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NEW SPECTROPHOTOMETRIC TECHNIQUES FOR THE ESTIMATION OF BREXPIPRAZOLE IN TABLET DOSAGE FORM

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ABSTRACT: Brexpiprazole is an atypical antipsychotic drug indicated for the treatment of schizophrenia. Four novels, simple, precise and accurate spectrophotometric methods were developed for the determination of Brexpiprazole (Rexulti) in pharmaceutical dosage forms. The absorption maxima was found to be at 214 nm in method A (0.1N HCl) and shows linearity over the concentration range of 0.002-0.02 µg/mL with regression equation 15.4517x + 0.0221 (r^2 = 0.9990). In Method B (Sodium acetate buffer, pH 4.5) the drug obeys Beer Lambert's law (λ_{max}214 nm) in the concentration range of 0.005-0.1 µg/mL with regression equation 23.457x - 0.0235 (r^2= 0.9992). First derivative spectrophotometric methods (C and D) were developed in 0.1N HCl and sodium acetate pH 4.5 in which Brexpiprazole obeys Beer Lambert's law 0.002-0.02 µg/mL and 0.005-0.1 µg/mL with regression equations 4.9605x + 0.0003 and 1.9990x - 0.0009 respectively. The proposed spectrophotometric methods were validated as per the ICH guidelines and can be applied for the determination of Brexpiprazole in pharmaceutical formulations.

INTRODUCTION: Brexpiprazole (BXP), chemically known as 7-{4-[4-(1-benzothiophene-4-yl) piperazin-1-yl] butoxy}-1, 2-dihydroquinoline-2-one is an atypical antipsychotic indicated for the treatment of schizophrenia and adjunctive treatment of MDD [1]. Brexpiprazole **Fig. 1** is a partial agonist at 5-HT1A and D2 receptors with similar potency, and an antagonist at 5-HT2A and adrenergic α1B/2C receptors. Compared with aripiprazole, brexpiprazole is more potent at 5-HT1A receptors and displays less intrinsic activity at D2 receptors [2].

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Literature survey revealed that Brexpiprazole was determined by UV-Visible spectroscopy [3] and HPLC [4, 5]. In the present study, the authors have proposed four simple validated spectrophotometric methods for the determination of Brexpiprazole in pharmaceutical dosage forms.

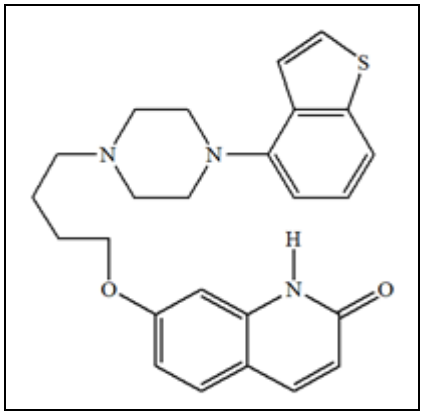

FIG. 1: STRUCTURE OF BREXPIPRAZOLE

MATERIALS AND METHODS:

Instrumentation: A double beam UV-VIS spectrophotometer (UV-1800, Shimadzu, Japan) connected to a computer loaded with spectra manager software UV Probe was employed with a spectral bandwidth of 1 nm and wavelength accuracy of ± 0.3 nm with a pair of 10 mm path length matched quartz cells. For scanning, the wavelength range selected was 400 nm to 200 nm with medium scanning speed. All weights were taken on the electronic balance (Shimadzu).

Chemicals and Reagents: HPLC grade Methanol (Merck), glacial acetic acid (Merck), sodium acetate trihydrate (Merck), Hydrochloric acid (Rankem) was used. Brexpiprazole, obtained as a gift sample from MSN Life Sciences Pvt. Ltd., (India), was used.

Preparation of Sodium Acetate Buffer (pH 4.5): Sodium acetate trihydrate (2.99 gm) were weighed accurately in a 1000 ml volumetric flask containing 1000 ml deionized water and mixed well, then 1.7 mL glacial acetic acid was added to it and the pH adjusted to 4.50 with glacial acetic acid.

Preparation of 0.1N HCl: 8.5 mL of 35% Conc. Hydrochloric acid was added to the 1000 mL volumetric flask containing 900 mL deionized water and mixed well. The volume was then made up to 1000 mL with water.

Preparation of Stock Solution: The standard solution of Brexpiprazole was prepared by dissolving accurately about 25 mg of the Brexpiprazole with methanol in a 25 ml volumetric flask.

The stock solution was further diluted with 0.1N HCl and pH 4.5 sodium acetate buffer for method A (0.002-0.02 µg/mL) and method B (0.005-0.1 µg/mL) respectively as per the requirement.

Procedure for Preparation of the Calibration Curve: The drug solutions were scanned (200-400 nm) against the reagent blank (0.1N HCl for method A and sodium acetate buffer pH 4.5 for method B) and the absorption spectra were recorded. The absorption maximum (λ_{max}) was observed at 214 nm for method A and B. The absorption spectra so obtained were converted in to first derivative spectra by the inbuilt software of the instrument, and the resulting spectrum shows both maxima and minima and therefore the magnitude of the amplitude was recorded against concentration for method C and D. Calibration curves were constructed by taking the concentration of the drug solutions on the x-axis and the corresponding absorbance values on the y-axis.

The Assay Procedure for the Marketed Formulations (Tablets): Brexpiprazole is available with brand name Rexulti (0.5 mg and 1mg of the drug per tablet; Otsuka America Pharmaceuticals Inc.) were purchased from the local market. Twenty tablets average weight was calculated and crushed into a fine powder. BXP equivalent to 25 mg was weighed, extracted with methanol by sonication for 40 min with intermittent shaking and makeup to volume with methanol in 250 ml volumetric flask (0.1 mg/mL) and centrifuged at 4000rpm for 10 min to collect the supernatant for further dilutions. The dilutions were made from this stock as per the requirement for method A, B, C and Dand the percentage recovery was calculated.

Precision and Accuracy: The precision and accuracy studies were performed as per the ICH guidelines. The absorbance of six replicates (0.01 µg/mL) for Method A and C (0.045 µg/mL) for Method B and D were noted and the % RSD was calculated.

Accuracy was evaluated as per the ICH guidelines by the percent recovery studies by the addition of 50%, 100%, and 150% of BXP solution extracted from the formulation was taken and the % RSD was calculated.

RESULTS: New spectrophotometric methods were developed for the determination of Brexpiprazole in pharmaceutical preparations. Brexpiprazole has shown absorption maxima (λ_{max}) at 214 nm in 0.1N HCl (Method A) and Sodium acetate buffer pH 4.5 (Method B) and the corresponding absorption spectra were shown in **Fig. 2** and **3**.

In method C, Brexpiprazole has shown zero crossing points at 214.86, 250.00, 255.64, 288.94, 322.87, 332.67 and 331.27 nm, with maxima at 334.49 nm and minima at 341.49 nm in **Fig. 4** and

therefore the amplitude has been taken against the concentration for the construction of the calibration curve. Similarly, in method D, Brexpiprazole has shown zero crossing point at 214.38, 250.39, 255.69, 273.94, 288.97, 322.41, 332.38, and 336.38 with maxima at 335.16 nm and minima at 341.15 nm in **Fig. 5** and therefore the amplitude has been taken against the concentration for the construction of the calibration curve.

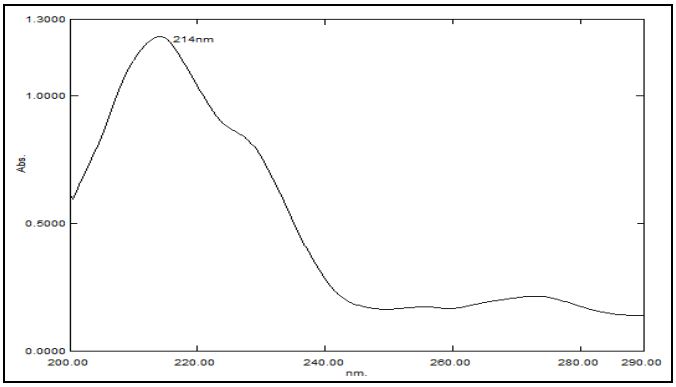

FIG. 2: ABSORPTION SPECTRUM OF BREXPIPRAZOLE (0.08 µg/mL) IN 0.1N HCl

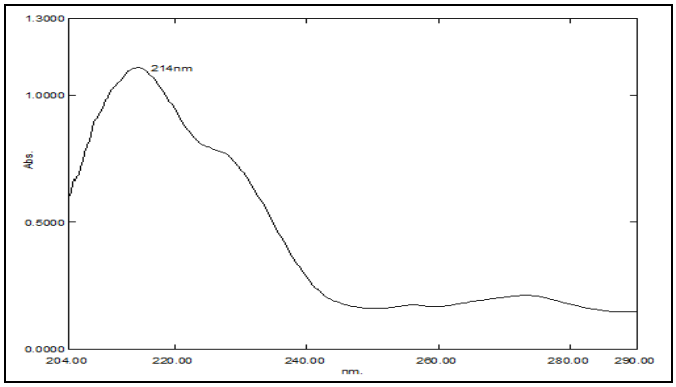

FIG. 3: ABSORPTION SPECTRUM OF BREXPIPRAZOLE (0.045 µg/mL) IN pH 4.5 ACETATE BUFFER

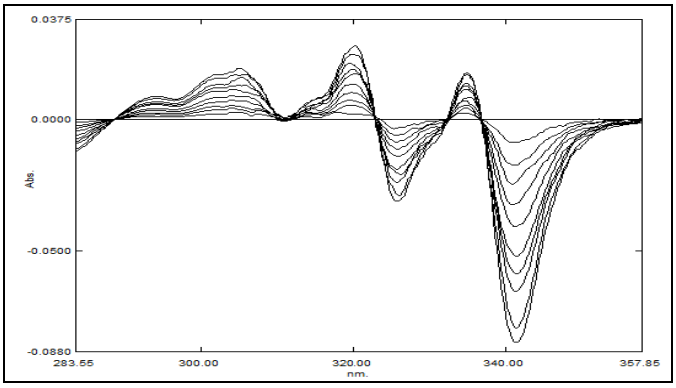

FIG. 4: OVERLAY FIRST DERIVATIVE SPECTRA (D_1) OF BREXPIPRAZOLE IN 0.1N HCl

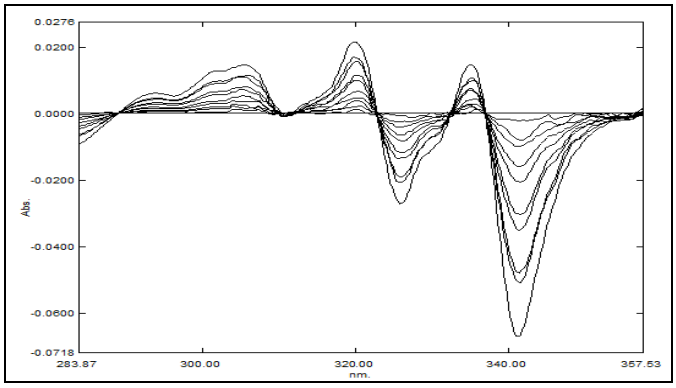

FIG. 5: OVERLAY FIRST DERIVATIVE SPECTRA (D_1) OF BREXPIPRAZOLE IN pH 4.5 ACETATE BUFFER

Beer's law was obeyed in the concentration range of 0.002-0.02 µg/mL for method A and Cand0.005-0.1 µg/mL for Method B and D. The linear regression equations were found to be y = 15.4517x + 0.0221, y = 23.4576x - 0.0235, y = 4.9605x + 0.0003 and y = 1.9990x - 0.0009 for method A, B, C and D respectively **Fig. 6** with correlation coefficient 0.9990, 0.9992, 0.9990 and 0.9991 respectively **Table 1**.

TABLE 1: OPTICAL CHARACTERISTICS OF BREXPIPRAZOLE

Parameters	Method			
	A	B	C	D
Beer-Lambert's limits (µg/mL)	0.002-0.02	0.005-0.1	0.002-0.02	0.005-0.1
λ_{max}/Amplitude range (nm)	214	214	339.49-341.49	335.16-341.15
Regression equation	15.4517x+0.0221	23.4576x-0.0235	4.9605x+0.003	1.9990x-0.0009
Slope	15.4517	23.4576	4.9605	1.9990
Intercept	0.0221	0.0235	0.003	0.0009
Correlation coefficient	0.9990	0.9992	0.9990	0.9991
Sandells Sensitivity	$6.11*10^{-5}$µgcm^{-2}	$7.29*10^{-5}$µgcm^{-2}	$1.8*10^{-4}$µgcm^{-2}	$5.00*10^{-4}$µgcm^{-2}

The % RSD values in precision studies were found to be 0.12, 0.48, 0.24 and 0.65 for method A, B, C and D respectively (RSD <2%) indicating that the method is more precise. The % Recovery values **Table 2** were found to be 99.18%, 99.28%, 99.54% and 99.08% with RSD 0.19, 0.22, 0.43 and 0.54 for method A, B, C and D respectively (RSD <2%) indicating that the proposed methods can be applied for the determination of pharmaceutical formulations and the method is more accurate.

LOQ is defined as the lowest amount of analyte which can be detected. LOD was defined as the lowest amount of analyte which can be quantitatively determined. LOD and LOQ of the drug were calculated as per ICH guidelines. The limit of detection and limit of quantification was found to be 0.002 µg/ml and 0.006 µg/ml (Method A and C) and 0.03 µg/mL and 0.0099 µg/mL (Method B and D) respectively.

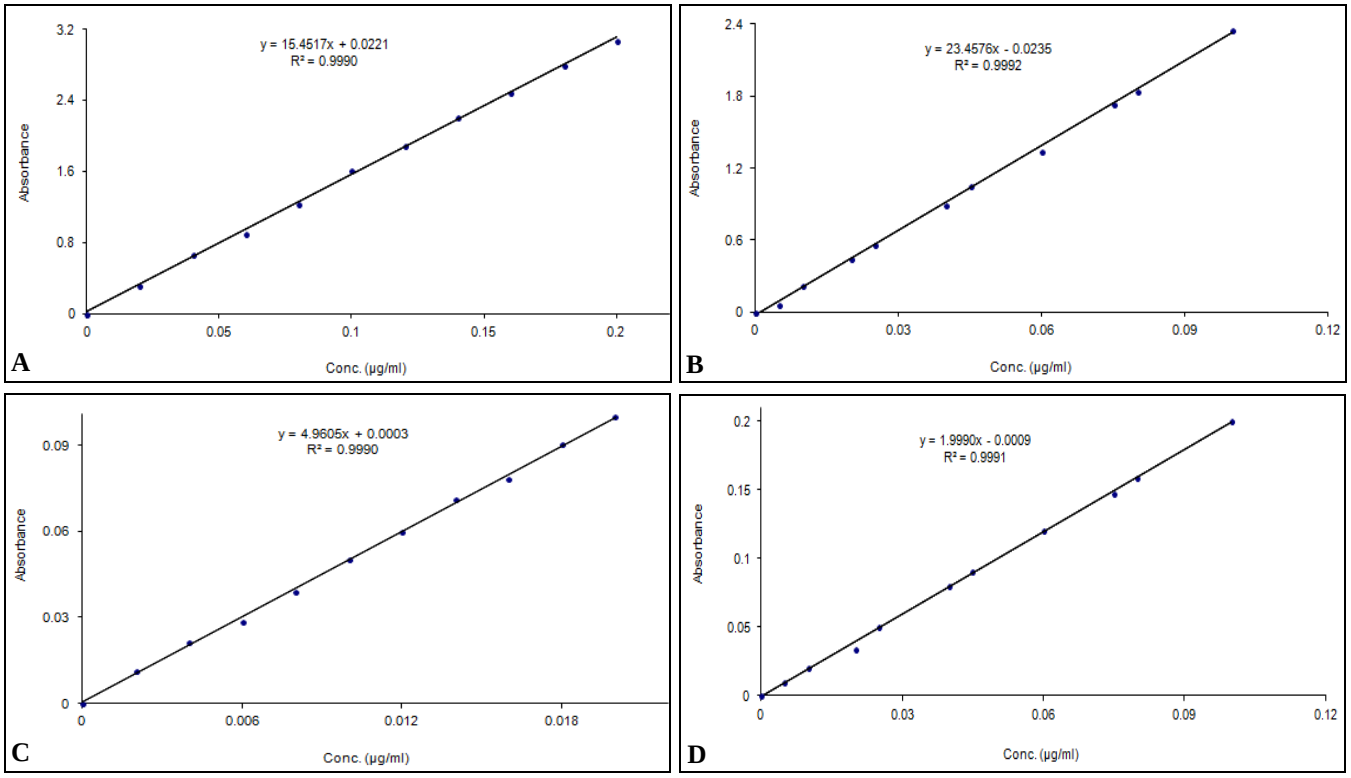

FIG. 6: CALIBRATION CURVES OF BREXPIPRAZOLE IN METHOD A, B, C AND D

TABLE 2: ASSAY OF A COMMERCIAL FORMULATION

Brand	Labeled Amount (mg)	*Amount obtained (mg)				% Recovery*			
		Method				Method			
		A	B	C	D	A	B	C	D
Rexulti	0.5	0.4959	0.4964	0.4977	0.4954	99.18	99.28	99.54	99.08
	1	0.9951	0.9901	0.9943	0.9982	99.51	99.01	99.43	99.82

*Each value is average of three determinations

DISCUSSION: The objective of the analytical procedure is to govern the validation characteristics which need to be evaluated. Typical validation characteristics which should be considered are listed below: Linearity, Accuracy, Precision, LOD, and LOQ. The linear regression data for the calibration plot were indicative of a good linear relationship between peak area and concentration over a wide range. The results have shown the best recoveries (98-102%) of the spiked drug at each added concentration, indicating that the method was accurate. The precision of Brexpiprazole was evaluated and the percentage relative standard deviation (% RSD) was found to be less than 2% which proves that the method was precise. And the limit of detection and limit of quantification was found to be 0.002 µg/ml and 0.006 µg/ml (Method A and C) and 0.03 µg/mL and 0.0099 µg/mL (Method B and D) respectively. Hence the proposed method was sensitive.

CONCLUSION: The present methods can be employed for the determination of Brexpiprazole in pharmaceutical formulations successfully and there is no interference of excipients during the study.

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CONFLICT OF INTEREST: There are no conflicts of interest.

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