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ORIENTAL JOURNAL OF CHEMISTRY
An International Open Free Access, Peer Reviewed Research Journal

www.orientjchem.org

ISSN: 0970-020 X
CODEN: OJCHEG
2017, Vol. 33, No.(6):
Pg. 2970-2982

Determination of Related Substances in Cabazitaxel Using Reverse Phase-liquid Chromatography Method

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http/:dx.doi.org/10.13005/ojc/330633

(Received: August 09, 2017; Accepted: September 17, 2017)

ABSTRACT

The present paper describes the reverse phase- high performance liquid chromatographic method and was validated as per ICH guidelines for the determination of related substances in Cabazitaxel. RP-Liquid chromatography technique was performed with pH 3.0 phosphate buffer and acetonitrile as mobile phase at a flow rate of 0.8 mL/min. on Waters 2489 UV 2695 pump, Waters 2998 PDA 2695 pump Software Empower[2] photodiode array detector using Zorbax SB C18 column with UV detection at 220 nm. Linearity was observed in the concentration range of Cabazitaxel LOQ–0.10% (R^2 = 0.9998), the concentration range of CBZM01 impurity 0.03–0.225% (R^2 = 0.9997), the concentration range of CBZM02 impurity 0.03–0.225% (R^2 = 0.9997), the concentration range of CBZN09 impurity 0.03–0.225% (R^2 = 0.9998). Limit of detection (%) and the limit of quantitation (ng/mL) were found to be CBZM01 impurity 0.002% and 73ng/mL, CBZM02 impurity 0.002 % and 71ng/mL, CBZN09 impurity 0.002 % and 6ng/mL and Cabazitaxel 0.002 % and 0.008 % respectively. The percent recovery was in good agreement with the labeled amount in the dosage forms and hence, the method is specific, simple, reproducible and accurate for the determination of Cabazitaxel.

Keywords: Cabazitaxel, Estimation of related substances, Liquid chromatography, Percent recovery and dosage forms.

INTRODUCTION

Cabazitaxel(CBT)(Figure 1.1) was a taxane group chemotherapy drug which is used to treat advanced hormone-refractory prostate cancer[1]. The IUPAC name of Cabazitaxel was 1S,2S,3R,4S,7R,9S,10S,12R,15S)-4-(Acetyloxy)-15-{[(2R,3S)-3-{[(tert-butoxy) carbonyl]amino}-2-hydroxy-3-phenylpropanoyl]oxy}-1-hydroxy-9,12-dimethoxy-10,14,17,17-tetramethyl-11-oxo-6-oxatetracyclo[11.3.1.03,10.04,7]heptadec-13-en-2-yl benzoate. CBZ was approved by EMA[2] and

USFDA[3] for the treatment metastatic prostate cancer [4-5] in combination with prednisone. Existing bibliographic survey reveals that very few analytical methods have been reported for the determination of Cabazitaxel using Spectrophotometry[6], HPLC[7-10], and LC-MS/MS[11-13]. Cabazitaxel is not official in any pharmacopoeia and there is no monograph containing methods to determine the Cabazitaxel. Literature survey gives the information on CBZ that there is not even a single method was reported for the determination of related substances in CBZ. Hence, the author was aimed to develop simple, fast and cost effective reverse phase-liquid chromatography method for the determination of related substances in Cabazitaxel and was validated. Chemical structures of related substances of Cabazitaxel such as CBZM01, CBZM02 and CBZM09 were presented in the Figure. 1.2-1.4.

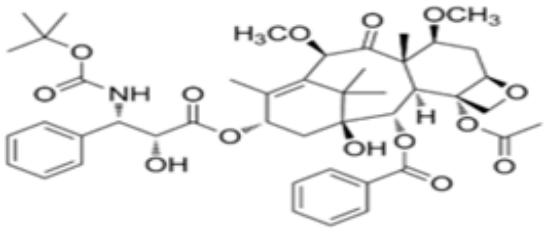

Fig. 1.1 Chemical Structure of Cabazitaxel (CBT)

Chemical structures of related substances:

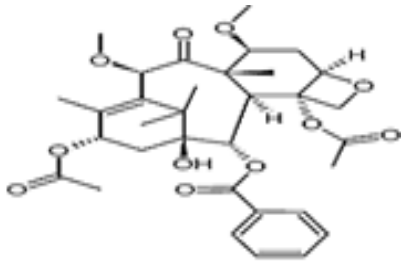

Fig. 1.2 Chemical Structure of 7, 10-dimethoxy-DAB (CBZM01)

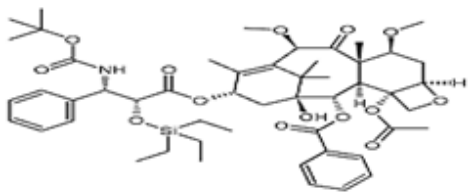

Fig. 1.3 Chemical Structure of TES-Cabazitaxel (CBZM02)

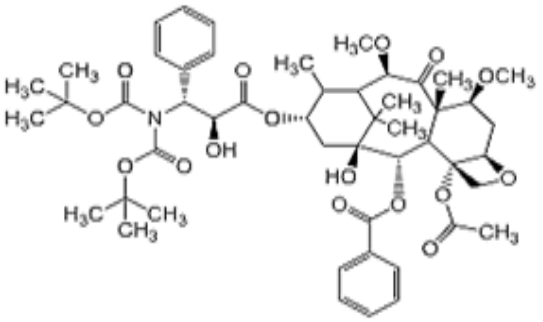

Fig 1.4 Chemical Structure of tigloyl-cabazitaxel (CBZN09),

EXPERIMENTAL

Instrumentation and chromatographic conditions

Chromatographic separation was achieved by using a Waters 2489 UV 2695 pump, Waters 2998 PDA 2695 pump Software Empower[2] photodiode array detector using Zorbax SB C18 (100mm×3.0mm, 1.8µm particle size) column with eluent-A: phosphate buffer eluent-B: acetonitrile as mobile phase at a flow rate of 0.8 mL/min. with UV detection at 220 nm. Column maintained at temperature 40ºC, sample temperature 10ºC. The overall run time was 22 min. and the flow rate was 0.8 mL/min. 3µL of sample was injected into the HPLC system.

Chemicals used

Orthophosphoric acid, Acetonitrile HPLC grade and water were obtained from Merck,India. All chemicals were of an analytical grade and used as received.

Preparation of mobile phase-A

1mL of H_3PO_4 is added to 1000mL of water and the solution is properly mixed. Filtered through 0.45µ membrane filter paper and degassed.

Preparation of mobile phase-B

Acetonitrile used as mobile phase-B.

Preparation of Diluent:

600mL Acetonitrile and 400mL water are mixed to prepare one litre of diluents and the solution is properly mixed.

METHOD VALIDATION

Specificity

Solutions of CBZM01 impurity, CBZM02 impurity, CBZN09 impurity, and Cabazitaxel each individually prepared and analysed. A spiked solution of each potential impurity to the Cabazitaxel drug substance and analyzed. Analysis was performed by PDA detector and peak purity was determined. Specificity chromatograms of

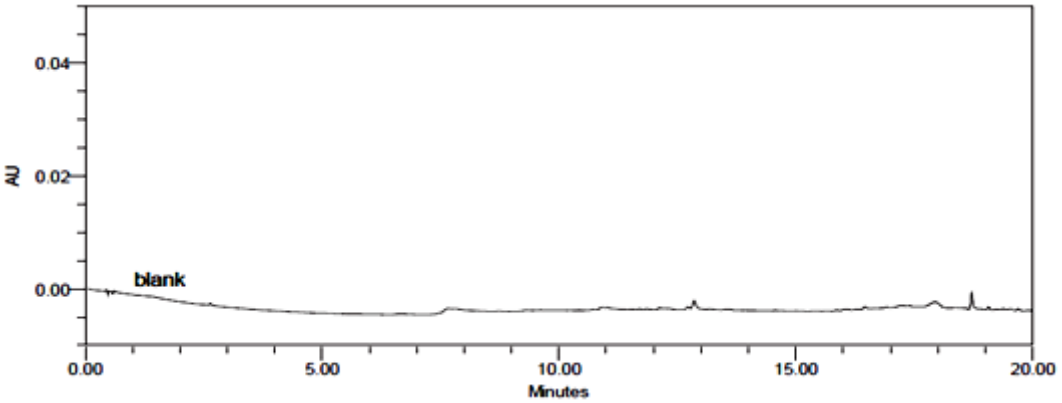

Fig. 1.5: Specificity chromatogram of blank solution

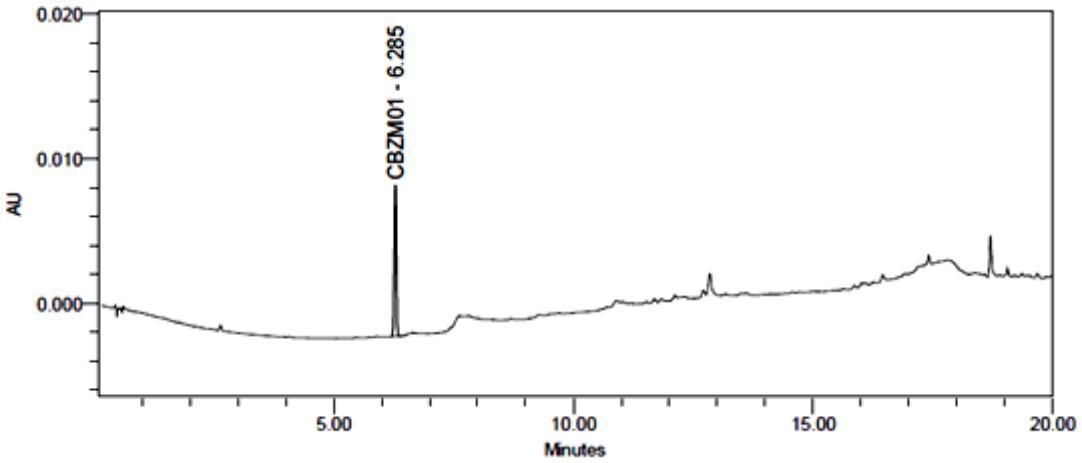

Fig. 1.6: Specificity chromatogram of CBZM01 solution

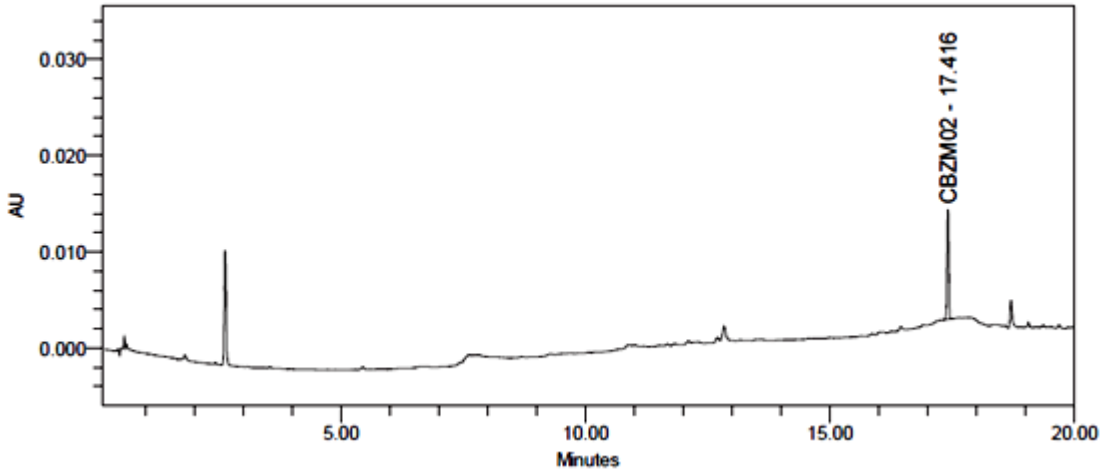

Fig. 1.7: Specificity chromatogram of CBZM02 solution

blank, CBZM01,CBZM02,CBZM09 and spiked solution were shown in Figure 1.5-1.9.

The above study reveals that all the known impurities of Cabazitaxel are adequately

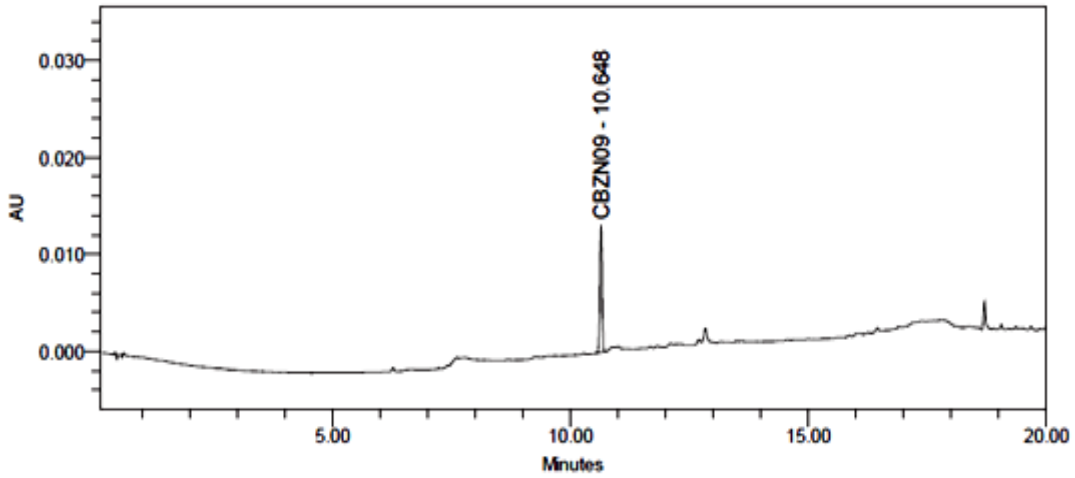

Fig. 1.8: Specificity chromatogram of CBZN09 solution

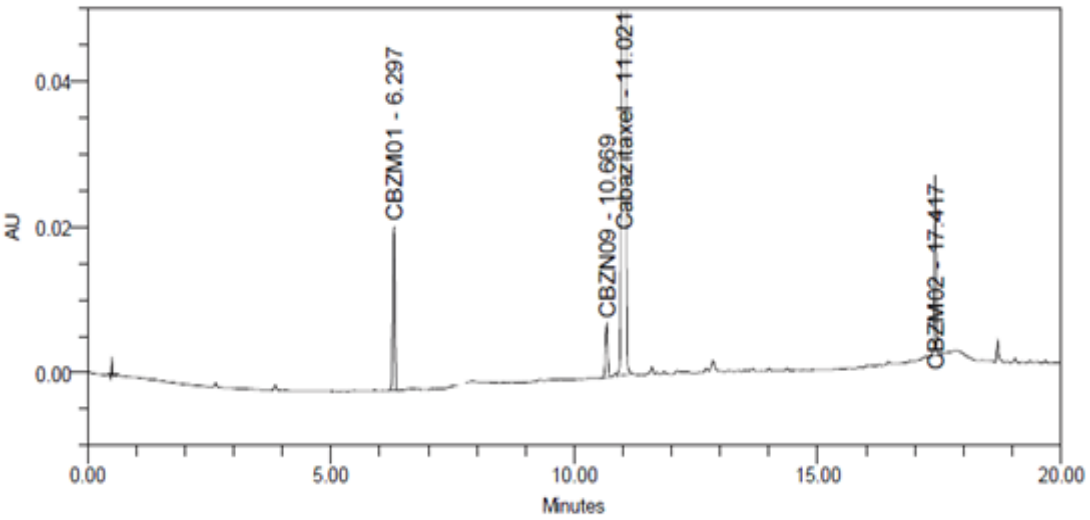

Fig. 1.9: Specificity chromatogram of spiked solution

Table 1.1: Summary of retention time, and relative retention time for known impurities

Peak Name	Retention Time	Relative retention time(RRT)
CBZM01	6.297	0.55
CBZM02	17.417	1.62
CBZN09	10.669	0.97
Cabazitaxel	11.021	1.00

resolved. Hence, the method is selective for the determination of related substances in Cabazitaxel. Retention time and relative retention time for known impurities were listed in the Table 1.1.

Table. 1.2: Summary of system suitability from standard solution

Retention times (min)			
CBZ	CBZM01	CBZM02	CBZN09
10.95	6.27	17.38	10.6
10.99	6.29	17.37	10.64
10.98	6.28	17.35	10.63
10.97	6.27	17.34	10.62
10.95	6.23	17.34	10.6
10.93	6.22	17.33	10.58
10.96	6.3	17.4	10.6
0.2	0.4	0.1	0.2

Table. 1.3: Summary of system suitability from standard solution

Sample	CBZ (%area)	CBZ (area)	RT(min)
Injection 1	99.609	3929399	10.81
Injection 2	99.611	3929019	10.85
Injection 3	99.567	3936249	10.84
Injection 4	99.612	3932766	10.82
Injection 5	99.603	3931681	10.85
Injection 6	99.609	3932064	10.86
Mean	99.66	3931863	10.8
RSD (%)	< 0.01	0.1	0.2

System precision

System suitability was performed by analyzing the reference solution six times. %RSD for replicate injections of each component from reference solution was calculated. Preparations of Cabazitaxel, CBZM01, CBZM02 and CBZN09 at concentrations of 0.15% of the nominal concentration of sample required by the method were analyzed in triplicate for each solution. Results of system suitability were presented in the Table 1.2-1.3.

Limit of Detection (LOD)

Detection limit of Cabazitaxel

Stock solution of CBZ standard at concentration level 1.0 mg/mL was prepared by weighing accurately about 25.029mg of CBZ standard and was transferred into a 25mL volumetric flask, dissolved in diluent and filled up with diluent to the volumetric mark (Table 1.4.). The stock solution was diluted 100times by dispensing 250µL into a 25mL volumetric flask, completed with diluent. This CBZ solution was further diluted into a 25mL volumetric flask, dosing 50µL. The final concentration (% level) of CBZ was (0.002 %). Details of CBZ detection limit was incorporated in the Table 1.5.

Detection limits of the specified impurities

The stock solutions of individual specified impurities at concentration level 1.0mg/mL were prepared (10.000 mg of specified impurity standard was weighed into a 10mL volumetric flask,

Table. 1.4: Stock solution preparation

	Sample Weight (mg)	Dilution (mL)	Potency (%)	Concentration (µg/mL)
CBZ stock	25.029	25	0.932	933.081

Table. 1.5: Evaluation of CBZ detection limit

S.No	Sample weight (mg)	Make up Volume (mL)	Dilution (µL)	Make up Volume	Dilution (µL)	Make up Volume (mL)	Concentration (%)	s/n
1	25.029	25	250	25	50	25	0.002	3.4
2	25.029	25	250	25	50	25	0.002	3.9
3	25.029	25	250	25	50	25	0.002	4.3
Mean			3.9					

Table. 1.6: Stock solutions preparation

	Sample Weight (mg)	Dilution (mL)	Concentration (mg/mL)
CBZM01_stock	9.301	10	0.9301
CBZN09_stock	9.399	10	0.9399
CBZM02_stock	9.370	10	0.9370

Table. 1.7: Evaluation of CBZM01 detection limit

S.No	Sample weight (mg)	Make up Volume (mL)	Dilution (µL)	Make up Volume	Dilution (µL)	Make up Volume (mL)	Concentration (%)	s/n
1	9.301	10	250	25	50	25	0.002	3.6
2	9.301	10	250	25	50	25	0.002	3.4
3	9.301	10	250	25	50	25	0.002	4.3
			Mean					3.9

Table. 1.8: Evaluation of CBZM02 detection limit

S.No	Sample weight (mg)	Make up Volume (mL)	Dilution (µL)	Make up Volume (mL)	Dilution (µL)	Make up Volume (mL)	Concentration (%)	s/n
1	9.3700	10	250	25	50	25	0.002	3.4
2	9.3700	10	250	25	50	25	0.002	3.4
3	9.3700	10	250	25	50	25	0.002	3.2
			Mean					3.4

Table. 1.9: Evaluation of CBZN09 detection limit

S.No	Sample weight (mg)	Make up Volume (mL)	Dilution (µL)	Make up Volume (mL)	Dilution (µL)	Make up Volume (mL)	Concentration (%)	s/n
1	9.399	10	250	25	50	25	0.002	4.3
2	9.399	10	250	25	50	25	0.002	3.9
3	9.399	10	250	25	50	25	0.002	4.3
			Mean					4.1

dissolved in diluent and filled up with diluent to the volumetric mark). (Table 1.6). The stock solution was diluted 100times by dispensing 250µL into a 25mL volumetric flask, completed with diluent. This solution was further diluted into 25mL volumetric flask, dosing 50µL. The final concentration (% level) of the specified impurity was 16.5-18.3ng/mL (0.002 %). The limit of detection values obtained for each impurity and Cabazitaxel are within the acceptance criteria. Detection limit evaluation of CBZ01, CBZ02 and CBZ09 were mentioned in the Table 1.7-1.9.

Limit of quantitation

Quantitation limit of CBZ

The stock solutions of individual specified impurities at concentration level 1.0mg/mL were prepared(about 10.000 mg of specified impurity standard was weighed into a 10mL volumetric flask, dissolved in diluent and filled up with diluent to the volumetric mark. The stock solution was diluted 100times by dispensing 250µL into a 25mL volumetric flask, completed with diluent. This solution was further diluted into 25mL volumetric flask, dosing 50µL. The final concentration (% level) of the specified impurity was 16.5-18.3ng/mL (0.002 %). Specified impurities mixed solution of the proper concentration was analysed three times. Results of CBZ quantitation limit was mentioned in the Table 2.0.

Table. 2.0: Evaluation of CBZ quantitation limit

S.No	Sample weight (mg)	Make up Volume (mL)	Dilution (µL)	Make up Volume (mL)	Dilution (µL)	Make up Volume (mL)	Concentration (%)	s/n
1	25.029	25	250	25	200	25	0.008	13.2
2	25.029	25	250	25	200	25	0.008	13.2
3	25.029	25	250	25	200	25	0.008	13.0
4	25.029	25	250	25	200	25	0.008	13.2
5	25.029	25	250	25	200	25	0.008	13.4
6	25.029	25	250	25	200	25	0.008	13.4
		Mean			13.2			

Quantitation limits of the specified impurities

Quantitation limit of the specified impurities (CBZM01, CBZN09 and CBZM02) was estimated

Table 2.1: Evaluation of CBZM01 quantitation limit

S.No	Sample weight (mg)	Make up Volume (mL)	Dilution (µL)	Make up Volume(mL)	Dilution (µL)	Make up Volume (mL)	Concentration (%)	s/n
1	9.301	10	250	25	200	25	0.008	14.8
2	9.301	10	250	25	200	25	0.008	14.8
3	9.301	10	250	25	200	25	0.008	14.1
4	9.301	10	250	25	200	25	0.008	14.5
5	9.301	10	250	25	200	25	0.008	14.5
6	9.301	10	250	25	200	25	0.008	14.5
		Mean						14.5

Table 2.2: Evaluation of CBZM02 quantitation limit

S.No	Sample weight (mg)	Make up Volume (mL)	Dilution (µL)	Make up Volume (mL)	Dilution (µL)	Make up Volume (mL)	Concentration (%)	s/n
1	9.370	10	250	25	200	25	0.008	13.0
2	9.370	10	250	25	200	25	0.008	13.4
3	9.370	10	250	25	200	25	0.008	13.4
4	9.370	10	250	25	200	25	0.008	13.4
5	9.370	10	250	25	200	25	0.008	14.1
6	9.370	10	250	25	200	25	0.008	13.0
			Mean					13.4

Table 2.3: Evaluation of CBZN09 quantitation limit

S.No	Sample weight (mg)	Make up Volume (mL)	Dilution (µL)	Make up Volume (mL)	Dilution (µL)	Make up Volume (mL)	Concentration (%)	s/n
1	9.399	10	250	25	190	25	0.007	13.0
2	9.399	10	250	25	190	25	0.007	13.2
3	9.399	10	250	25	190	25	0.007	13.2
4	9.399	10	250	25	190	25	0.007	13.0
5	9.399	10	250	25	190	25	0.007	13.6
6	9.399	10	250	25	190	25	0.007	13.9
			Mean					13.4

based on the detection limit results. Quantitation limit was verified by six injections of each specified impurity solution on the estimated concentration which would result in required S/N <8-15>. The limit of quantitation values obtained for each impurity and Cabazitaxel are within the acceptance criteria. Determined quantitation limit for CBZM01 is 73ng/mL (0.008 %), for CBZM02 is 71ng/mL (0.008 %) and for CBZN09 is 66ng/mL (0.007 %). The detailed results regarding quantitation limit of various impurities were listed in the Table 2.1-2.3.

Linearty and Range

The linearity is determined by injecting the solutions in duplicate containing known impurities and Cabazitaxel ranging from 0.05 to 1.13% and impurities ranging from 0.05% to 0.22% of the specified limit. Regression analysis was performed and correlation coefficient was determined (Table 2.4 and Figure 2.0). Response factor for each impurity was determined with respect to Cabazitaxel.

The linearity range as the range for determining the impurities were reported. The details of the results were presented in the Table 2.5-2.7 and Figure 2.1-2.3 show the line of best fit for peak area versus concentration for each impurity. The linearity results for Cabazitaxel and all the impurities in the specified concentration range are found satisfactory, with a correlation coefficient greater than 0.99.

Table 2.4: Linearity of Cabazitaxel

% Level of Cabazitaxel	Concentration (µg/mL)	Average peak area
30	0.280	1468
60	0.555	2530
80	0.742	3342
100	0.925	4063
120	1.119	4944
150	1.391	6023
220	2.052	8775
Slope	5514	
Intercept	166.7	
Correlation coefficient(R^2)	0.9998	

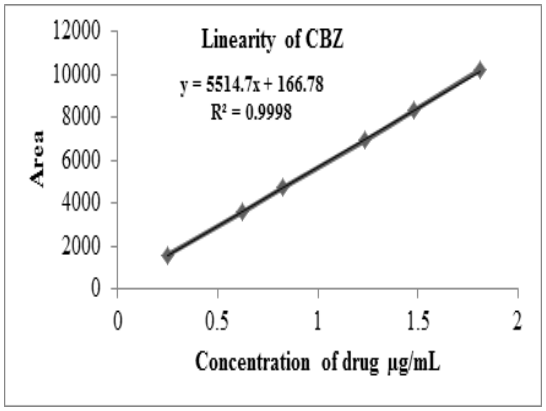

Fig. 2.0: Linearity graph of Cabazitaxel

Table 2.5: Linearty of CBZM01

% Level CBZM01	Concentration (µg/mL)	Average peak area
20	0.274	1148
50	0.696	3019
70	0.912	4020
100	1.373	5886
120	1.646	7094
150	2.005	8661

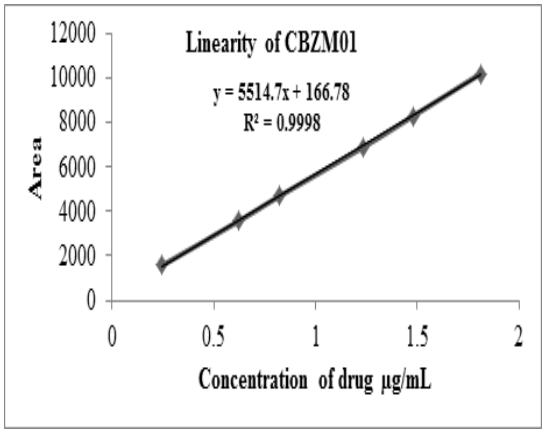

Fig. 2.1: Linearity graph of CBZM01

Table 2.6: Linearity of CBZM02

% Level of CBZM02	Concentration (µg/mL)	Average peak area
20	0.268	1081
50	0.681	2715
70	0.893	3527
100	1.345	5390
120	1.607	6290
150	1.964	7690

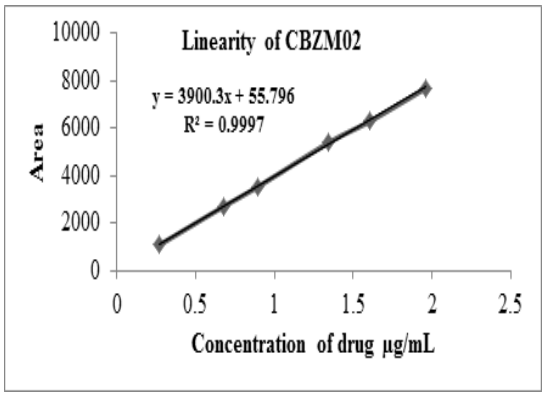

Fig. 2.2: Linearity graph of CBZM02

Table 2.7: Linearity of CBZN09

% Level of CBZN09	Concentration (µg/mL)	Average peak area
20	0.247	1578
50	0.625	3592
70	0.823	4698
100	1.234	6905
120	1.480	8312
150	1.811	10217

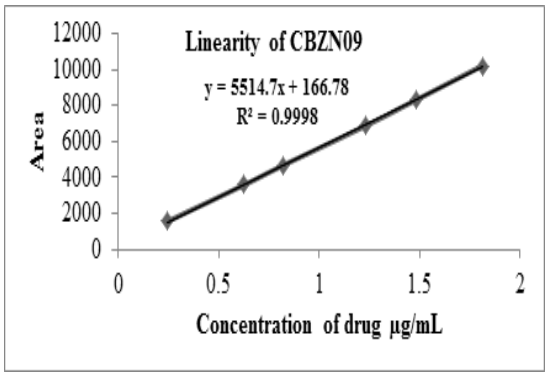

Fig. 2.3: Linearity graph of CBZN09

Accuracy

Analyses performed triple injections performed on 0.10%, 0.15% and 0.22% of the nominal concentration, respectively) were used. From linear regressions, theoretical contents corresponding to the peak areas obtained from the triple analyses and deviations of these values from the actual concentrations were calculated. The percentage recovery values obtained for each impurity are in the range of about 97.3-101.8, which are within the specified criteria. Summary of % recovery of CBZ and its impurities were listed in the Table 2.8-3.1.

Table 2.8: Summary of % recoveries for Cabazitaxel

% of Cabazitaxel	Theoretical conc. (mg/mL)	Measured conc. (mg/mL)	% Recovery	Average
LOQ	0.2798	0.2677	95.7	96.8
	0.2798	0.2692	96.2	
	0.2798	0.2641	94.4	
100%	0.9249	0.9157	99.0	99.1
	0.9249	0.9184	99.3	
	0.9249	0.9160	99.0	
150%	1.3907	1.3889	99.9	99.9
	1.3907	1.3848	99.6	
	1.3907	1.3957	100.4	
220%	2.0520	2.0534	100.1	100
	2.0520	2.0495	99.9	
	2.0520	2.0509	100.0	

Table 2.9: Summary of % recoveries for CBZM01

% of CBZM01	Theoretical conc. (mg/mL)	Measured conc. (mg/mL)	% Recovery	Average
LOQ	0.2743	0.2728	99.5	98.8
	0.2743	0.2733	99.6	
	0.2743	0.2712	98.9	
100%	1.3735	1.3630	99.2	99.1
	1.3735	1.3634	99.3	
	1.3735	1.3588	98.9	
150%	2.0054	2.0062	100.0	100.1
	2.0054	2.0104	100.3	
	2.0054	2.0027	99.9	

Table 3.0: Summary of % recoveries for CBZM02

% of CBZM02	Theoretical conc. (mg/mL)	Measured conc. (mg/mL)	% Recovery	Average
LOQ	0.2679	0.2606	97.3	97.3
	0.2679	0.2608	97.4	
	0.2679	0.2639	98.5	
100%	1.3447	1.3678	101.7	101.8
	1.3447	1.3678	101.7	
	1.3447	1.3691	101.8	
150%	1.9643	1.9575	99.7	99.3
	1.9643	1.9455	99.0	
	1.9643	1.9467	99.1	

Table 3.1: Summary of % recoveries for CBZN09

% of CBZN09	Theoretical conc. (mg/mL)	Measured conc. (mg/mL)	% Recovery	Average
LOQ	0.2467	0.2364	95.8	97.1
	0.2467	0.2352	95.3	
	0.2467	0.2359	95.6	
100%	1.2344	1.2219	99.0	98.1
	1.2344	1.2063	97.7	
	1.2344	1.2031	97.5	
150%	1.8107	1.8225	100.7	100.4
	1.8107	1.8120	100.1	
	1.8107	1.8187	100.4	

RESULTS AND DISCUSSION

A simple, economic, accurate and precise reverse phase liquid chromatography method was successfully developed using Zorbax SB C18 (100 mm×3.0 mm, 1.8µm particle size). Injection volume of 3µL is injected and eluted with the mobile phase eluent-A: pH 3.0 phosphate buffer and eluent-B: acetonitrile, which is pumped at a flow rate of 0.8 mL/min. Detection, was carried out at 220 nm.

For Selectivity, the chromatograms were recorded for standard and sample solutions of Cabazitaxel and its related substances. Selectivity studies reveal that the peak is well separated from each other. Therefore the method is selective for the determination of related substances in Cabazitaxel.

The limit of detection (LOD) and limit of quantitation (LOQ) for CBZM01 impurity 0.002% and 0.008%, CBZM02 impurity 0.002% and 0.008%, CBZN09 impurity 0.002% and 0.007% and Cabazitaxel 0.002% and 0.008% respectively. Using the optimized chromatographic conditions, the retention times (in min) of impurities were 6.297 for CBZM01 impurity, 17.417 for CBZM02, 10.669 for CBZN09 and 11.021 for Cabazitaxel. The linearity results for Cabazitaxel and all the impurities

in the specified concentration range are found satisfactory, with a correlation coefficient greater than 0.99.Calibration curve was plotted and correlation coefficient for Cabazitaxel and its impurities found to be 0.9997, 0.9997, 0.9998 and 0.9998 respectively.

The accuracy studies were shown as % recovery for Cabazitaxel and its impurities at specification level. The limit of % recovered shown is in the range of 90 and 110% and the results obtained were found to be within the limits. Hence the method was found to be accurate. The accuracy studies showed % recovery of the Cabazitaxel and its related substances in the range 97.3 to101.8 respectively.

For Precision studies six replicate injections were performed. %RSD was determined from the peak areas of Cabazitaxel and its impurities. The acceptance limit should be not more than 10, and the results were found to be within the acceptance limits.

CONCLUSIONS

Chromatographic method developed by the author for the determination of Cabazitaxel and its related substances was rapid, simple, sensitive, precise, and accurate. Therefore, the proposed method can be successfully applied for the routine analysis of the active pharmaceutical ingredients for assurance of its quality during its formulation.

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