K_T and the sum of absorbance was achieved.

The concentration of the analyte X in a solution is calculated by using the equation.

$$C_x = \frac{A_T - K_T}{(a + b + c + d)}$$

MATERIALS AND METHODS

Chemicals and Reference standard

Methanol

BRM was donated by Maneesh Pharmaceutical Ltd, Solan district (HP).

Instrumentation

Table 1: Instruments used

Name	Make model
UV Spectrophotometer	LABINDIA UV 3092 double beam UV -VIS spectrophotometer (200-400 range)
Sonicator	Soni clean sonicator (modal 160T, Thebarton-Australia)
Weighing balance	Analytical balance (AS 245, Mettler Toledo, India)

Preparation of standard

Consider 2.5 mg of BRM API, place it in a 25ml volumetric flask, and dissolve it in methanol. Sonicate for 10 minutes, make up the volume with methanol, and filter the solution with Whatman grade 42 circular filter paper1ml of the aforesaid stock solution should be transferred into a 10ml volumetric flask. Make up the volume with methanol, which yields 10g/ml.

Working solution

From the above stock solution 7-13 µg mL^{-1} solution was prepared by using methanol as solvent.

Extraction of BRM from tablet and sample preparation

Consider 10 tablets of 2.5mg BRM tablets. Weigh tablets individually and note the readings. Crush the tablets in the motor with a pestle. Take 2.5mg of powdered

tablet and dissolve in methanol in a 25ml volumetric flask. Sonicate for 10minutes, make up the volume with methanol, and filter the solution with Whatman grade 42 circular filter papers. Fill a 10 ml volumetric flask with 1 ml of the specified stock solution. Make up the difference in volume with methanol, yielding a 10 µg mL^{-1} solution. From the 10µg mL^{-1} solution prepare 7, 8, 9, 10, 11, 12, 13 µg mL^{-1} solutions.

Determination of absorption maxima (λ max):

The λ max was determined for a 10 µg mL^{-1} solution made by adequate dilution of the standard stock solution, and it was found to be 303nm. To increase the correlation coefficient and reduce instrumental fluctuations, the absorbance of the solutions was measured across the max (303) range, i.e., 283, 293, 303, 313, 323 nm.

Method validation:

The technique was tested for linearity, sensitivity, precision, and accuracy applying ICH Q2B criteria.

Linearity

BRM stock solution and sample solution were diluted with methanol to achieve concentrations of 14-26 µg mL-1 (1.4, 1.6, 1.8, 2, 2.2, 2.4, and, 2.6 µg mL^{-1}). The absorbance of the solutions was measured throughout a range of wavelengths about (303nm), i.e., 283, 293, 303, 313, 323nm, in order to improve correlation and reduce instrumental variability. In addition, with the MVC approach, the absorbance of the linearity solution across the specified wavelength was recorded and analysed.

Precision

The repeatability of the precision was evaluated using intraday and Interday precision. BRM 10 µg mL^{-1} standard solution was used to evaluate various degrees of accuracy. To determine the repeatability, the study was conducted at 5 different wavelengths. The system precision, inter-day precision, and intra-day precision was measured. Furthermore, the absorbance of this consecutive days is also used to create inter-day variance.

Limit of detection

The Limit of Detection and Limit of Quantification for BRM was estimated using the following equations based on the calibration curve of different wavelengths.

Accuracy

The accuracy of BRM was evaluated at 80 percent, 100 percent, and 120 percent of the pre-analysed test solutions, and the percent Recovery values were estimated.

RESULTS AND DISCUSSION

Stability of solution

The persistence of sample solutions containing 10 µg mL^{-1} BRM was examined at 4 °C for two weeks and at room temperature for six hours. The analysis demonstrated that drug durability in the

absence of spectrophotometric fluctuations under these circumstances, which haven't affects the wavelengths or absorption values of a drug significantly.

The obtained % RSD values were less than 2%. Standard solutions which are refrigerated for the last two weeks. Using this proposed procedure, the concentrations of newly created and aged solution is determined over a two-week period. The difference was below 2%.

Linearity:

According to ICH Q_2 R_1 criteria the linearity results of the proposed approach were scanned between 70 -130% of 10 µg mL^{-1} (14-26 µg mL^{-1}) solution. The absorbance of diluted standard solutions was measured at five different wavelengths, and a calibration curve was developed. The derived regression equations were calculated, and linearity for BRM was discovered over the concentration range and sum of MVC regression equations was Y = 0.0278x + 0.0174, with an R2 of 0.9998, demonstrating that the proposed technique obeys Beers rule, as shown in **Table 2** and **Figure 3, 4**.

Limit of Detection and Limit of Quantification

The Limit of Detection and Limit of Quantification established by estimating the linearity slope were validated by independent sample analysis, which revealed that detection is realistically achievable at those ranges. The LOD value for BRM was found to be 0.9822 and LOQ was 2.9764.

Precision

The interday precision, system precision and intraday precision were found to have a percent RSD was < 2%, shows that this technique is accurate for determining the drugs, and the outcomes were depicted. The new approach has the same accuracy as the previously described methods. The system precision, Interday precision, Intraday precision spectra was represented in **Figure 5, 6, 7 and Table 3**.

Accuracy

The proposed UV approach was applied to BRM sample with concentrations ranging from 14 to 26 µg mL^{-1}. There was no discernible change in accuracy or precision. The UV techniques were compared with the described method employing methanol diluent, respectively. The accuracy spectra were depicted in **Figure 8** and **Table 4**.

Assay

The suggested spectrophotometric method investigated the BRM in tablet preparation. The commercial tablet's UV absorption spectrums were met in three replicates, high analytical recovery values suggest that the pharmaceutical formulation extraction and filtering technique does not result in considerable loss. Additionally, the outcomes of active substance reported are consistent with the claims made by

manufacturers. The results were shown and demonstrated a superior outcome when compared to previously published approaches. Furthermore, the suggested method's use might be broadened to different pharmaceutical formulations. The results were depicted in **Figure 9 and Table 5**. The student t-test value was 0.670, and the F-test value was 1.8571 for the suggested comparison techniques and the reference method using statistical analysis. When the values were compared to the table, the T-value was 2.776 and the F-value was 19.

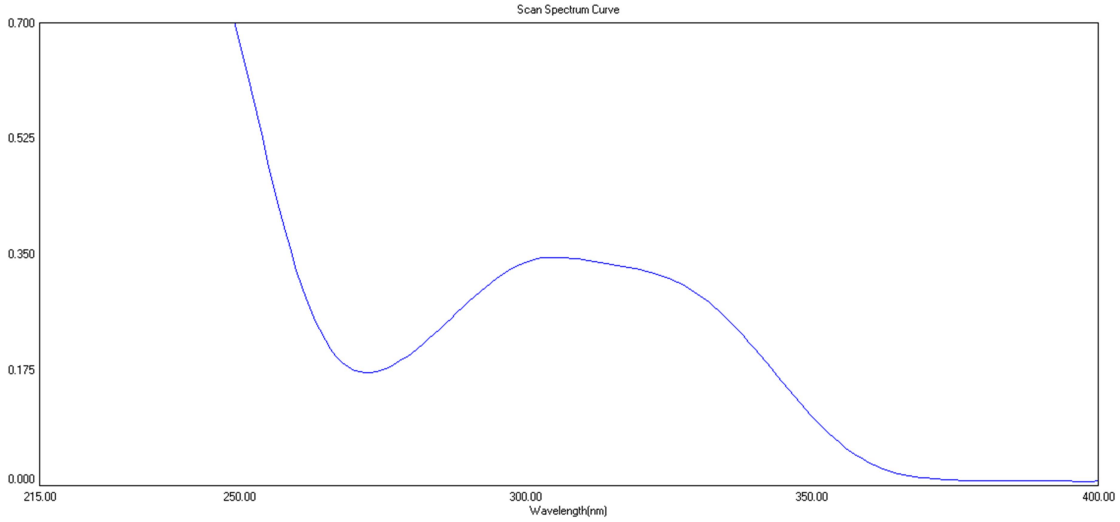
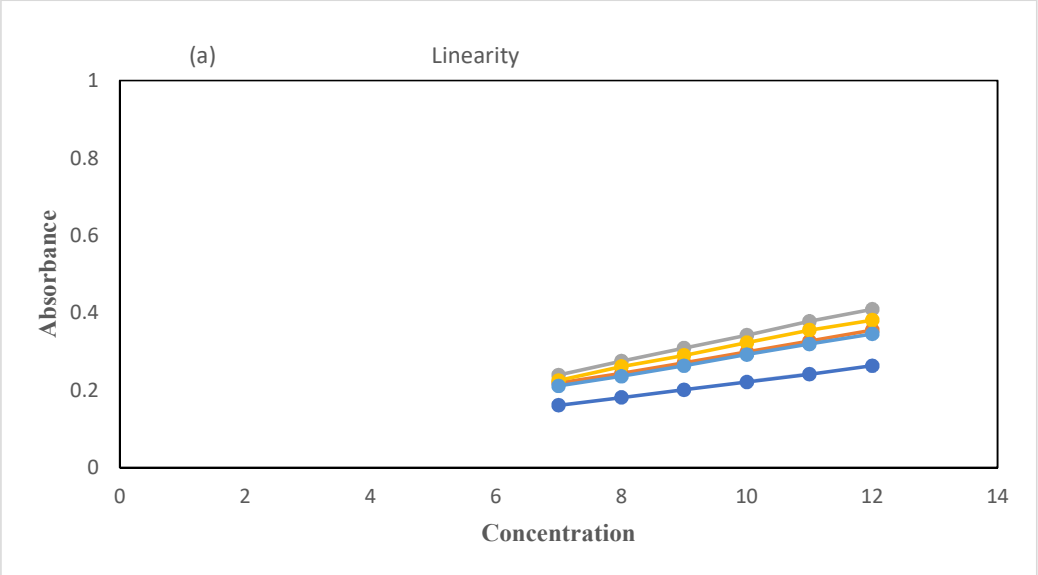


Figure 2: UV spectrum of standard BRM (10 µg mL^{-1})



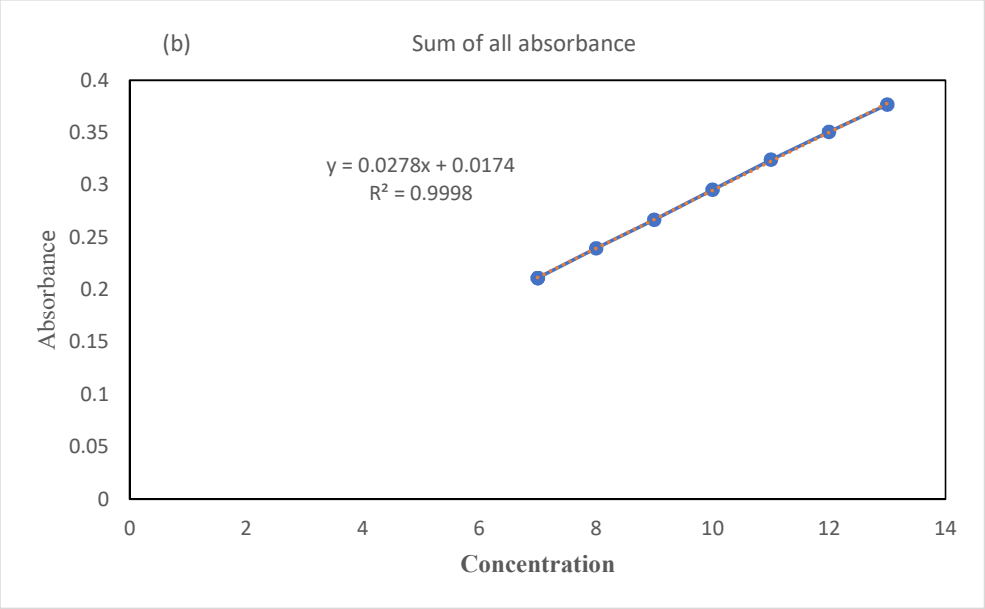


Figure 3: MVC graph (a) and Sum of all absorbance (b) for BRM

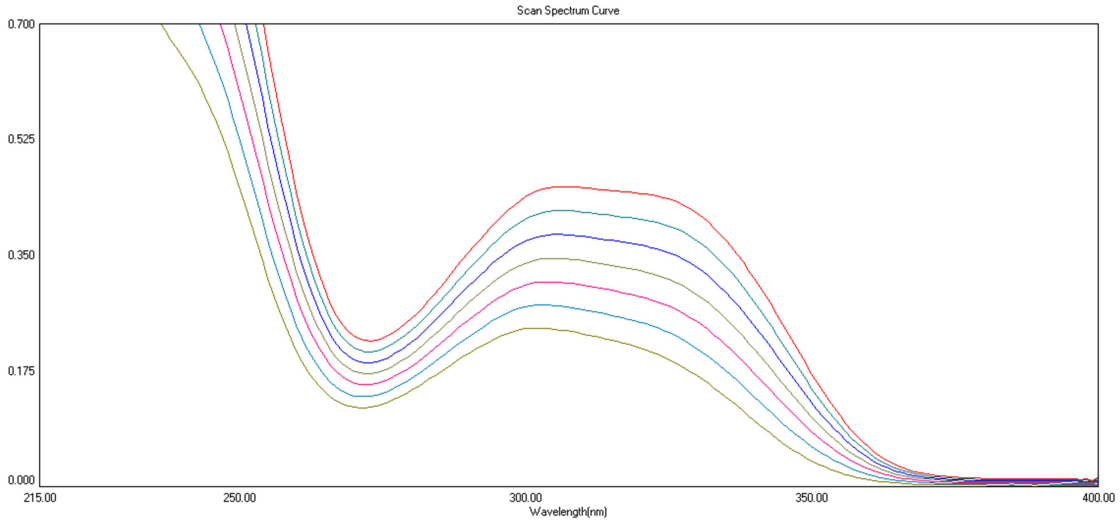


Figure 4: Linearity Spectrum of BRM (14-26 µg mL^{-1})

Table 2: Linearity table

Best-fit values	283 nm	293 nm	303 nm	313 nm	323 nm
slope	0.0200357	0.0275	0.03389286	0.0301786	0.02714286
Y-Intercept When X=0	0.0207857	0.0247143	0.00321429	0.0182143	0.01985714
R^2	0.9996	0.9997	0.9998	0.9967	0.9998

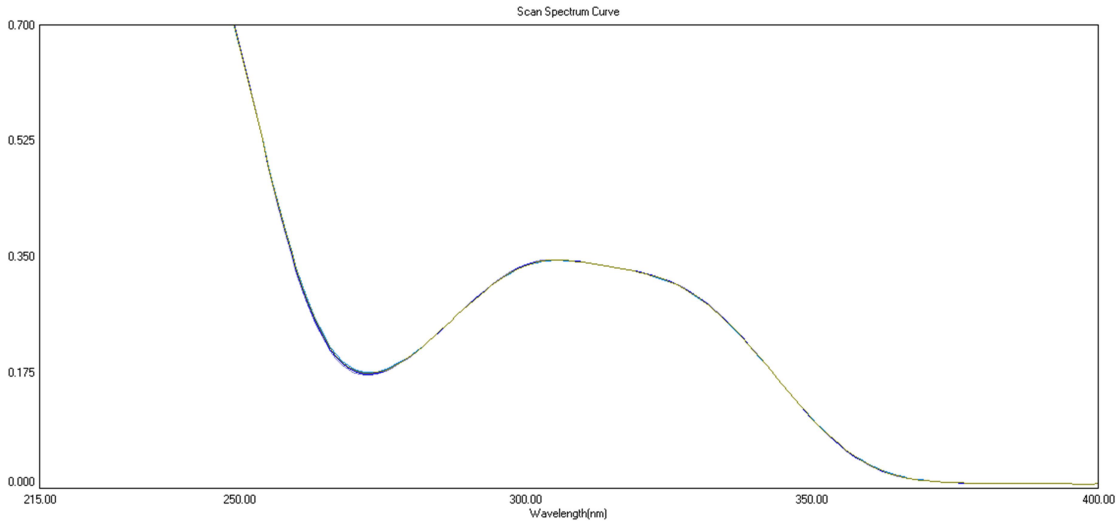


Figure 5: System precision overlay spectra

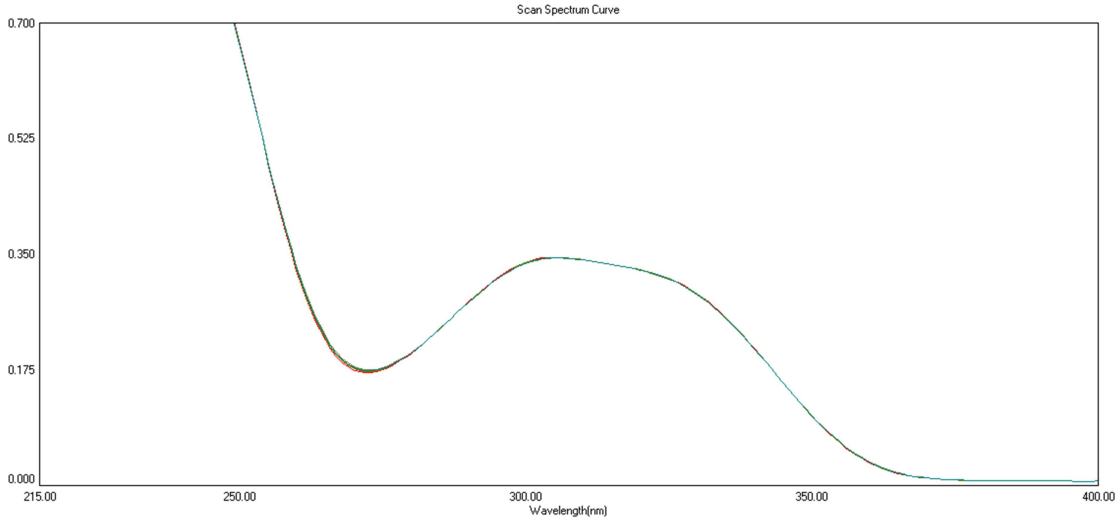


Figure 6: Interday precision overlay spectra

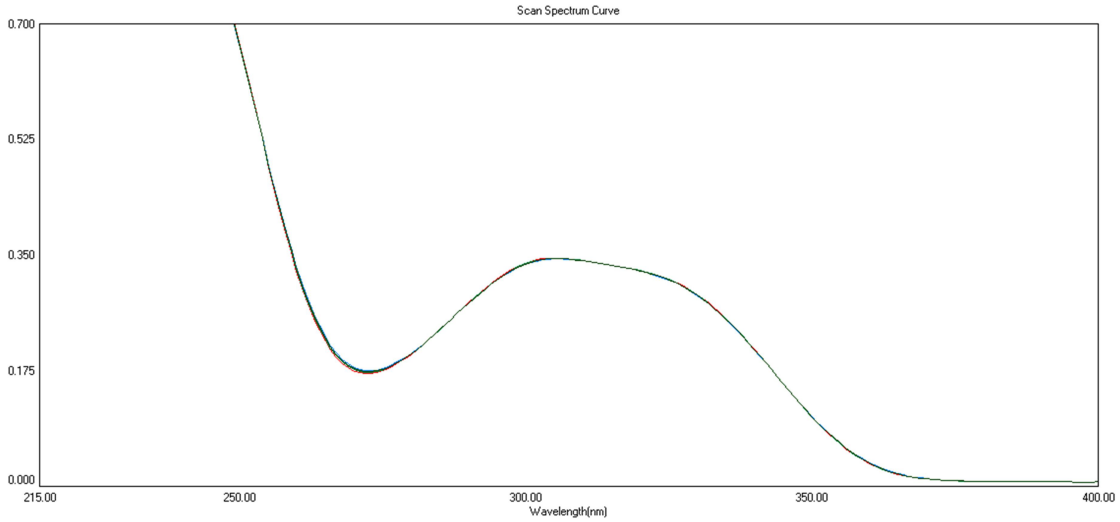


Figure 7: Intraday precision overlay spectra

Table 3: System precision, intra-day and inter- day precision data for the proposed method of BRM

	System precision	Interday and intraday precision		
	Absorbance of standard for 10 µg mL^{-1}	% Recovery of sample equivalent to 10µg mL^{-1}		
		Day 1	Day 2	Day 3
1	0.342	99.32	98.51	98.49
2	0.338	99.15	98.85	99.64
3	0.351	99.42	98.49	99.32
4	0.354	98.85	99.77	99.32
5	0.344	98.54	99.29	99.56
6	0.341	98.74	98.45	99.47
Mean	0.345	99.00	99.89	99.30
SD	0.006	0.35	0.54	0.42
%RSD	1.80	0.35	0.54	0.42
Alpha	0.05	0.05	0.05	0.05
n(obser)	6	6	6	6
CI	0.0050	0.2779	0.4285	0.3336

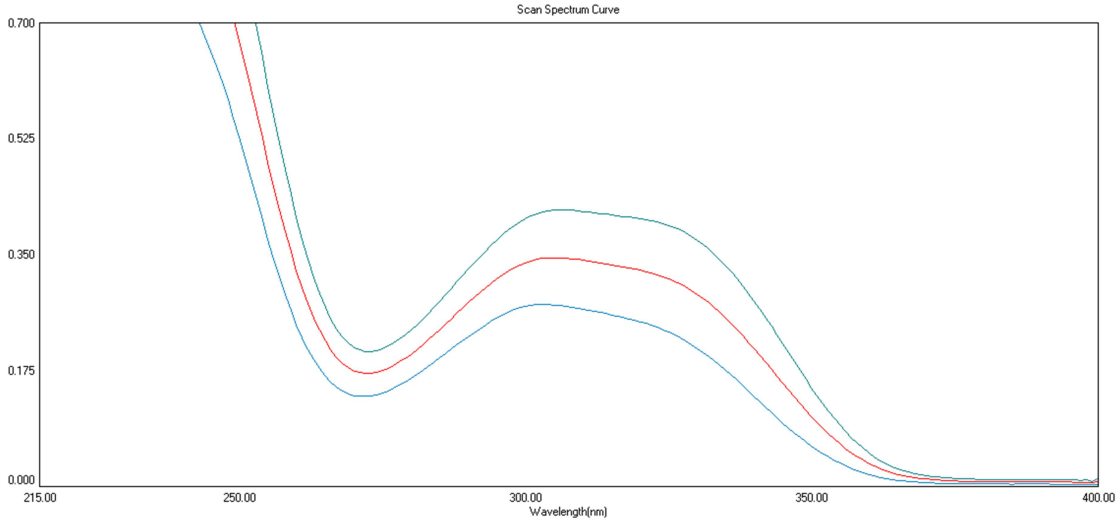


Figure 8: Overlay spectra of accuracy of BRM 80,100 and 120 %

Table 4: Accuracy data for proposed method of BRM

Concentration Levels (%)	Amount present	Amount added (µg mL^{-1})	Amount recovered (µg mL^{-1})	Mean % recovery	SD
80	5	3	7.946	99.33	0.3818
100	5	5	9.926	99.27	0.3511
120	5	7	11.916	99.31	0.2926

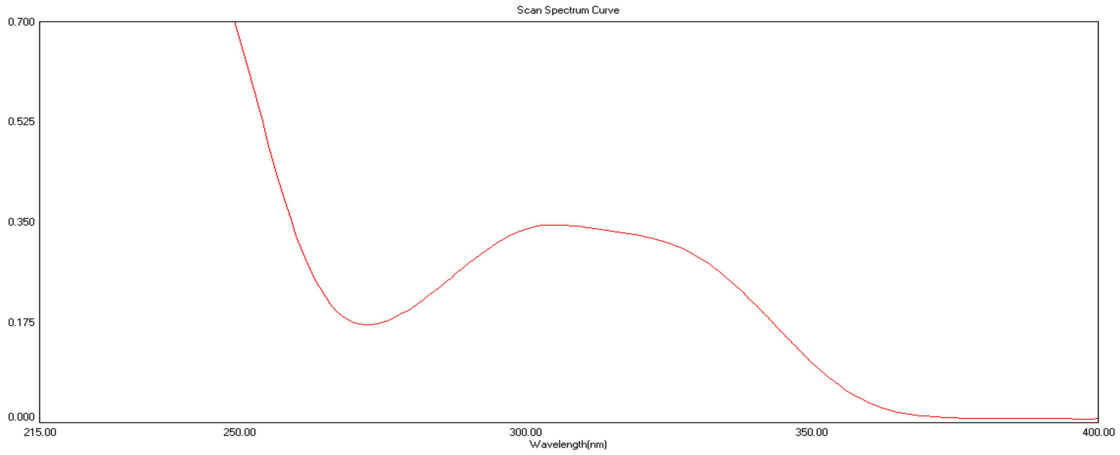


Figure 9: UV spectrum of BRM sample (10µg mL^{-1})

Table 5: Assay findings for two commercially available formulations of BRM

Commercial formulation	Label claim (mg)	Mean ± SD (n=3)	% RSD
Batch 1	2.5	2.47 ± 0.02	0.843
Batch 2	2.5	2.48 ± 0.02	0.616

CONCLUSION

The proposed MVC approach was a simple, novel, accurate, precise technique for estimating BRM in Pharmaceuticals. It is strongly advised to create a new approach for routine BRM analysis in Quality control department. All validation parameters were evaluated and confirmed to be within limits when compared to ICH guidelines.

ACKNOWLEDGEMENT

The authors are thankful to the management of SRM Institute of Science and Technology and SRM College of Pharmacy, Kattankulathur for providing various reprographic sources for carrying out this research work successfully.

CONFLICT OF INTEREST

The authors report no conflicts of interest on the study**.**

REFERENCES

[1] Z. A. Hussein, "A Formulation And Characterization Of Bromocriptine Mesylate as Liquid Self nano Emulsifying Drug Delivery System," *Iraqi J. Pharm. Sci. (P-ISSN 1683 - 3597 , E-ISSN 2521 - 3512)*, vol. 27, no. 2, pp. 93–101, Dec. 2018, doi: 10.31351/vol27iss2pp93-101.

[2] "Pub Chem," *National Library of Medicine*, 2005. https://pubchem.ncbi.nlm.nih.gov/compound/6134.

[3] C. Identifiers, G. Name, D. A. Number, and B. Names, "Bromocriptine," *DrugBank Onlin*. pp. 1–15, 2021, [Online]. Available: 21/21, 10:22 AM Bromocriptine: Uses, Interactions, Mechanism of Action %7C DrugBank Online%0Aactivity (in order of decreasing binding affinity) on 5-hydroxytryptamine (5-HT) , dopamine D , 5-%0A1D 3%0AHT , 5-HT , 5-HT , and 5-HT receptors, antagonist acti.

[4] Z. Kopitar, B. Vrhovac, L. Povšić, F. Plavšić, I. Francetić, and J. Urbančič, "The effect of food and metoclopramide on the pharmacokinetics and side effects of bromocriptine," *Eur. J. Drug Metab. Pharmacokinet.*, vol. 16, no. 3, pp. 177–181, Jul. 1991, doi: 10.1007/BF03189956.

[5] M. Ozery and R. Wadhwa, "Bromocriptine," *NCBI Bookshelf*, pp. 3–8, 2021, [Online]. Available: https://www.ncbi.nlm.nih.gov/books/NBK555948/.

[6] U. S. P. The National Formulary,

The United States Pharmacopoeia. Convention, Rockville, 2011.

[7] "The British Pharmacopeia," Her Majesty's Stationery Office, 2011.

[8] N. H. Foda and F. El Shafie, "Journal of Liquid Chromatography & Related Technologies Quantitative Analysis of Bromocriptine Mesylate in Tablet Formulations by HPLC," no. March 2015, pp. 37–41, doi: 10.1080/10826079608015818.

[9] M. A. Raggia, F. Lucchini, and P. Da Rec, "X-RAY FLUORESCENCE SPECTROSCOPIC ANALYSIS OF BROMINE IN PHARMACEUTICAL FORMULATIONS inorganic or organic matrices in pharmaceutical formulations . The classical Volhard titration , recommended by FU (ref . 1), BP (ref . 2) and AOAC (ref . 3) is grad," vol. 56, no. 220, pp. 2229–2233, 1991.

[10] A. Radi, M. S. El-Shahawi, and T. Elmogy, "Differential pulse voltammetric determination of the dopaminergic agonist bromocriptine at glassy carbon electrode," *J. Pharm. Biomed. Anal.*, vol. 37, no. 1, pp. 195–198, 2005, doi: 10.1016/j.jpba.2004.10.013.

[11] J. S. Bevan, D. Baldwin, and C. W. Burke, "Sensitive and specific bromocriptine radioimmunoassay with iodine label: Measurement of bromocriptine in human plasma," *Ann. Clin. Biochem.*, vol. 23, no. 6, pp. 686–693, 1986, doi: 10.1177/000456328602300611.

[12] D. G. Phelan, N. H. Greig, S. I. Rapoport, and T. T. Soncrant, "High-performance liquid chromatographic assay of bromocriptine in rat plasma and brain," *J. Chromatogr. B Biomed. Sci. Appl.*, vol. 533, pp. 264–270, Jan. 1997, doi: 10.1016/S0378-4347(00)82212-4.

[13] A. Salvador, D. Dubreuil, J. Denouel, and L. Millerioux, "Sensitive method for the quantitative determination of bromocriptine in human plasma by liquid chromatography-tandem mass spectrometry," *J. Chromatogr. B Anal. Technol. Biomed. Life Sci.*, vol. 820, no. 2, pp. 237–242, 2005, doi: 10.1016/j.jchromb.2005.03.029.

[14] N. Venisse, P. Marquet, E. Duchoslav, J. L. Dupuy, and G. Lachâtre, "A General Unknown Screening Procedure for Drugs and Toxic Compounds in Serum using Liquid Chromatography-Electrospray-Single Quadrupole Mass Spectrometry," *J. Anal. Toxicol.*, vol. 27, no. 1, pp. 7–14, Jan. 2003, doi: 10.1093/jat/27.1.7.