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METHOD DEVELOPMENT AND VALIDATION OF BREXPIPRAZOLE BY USING SPECTROSCOPIC AND CHROMATOGRAPHIC METHOD

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ABSTRACT

Brexpiprazole is an antipsychotic medication. It works by changing the actions of chemicals in the brain. Brexpiprazole is used to treat the symptoms of schizophrenia. It is also used together with other medications to treat major depressive disorder in adults. Brexpiprazole is a novel D2 dopamine and serotonin 1A partial agonist, called serotonin-dopamine activity modulator (SDAM). Brexpiprazole is non hygroscopic, with white to off-white crystals or crystalline powders, and a melting point of 178-181°C (decomposition). It is practically insoluble in water. Present investigation involves the development and validation of chromatographic method for brexpiprazole in bulk drug as per ICH guideline. The spectrophotometric determination was performed in UV Model: UV- Labman 1900 separation was conducted by using mobile phase consisting of Formic Acid and Methanol (50:50) The wavelength was found at wavelength 218 nm.

KEYWORDS: Brexpirazole, UV, HPLC, Method validation.

INTRODUCTION

Brexpiprazole is a new dopamine D2 receptor partial agonist that received approval for the treatment of schizophrenia and for adjunctive use for the treatment of major depressive disorder (MDD) based on a clinical trial development programme that included two pivotal Phase III trials of brexpiprazole monotherapy in acute schizophrenia. It is also used together

with other medications to treat major depressive disorder in adults. This drug has high affinity for 5-HT1A, 5-HT2A, D2 and α1B, 2C receptors. It displays partial agonism at 5-HT1A and D2 receptors and potent antagonism at 5-HT2Aand α1B, 2C adrenergic receptors. It also has some affinity for D3, 5-HT2B, 5-HT7 and α1A, 1Dreceptors, and moderate affinity for H1 and low affinity for M1 receptors. . Brexpiprazole is chemically designated as 7-{4-[4- (1-benzothiophen-4-yl) piperazin-1-yl]butoxy}-1,2- dihydroquinolin-2-one. Its molecular formula is C25H27N3O2S, and its molecular weight is 433.57. Brexpiprazole is a white-to-off white powder.

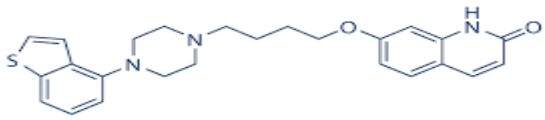


Fig 1: Structure of Brexpiprazole.

MATERIALS AND METHOD

Chemicals

Table 1: list of chemicals for the method development.

Sr. No.	Name of Reagent	Grade
1	Methanol	Analytical Grade
2	Fomic acid	Analytical Grade

Instruments

Table 2: Used instruments for the method development.

Sr. No	Name of Equipment	Source
1	HPLC	Agilent 1260 Infinity II
2	Detector	Variable wavelength detector
3	UV	Labman 1900
4	Electronic weighing balance	Sartorius Minebea co. Ltd
5	Sonicator	The ultrasonic PCi Analytics sonicator

OBSERVATIONS AND RESULTS

Standard Preparation

a. Initially Prepare a Standard Stock Solution (SSS-I) of Brexpiprazole by adding 5mg in 10 ml volumetric flask & add 5 ml diluent and Mix and sonicate for 5 minutes. Make up the volume to 10 ml with diluent. (Conc. = 500 µg/ml).

b. Pipette out 1.0 ml of SSS-I in 10 ml volumetric flask. Add 5 ml diluent and vortex; make up the volume with diluent. (Conc. of Brexipiprazole = 50µg/ml) SSS-2.

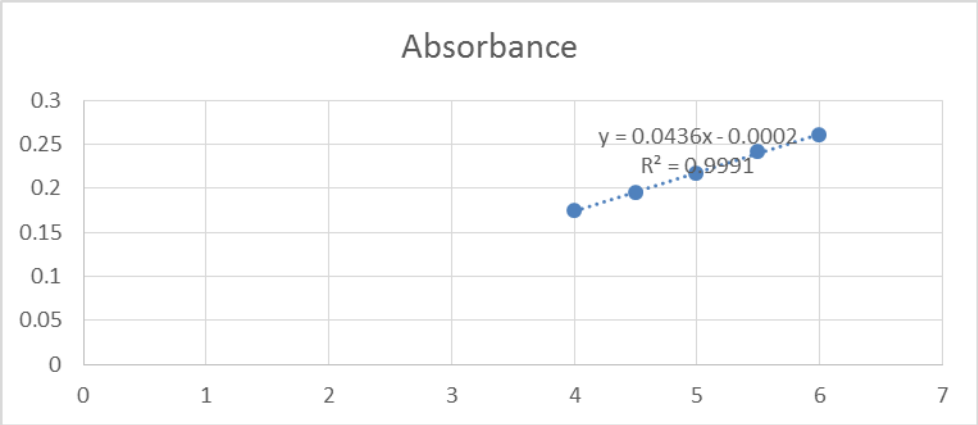
c. Pipette out 1.0 ml of above solution and transfer it to 10 ml volumetric flask. Add 5 ml diluent and vortex; make up the volume with diluent. (Conc. of Brexipiprazole= 5µg/ml) SSS-3 7.2 Selection of wavelength 5µg/ml of Brexipiprazole Working Standard was scanned in the UV range of 190-400 nm.

From the spectrum wavelengths 218 nm (λ max of brexipiprazole) was selected for analysis of both drug. (λ1-218 nm). The observed λ max is 218nm.

LINEARITY

Table No. 3: Linearity data.

Brexipiprazole		
% Level	**Concentration (ug/ml)**	**Absorbance**
80	4	0.175
90	4.5	0.195
100	5	0.217
110	5.5	0.241
120	6	0.261



Calibration curve

Table No. 4: LinearityParameters.

Parameter	UV method
Range	4-6µ/ml
Correlation coefficient	0.999
Slope	0.043x

LIMIT OF DETECTION AND LIMIT OF QUANTIFICATION

Table No 5 –LOD and LOQ data.

LOD	**2.12**
LOQ	6.55

ACCURACY

Table No 6: Accuracy Data.

Brexipiprazole								
% Level	Reps	Spiked Conc (ug/ml)	Abs	Amount Recovered (ug/ml)	% Recovery	AVG	STDEV	RSD
80	Rep 1	4.00	0.175	4.03	100.81	101.00	0.33	0.33
	Rep 2	4.00	0.176	4.06	101.38			
	Rep 3	4.00	0.175	4.03	100.81			
100	Rep 1	5.00	0.217	5.00	100.00	99.85	0.27	0.27
	Rep 2	5.00	0.216	4.98	99.54			
	Rep 3	5.00	0.217	5.00	100.00			
120	Rep 1	6.00	0.26	5.99	99.85	100.10	0.22	0.22
	Rep 2	6.00	0.261	6.01	100.23			
	Rep 3	6.00	0.261	6.01	100.23			

PRECISION

Table No 7: IntradayandInterdayprecision Data.

Condition	Sample ID	Interval	Brexpiprzole	
			Conc (ug/ml)	% Assay
Intraday	WS	Mrng	5.00	-
	DP	Mrng	4.96	99.20
	WS	Evng	5.00	-
	DP	Evng	4.94	98.80
Interday	WS	Day 2	5.00	-
	DP	Day 2	4.88	97.60

Repeatability

Table No 8: repeatability.

Sample ID	Brex Abs
100% Rep 1	0.217
100% Rep 2	0.214
100% Rep 3	0.213
100% Rep 4	0.217
100% Rep 5	0.219
100% Rep 6	0.213
AVG	0.216
STDEV	0.003
RSD	1.16

Assay

Table no.9: assay.

Sample	Brexipiprazole	
	Conc (ug/ml)	% Assay
DP-1	4.93	49.30
DP-2	4.88	48.80
DP-3	4.92	49.20
DP-4	4.85	48.50
DP-5	4.95	49.50
AVG		49.06
STDEV		0.40
RSD		0.82

RESULT OF HPLC

Chromatographic Trials for obtaining Optimized Method

Table No. 10: Chromatographic condition for trial 1.

Mobile Phase	Ratio	Diluent	Column	Wavelength	RT	Asymmetry	TP	Peak Purity
0.1% Formic Acid : CAN	50-50	50 Water : 50 ACN	Agilent Zorbax Bonus RP (250 x 4.6 mm, 5 µ)	227 nm	1.92	1.04	9372	1.00

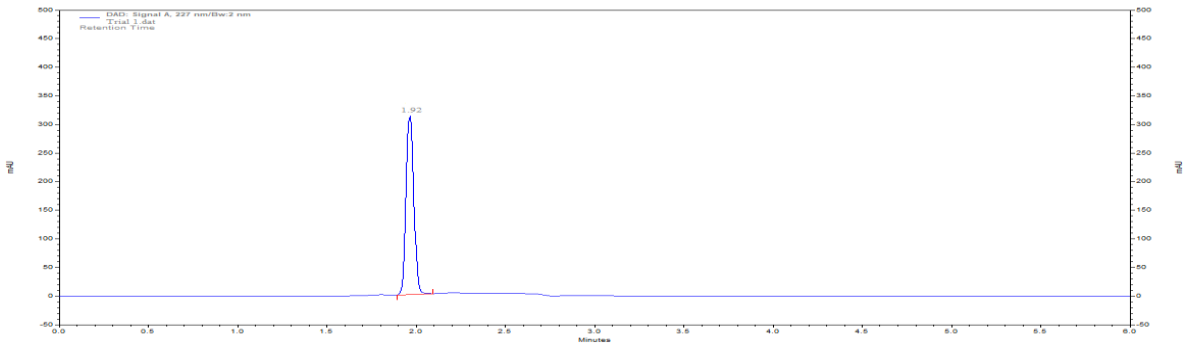


Table No. 11: Chromatographic condition for trial 2.

Mobile Phase	Ratio	Diluent	Column	Wavelength	RT	Asymmetry	TP	Peak Purity
0.1% Formic Acid : Acetonitrile	60-40	50 Water : 50 ACN	Agilent Zorbax Bonus RP (250 x 4.6 mm, 5 µ)	227 nm	2.18	1.01	11061	1.00

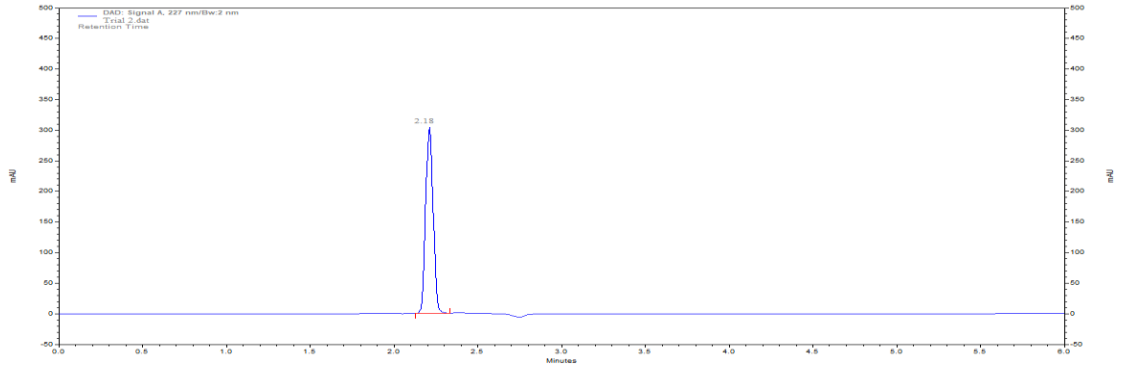
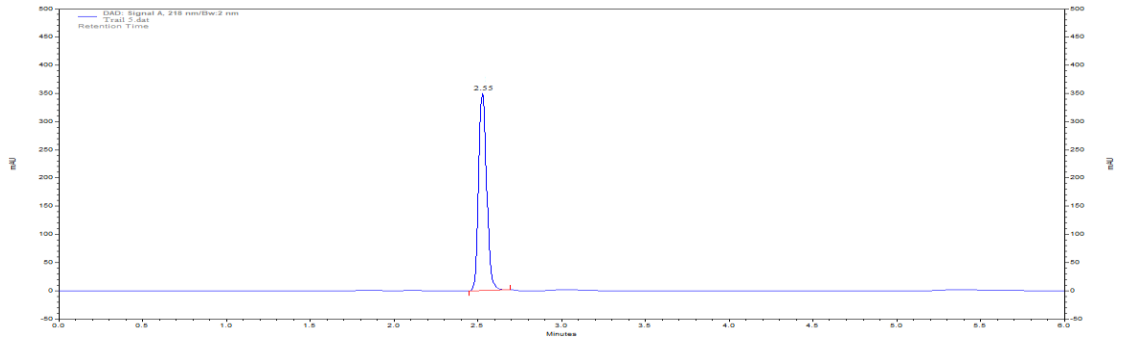


Table No. 12: Chromatographic condition for trial 3.

Mobile Phase	Ratio	Diluent	Column	Wavelength	RT	Asymmetry	TP	Peak Purity
0.1% Formic Acid : ACN	65-35	65 0.1% FA: 35 CAN	Agilent Zorbax Bonus RP (250 x 4.6 mm, 5 µ)	218 nm	2.55	1.02	22032	1.00



METHOD VALIDATION

SPECIFICITY

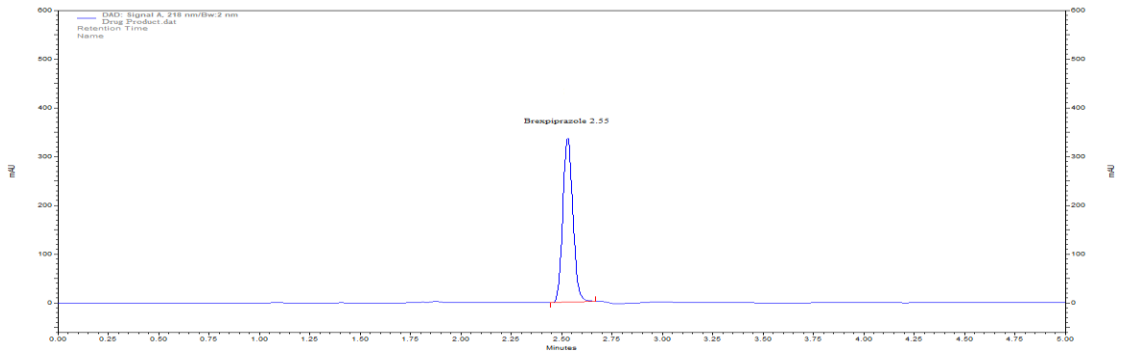


Fig 3: specificity working standard bexpiprazole.

System Suitability

Sample ID	RT	Asymmetry	TP
100% Rep 1	2.55	1.02	22032
100% Rep 2	2.55	1.01	22131
100% Rep 3	2.55	1.03	22103
100% Rep 4	2.55	1.02	22110
100% Rep 5	2.55	1.01	22142
100% Rep 6	2.55	1.02	22031
AVERAGE	2.55		
STDEV	4.86E-16		
% RSD	0.00		

PRECISION (REPEATABILITY)

Sample ID	Area
100% Rep 1	457216
100% Rep 2	457021
100% Rep 3	456895
100% Rep 4	457032
100% Rep 5	457125
AVERAGE	457058
STDEV	120.48527
% RSD	0.03

LINEARITY

linearity data

% Conc.	Conc (ug/ml)	Area
80	40	1970776
90	45	2211335
100	50	2457163
110	55	2719305
120	60	2968110

Table No 29- Linearity parameter.

Parameter	HPLC method
Range	40-60µ/ml
Correlation coefficient	0.999
Slope	50053x

LOD& LOQ

Table no 30: LOD& LOQ.

LOD	3.24.	ug/ml
LOQ	6.20	ug/ml

ACCURACY

Table no. 15: Accuracy Data.

Std area	Stdwt (mg)	% Purity	Stock Conc. (ug/ml)
457216	5	99.7	498.5

Sample ID	Reps	Spiked Conc. (ug/ml)	Area	Amount Recovered (ug/ml)	% Recovery	AVG	STDEV	% RSD
80%	Rep 1	39.88	365472	39.85	99.92	99.88	0.05138	0.05
	Rep 2	39.88	365124	39.81	99.82			
	Rep 3	39.88	365421	39.84	99.90			
100%	Rep 1	49.85	457021	49.83	99.96	99.99	0.03334	0.03
	Rep 2	49.85	457124	49.84	99.98			
	Rep 3	49.85	457321	49.86	100.02			
120%	Rep 1	59.82	548412	59.79	99.95	99.94	0.014787	0.01
	Rep 2	59.82	548254	59.78	99.93			
	Rep 3	59.82	548365	59.79	99.95			

SUMMARY AND CONCLUSION

The results and the statistical parameters demonstrate that the proposed UV spectrophotometric method is simple, rapid, specific, accurate and precise. The method showed acceptable linearity and accuracy. Robust methods which can produce consistent, reliable, and quality data throughout the process and also save time and money. UV Spectoscopic method was safe for operator, environmentally friendly and economical in terms of cost of chemicals and waste management.

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