

Eco Green RP-HPLC Method Development and Validation for Quantitative Estimation of Bortezomib in its Bulk and Pharmaceutical Formulation

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Abstract: An eco-green reversed-phase high-performance liquid chromatography (RP-HPLC) method was developed for the quantitative estimation of bortezomib in pharmaceutical dosage forms. Chromatographic separation was achieved using a n C18 reversed-phase column (e.g., 250 mm × 4.6 mm, 5 µm particle size) column with a mobile phase consisting Methanol: Water (0.05% OPA + 0.05% TEA) = 60: 40 v/v (column temperature 35C), delivered at a flow rate of 1 mL/min. Detection was carried out at a wavelength of 280 nm, and bortezomib was eluted at a retention time of 4.5 min. The method was designed following the principles of green analytical chemistry by employing environmentally benign solvents and minimizing solvent consumption and analysis time. The developed method was validated according to regulatory guidelines and showed acceptable linearity over the concentration range of 25-125 µg/mL, along with satisfactory accuracy, precision, specificity, and robustness. Owing to its simplicity, reliability, cost-effectiveness, and reduced environmental impact, the proposed eco-green RP-HPLC method is suitable for routine quality control analysis of bortezomib in pharmaceutical formulations.

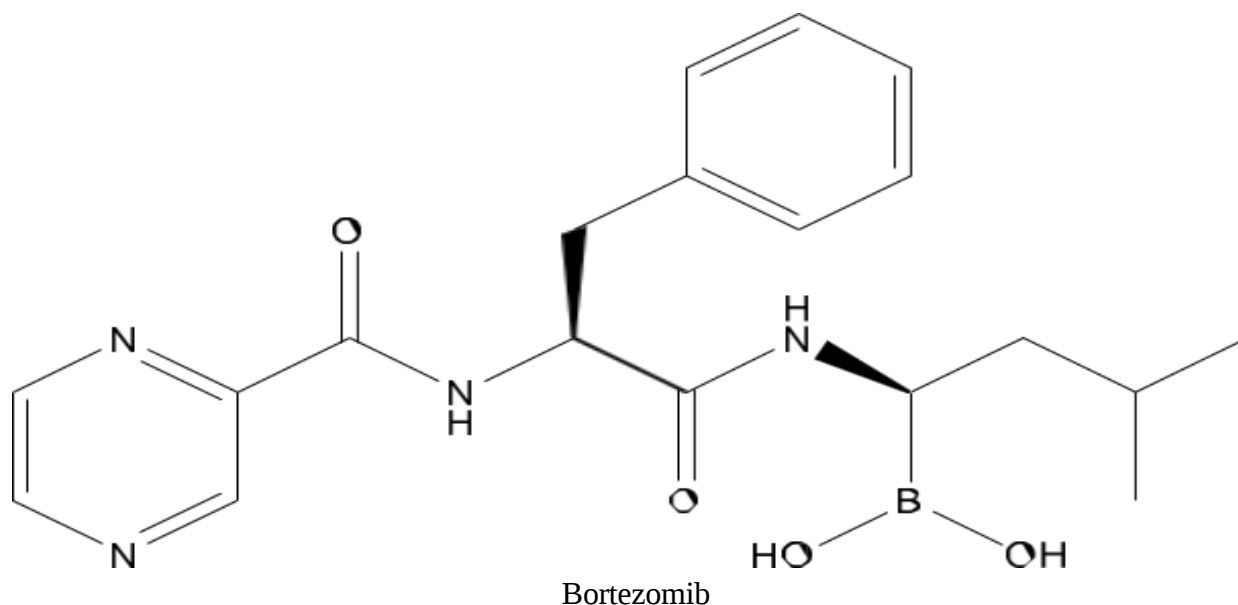
Index-terms: Bortezomib, RP-HPLC, Injection, Accuracy, Linearity and Precision.

I. INTRODUCTION

Bortezomib:

The chemical name of Bortezomib is [(1R)-3-Methyl-1-[[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)amino] propyl] amino] butyl] boronic Acid.

It has a molecular formula of C₁₉H₂₅BN₄O₄ with molecular weight 384.237 gm/mol.



II. MATERIALS AND METHODS

Materials

Drug Substance Bortezomib reference standard Brand name: Bortenat

Product name: Bortezomib Manufacturer: Local pharmacy

Instrumentation:

HPLC instrument with UV-visible detector Shimadzu LC-2040C

Software: Open lab

Column - Hypersil BDS C18 (250×4.6mm, 5µm)

UV-visible Spectrophotometer - SHIMADZU 1601 Software - UV probe, version- 2.34 Digital Analytical Balance- Sartorius

Ultra Sonicator - Labman Instruments

Controlled temperature water bath Hot air Oven – Kesar FTIR – SHIMADZU

Melting Point Apparatus – ANALAB Model: ThermoCal50

III. PREAPARTION OF SOLUTIONS:

Preparation of Standard Solutions:

Accurately 20 mg of Bortezomib standard was transferred into a 100 mL volumetric flask, dissolved in a suitable diluent (methanol or mobile phase), sonicated for 10 minutes, cooled to room temperature, and volume is adjusted up-to the mark. This gave a stock concentration of 200 µg/mL.

Preparation of working solution :

From the above stock solution, appropriate aliquots were pipetted into separate volumetric flasks and diluted with diluent to obtain working standard solutions in the desired concentration range of 25µg/ml to 125µg/ml

Preparation of sample solution :

The contents of one vial of bortezomib for injection (3.5 mg) were reconstituted with 3.5 mL of 0.9% sodium chloride (as per manufacturer's instructions) to give a concentration of 1 mg/mL. An appropriate aliquot was transferred to a volumetric flask and diluted with diluent to achieve a concentration within the linearity range. The solution was filtered through a 0.45 µm PVDF syringe filter, discarding the first few millilitres of filtrate.

IV. IDENTIFICATION & CHARACTERIZATION OF DRUG

The identification of taken standard API for experimental work had done for confirmation of its identity, standard quality and purity. The identification had done by taking IR and UV spectra, solubility study and melting point determination.

Solubility Analysis :

Solubility was carried out as per IP 2014.

1 gram of drug powder was dissolved in particular amount of different-different solvents and according to described in IP 2014 solubility table, solubility study was carried out.

Table:1 Solubility Table

Description Terms	Relative Quantities of solvent for 1 Parts of solute
Very soluble	Less than 1 part
Freely soluble	From 1 to 10 parts
Soluble	From 10 to 30 parts
Sparingly soluble	From 30 to 100 parts
Slightly soluble	From 300 to 1000 parts
Very slightly soluble	From 1000 to 10000 parts
Practically Insoluble	More than 10000 parts

Table: 2 Solubility Data

Solvent System	Approx. solubility
Water (pure)	~0.6 mg/mL very slightly solubility
Ethanol	=10 mg/mL very slightly solubility
Methanol	Slightly soluble
Acetonitrile (ACN)	Soluble at analytical concentrations (Sparingly soluble)
Chloroform	Soluble
Ethyl acetate	Soluble

Melting Point Determination:

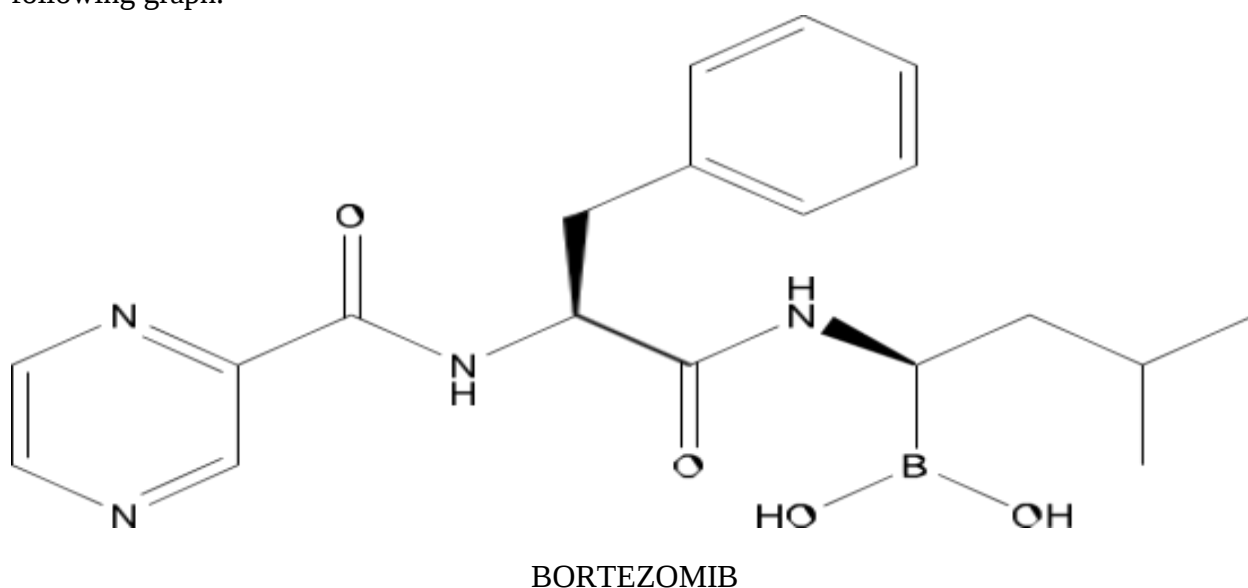
The melting point of Bortezomib were determined by using melting point apparatus. Melting point for both the drug was observed and recorded in following table

Table 3 Melting Point of Drugs

Sr.No.	APIs	Melting Point	
		Reported	Measured
1	Bortezomib	122-124°C	121-123°C

IR Spectra:

The IR Spectra of Bortezomib along with its functional group identification, were shown in the following graph.



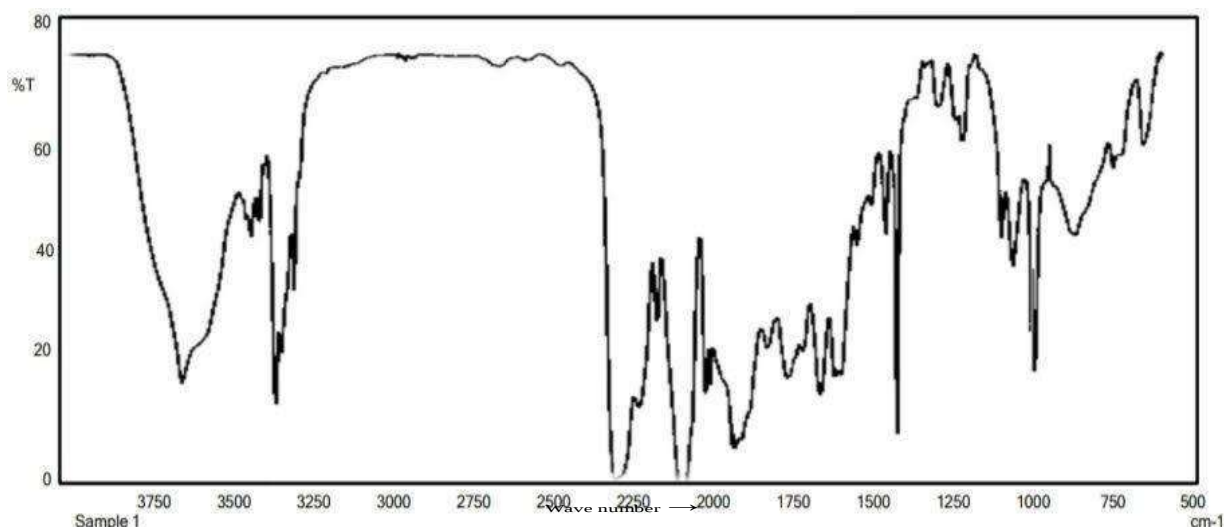


FIG 1: IR Spectra of Bortezomib

Table 4 IR Spectra Interpretation for Bortezomib

Wavenumber (cm ⁻¹)	Assignment
3387–3304	O–H stretching (boronic acid), N–H stretching (amide)
2953–2868	Aliphatic C–H stretching
1627	Amide C=O stretching
1455–1400	Aromatic C=C and C–H bending
1201–1150	B–O and C–N stretching
1020	C–O / B–O stretching
747–702	Aromatic C–H out-of-plane bending

Preparation of Mobile Phase

HPLC method was followed by isocratic elution technique. Mobile phase comprised of Methanol: Water (0.05% OPA + 0.05% TEA) = 60: 40 was selected because it elutes the drug's peak efficiently in short time with satisfactory resolution, tailing factor and theoretical plates. Mobile phase was prepared by following method:

- Transfer approximately 350 mL of HPLC-grade water into a clean beaker.
- Add 0.5 mL of ortho-phosphoric acid (OPA) to the water and mix well.
- Add 0.5 mL of triethylamine (TEA) to the same solution and mix thoroughly.
- Make up the aqueous phase volume to 400 mL with HPLC-grade water and mix well to obtain 0.05% OPA + 0.05% TEA solution.
- Measure 600 mL of HPLC-grade methanol using a measuring cylinder.
- Add the measured methanol slowly to the prepared aqueous solution while stirring to obtain

the final mobile phase composition (60:40 v/v).

- Mix the mobile phase thoroughly until a homogeneous solution is obtained.
- Filter the prepared mobile phase through a 0.45 μm membrane filter.
- Degas the mobile phase by sonication for 10–15 minutes or using an inline degasser before use.

Method validation Linearity and range

Preparation of Solution for linearity studies: For the purpose of linearity, accurately weighed amount of Bortezomib (10 mg) was taken into the volumetric flask (10 ml) and volume of the flask was raised to 10 ml with mobile phase to give stock solution containing 1000 $\mu\text{g/ml}$ of Bortezomib. Various aliquots from this stock solution were transferred to another 10 ml volumetric flask and volume was raised to the mark with mobile phase to give final solutions containing 25, 50, 75, 100 and 125 $\mu\text{g/ml}$ of Bortezomib, respectively.

Precision

Prepared standard working solution of mixtures having concentration of Bortezomib (75 $\mu\text{g/ml}$) was injected at volume of 20 μL into column by employing optimized chromatographic conditions. Each standard mixture was injected 6 time and peak area was monitored. Each concentration was monitored for repeatability by RSD.

Intra-day and Inter- day Precision

- Method precision was determined by performing intraday and inter day precision.
- Mixture that represents overall range (Bortezomib = 25, 75 and 125 $\mu\text{g/ml}$) was analyzed on same day at different time interval for intraday precision.
- Mixture that represents overall range (Bortezomib = 25, 75 and 125 $\mu\text{g/ml}$) was analyzed on different days for inter-day precision.

System Suitability Parameters

Solution of Bortezomib (50 $\mu\text{g/ml}$) was injected 3 times for determination of System suitability parameters which includes Retention time (Rt), Tailing factor (Tf), Resolution (Rs) and number of theoretical plates. System suitability parameters for selected concentration were determined by C.V.

Accuracy

Accuracy of the analytical method has been performed by spiking of sample with the standard. Spiking of the placebo was performed at 80, 100 and 120 % of the target concentration

Limit of detection and Limit of Quantification

The limit of detection (LOD) and the limit of quantification (LOQ) were calculated using the standard deviation of y-intercept of calibration curve. The limit of detection (LOD) and the limit

of quantification (LOQ):

LOQ = $10 \sigma/s$ and LOD = $3.3 \sigma/s$

Where, σ = the standard deviation of the response. S = the slope of the calibration curve

Robustness

Following parameters were altered one by one for determination of robustness of the method and their effect was observed by comparing with the standard preparation. Mobile phase flowrate (± 0.2 mL/min), optimized flowrate was 2.0 mL/min. change in wavelength. Bortezomib = 25 $\mu\text{g/mL}$ for each alteration were carried out and RSD was measured

Assay

A quantity of topical solution equivalent to about 100 mg of Bortezomib was weight accurately and it was transferred to a 100 ml volumetric flask. Mobile phase was added and the solution was sonicated for 10–15 minutes to extract the drug. The mixture was cooled and diluted up to volume with mobile phase. It was filtered through 0.45 μm membrane filter and diluted further to obtain $\sim 75 \mu\text{g/mL}$.

75 $\mu\text{g/mL}$ solution was injected three times under optimized conditions.

Result and Discussion Selection of Wavelength

To determine wavelength for measurement, standard spectra of Bortezomib was scanned between 200–400 nm against diluents. Absorbance maxima of Bortezomib detected at 280 nm.

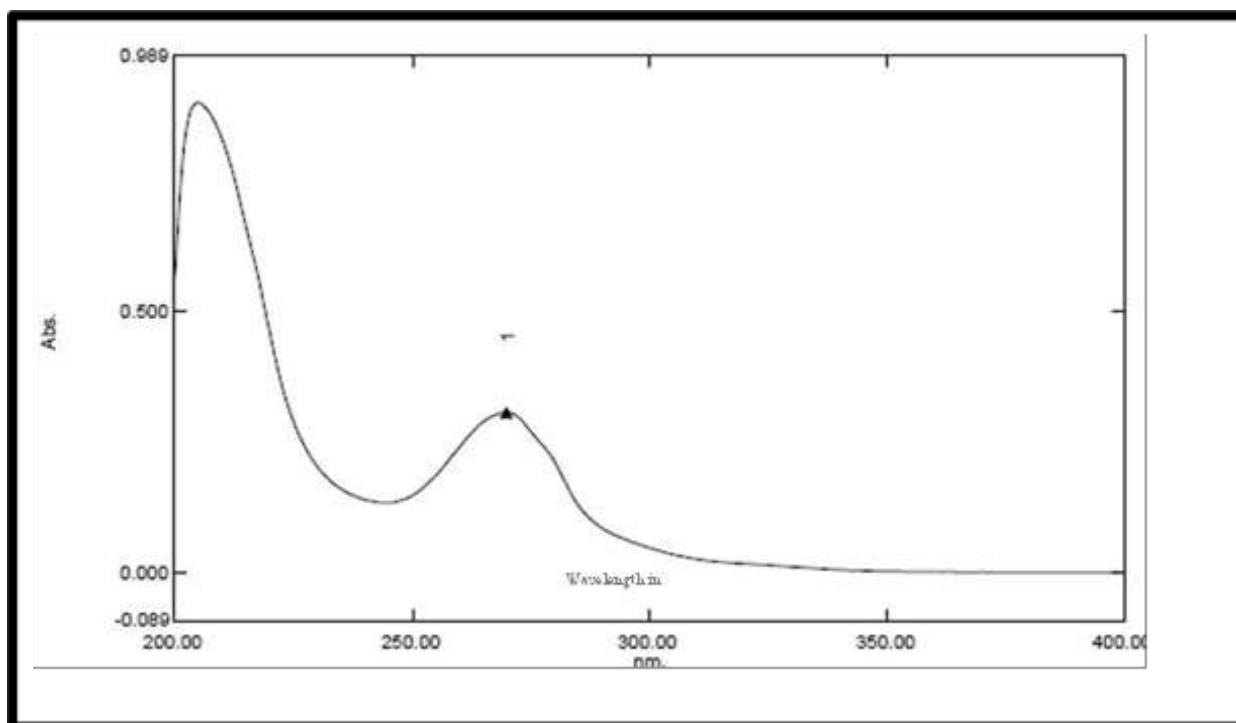


Fig 4: UV spectra of Bortezomib

Selection of Mobile phase Trail 1

Column: C-18 (id 4.6 x 150 mm, 5 μ m)

Mobile Phase: Methanol: Water + 0.1% OPA, (50:50%v/v)

Temperature: room temperature

Detection: 280 nm

Flow rate: 1 ml/min Run

Time: 10 minutes

Observations: fronting

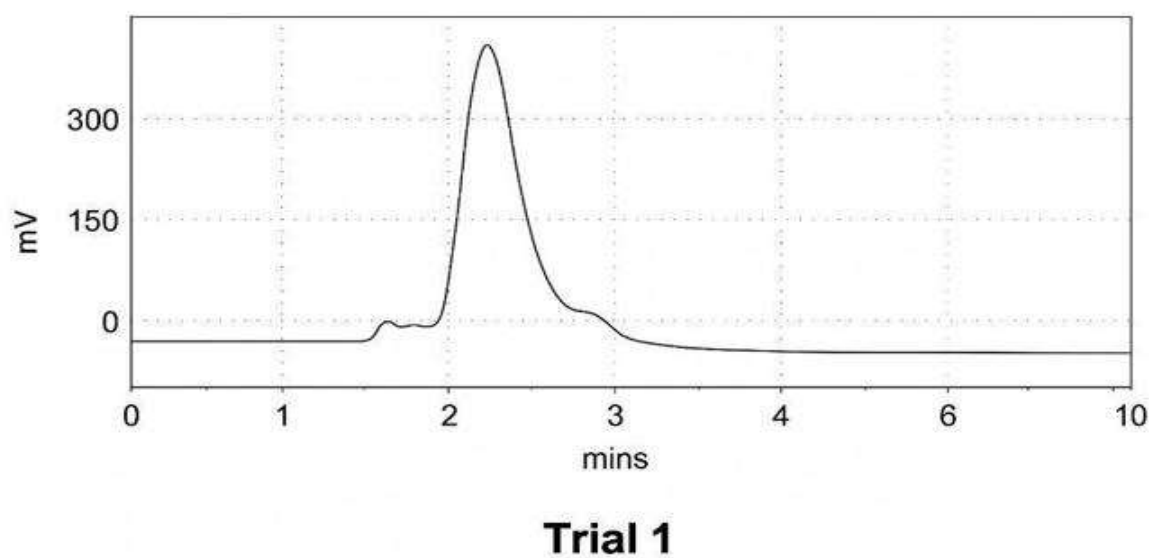


Fig 5 Trial 1 Chromatogram of BTZ in Methanol: Water + 0.1% OPA, (50:50%v/v)

Trial 2

Column: C-18 (id 4.6 x 150 mm, 5 μ m)

Mobile Phase: Methanol: water + 0.1% OPA, (60:40 %v/v)

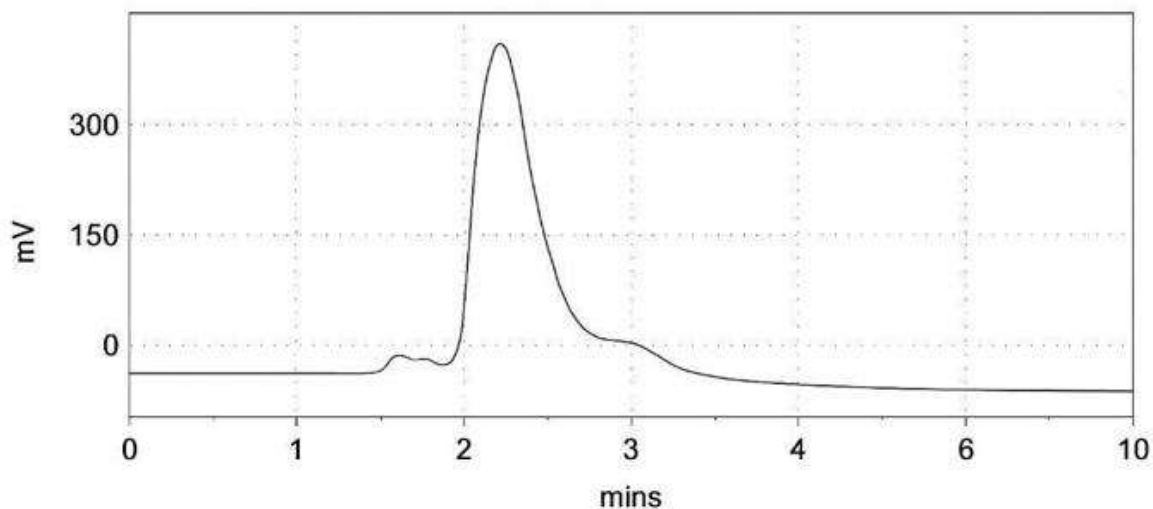
Temperature: 33C

Detection: 280 nm

Flow rate:1 ml/min

Run Time: 10 minutes

Observations: severe peak tailing.



Trial 2

FIG 6: Trial 2 – Chromatogram of BTZ in Methanol: water + 0.1% OPA, (60:40%v/v)

Trial 3

Column: C-18 (id 4.6 x 150 mm, 5 μ m).

Mobile Phase: Methanol: Water (0.1% OPA) (65:35 %v/v)

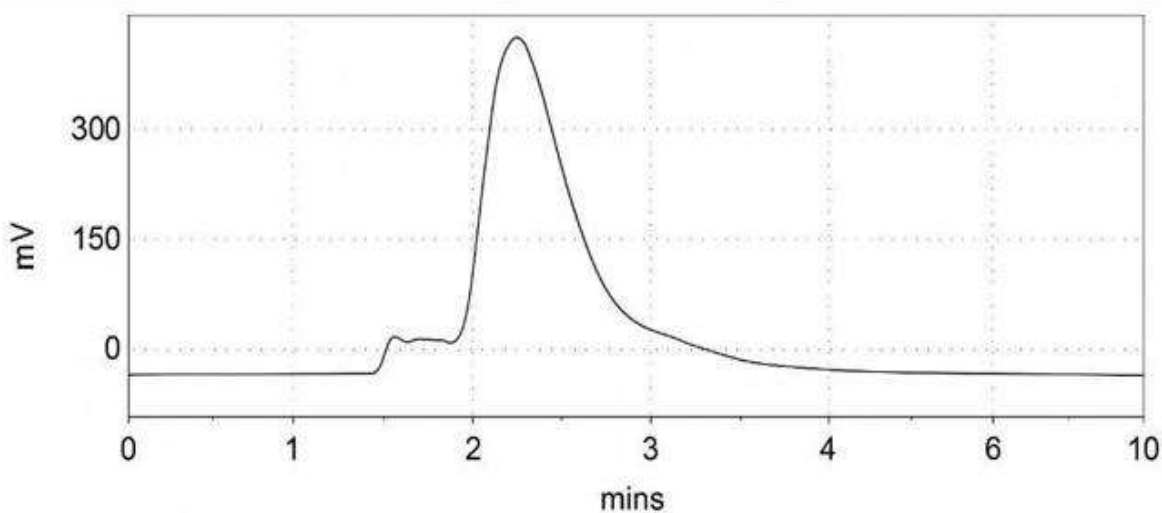
Temperature: 33C

Detection: 280 nm

Flow rate:1.2 ml/min

Run Time: 10 minutes

Observations: broad peak with tailing.



Trial 3

Fig 7 Trial 3 – Chromatogram of BTZ in Methanol: Water (0.1% OPA) (65:35 %v/v)

Trial 4

Column: C-18 (id 4.6 x 150 mm, 5 μ m)

Mobile Phase: Methanol: Water (0.05% OPA) (65:35 %v/v)

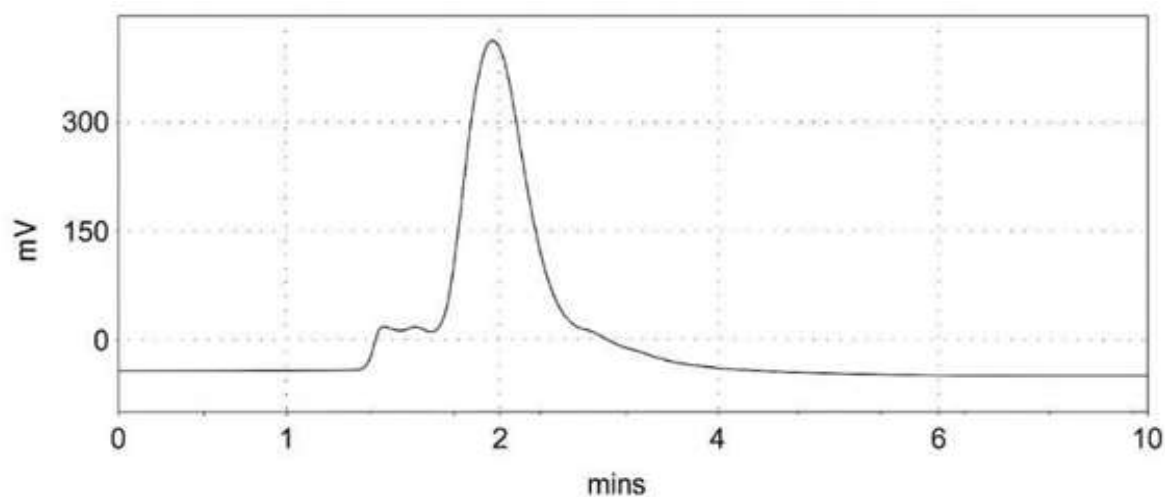
Temperature: 35C

Detection: 280 nm

Flow rate: 1ml/min

Run Time: 10 minutes

Observations: Broad, inefficient peak



Trial 4

Fig 8 Trial 4 – Chromatogram of BTZ in Methanol: Water (0.05% OPA) (65:35 %v/v)

Chromatographic conditions for optimized mobile phase trial

Stationary phase: C-18 (id 4.6 x 150 mm, 5 μ m)

Mobile Phase: Methanol: Water (0.05% OPA + 0.05% TEA) (60:40 %v/v)

Temperature: 35 °C

Detection: 280 nm

Flow rate: 1ml/min Run

Time: 10 minutes

Detector: UV detector

Injection volume: 20 μ l

Column Temperature: 40°C

Mode: Isocratic

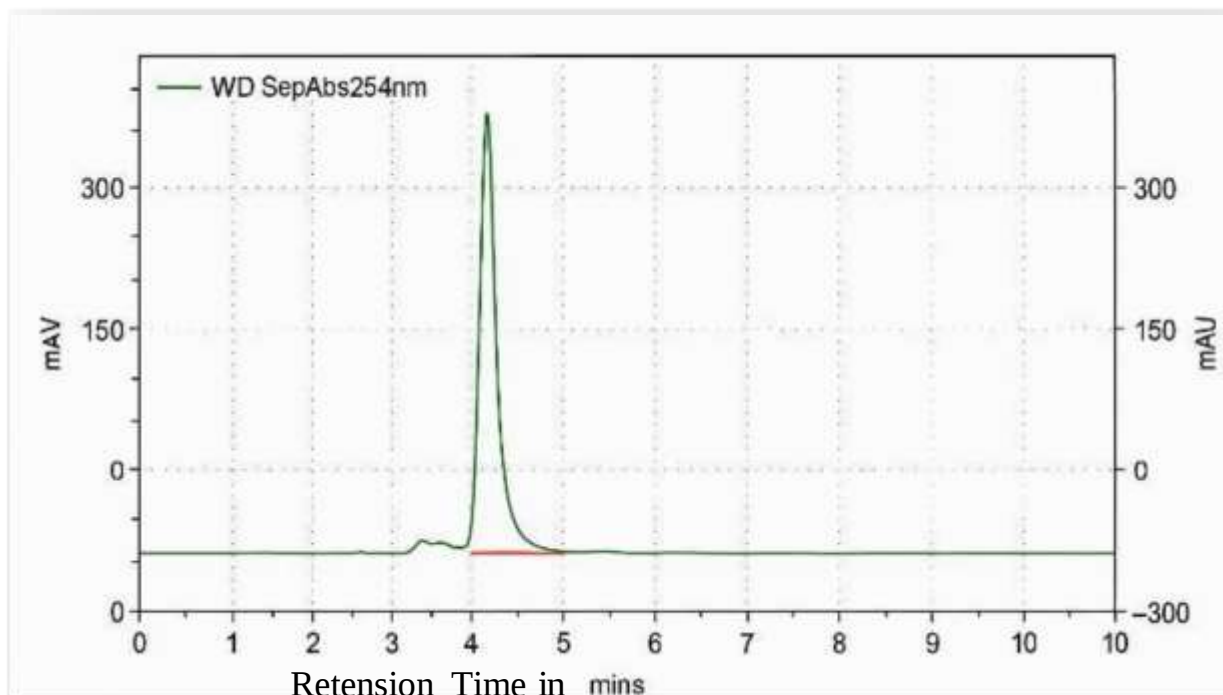


Fig 9: Optimized chromatogram of BTZ in Methanol: Water (0.05% OPA + 0.05% TEA) (60:40 %v/v)

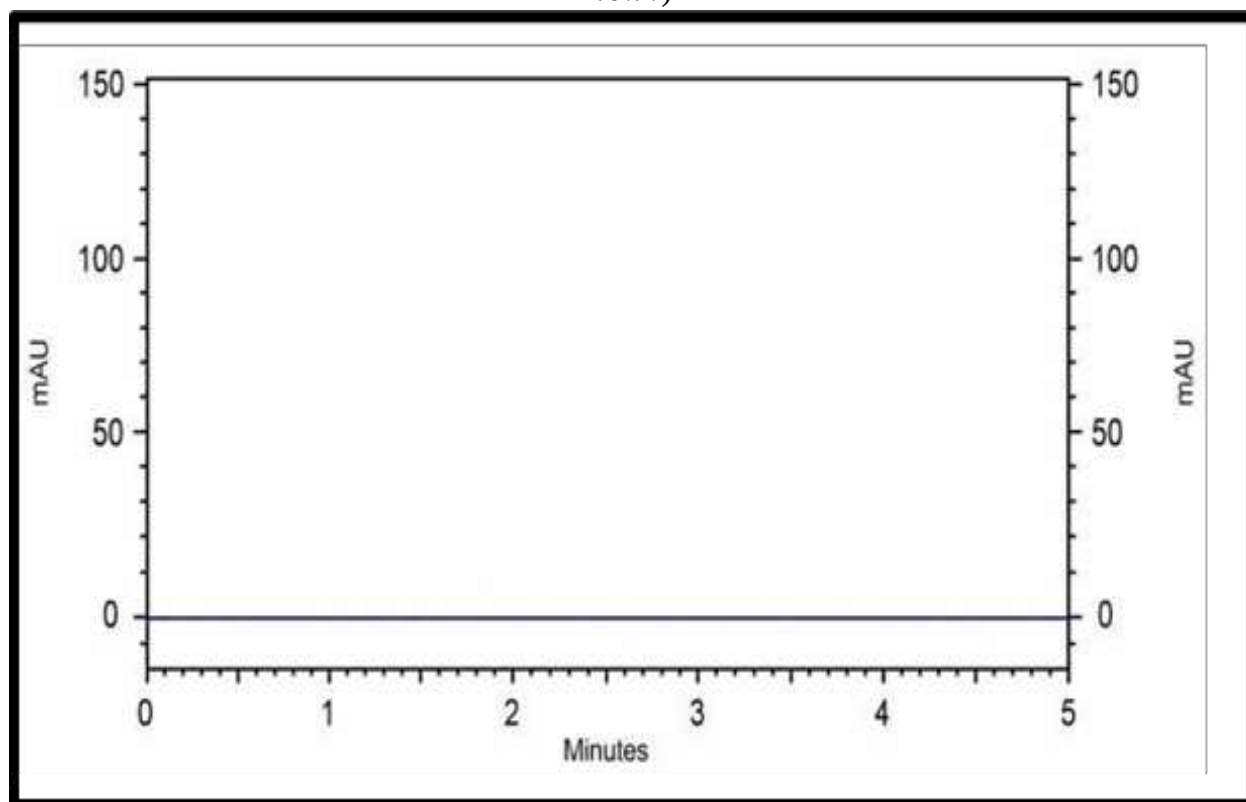


Fig 7.6: Chromatogram of blank in Methanol: Water (0.05% OPA + 0.05% TEA) (60:40 %v/v)

Method Validation Linearity

Preparation of Solution for linearity studies: For the purpose of linearity, accurately weighed amount of Bortezomib (10 mg) was taken into the volumetric flask (10 ml) and volume of the flask was raised to 10 ml with mobile phase to give stock solution containing 1000 µg/ml of Bortezomib. Various aliquots from this stock solution were transferred to another 10 ml volumetric flask and volume was raised to the mark with mobile phase to give final solutions containing 25, 50, 75, 100 and 125 µg/ml of Bortezomib, respectively.

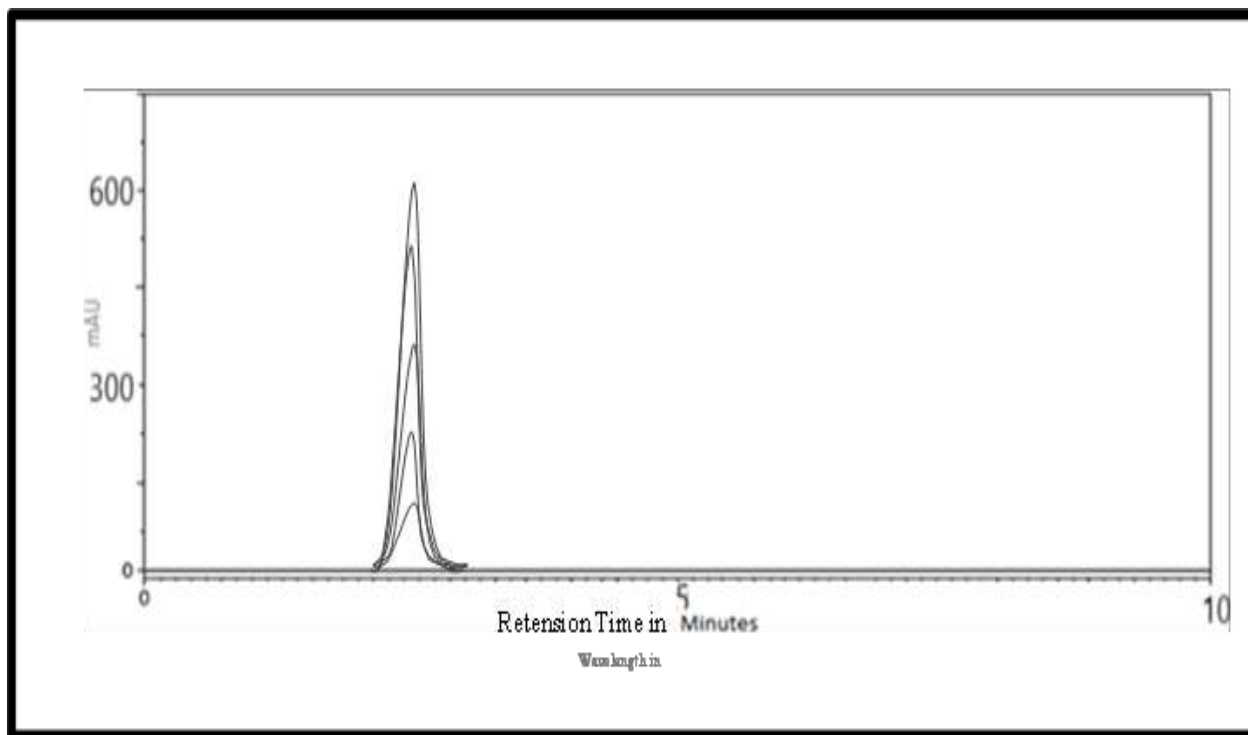


Fig 13: overlain spectra of Bortezomib

Table 7 Linearity data for Bortezomib

Concentration (%)	Peak area ratio	Statistical analysis
25	16044	Slope: 0.0015382 Intercept: 0.1235826 Correlation coefficient: 0.999
50	32145	
75	49009	
100	65050	
125	81263	

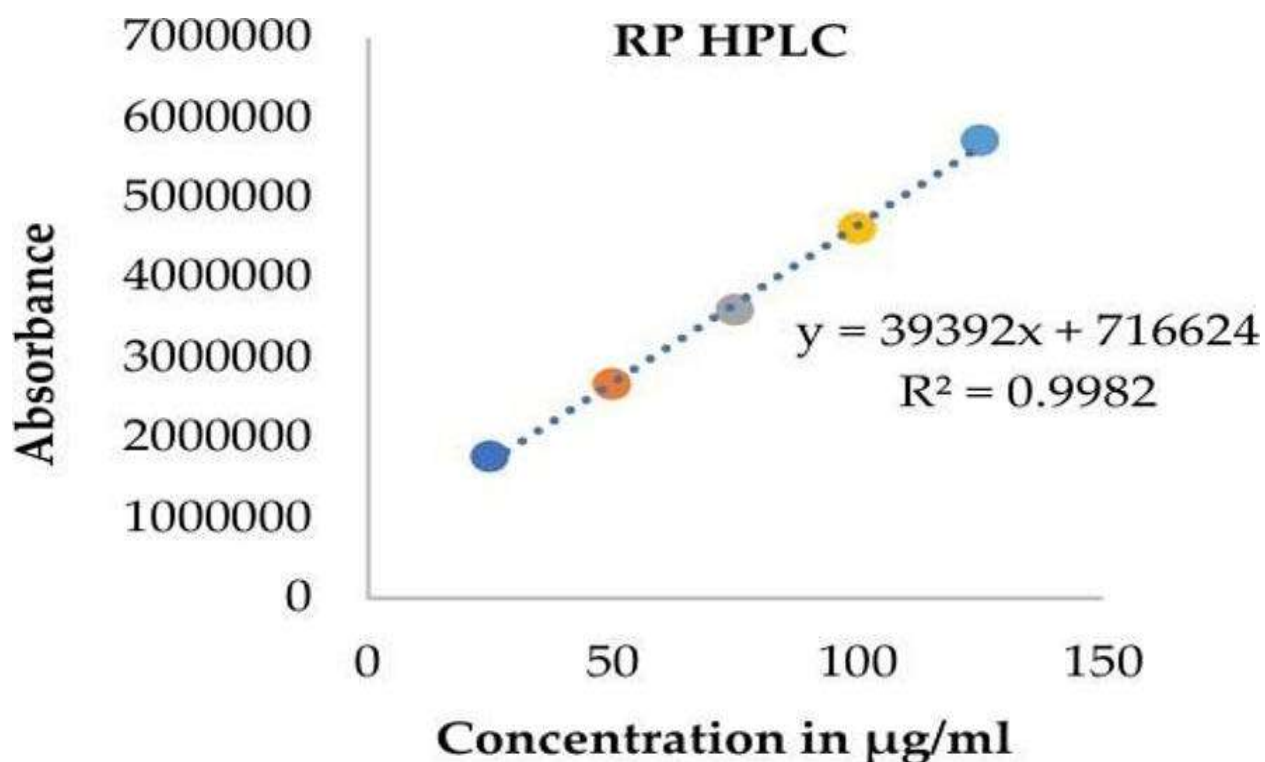


Fig 14: calibration curve

Precision Repeatability

The data for repeatability for Bortezomib is shown in table 7.2. The % R.S.D For Repeatability data was found to be 0.12 % for Bortezomib.

Table 9 2 Repeatability data for Bortezomib

Concentration ($\mu\text{g/ml}$)	Peak area	Mean $\pm$ SD	%RSD
75	49250	49009 $\pm$ 234	0.479
75	48810		
75	49190		
75	48950		
75	48790		
75	49070		

Inter-day precision

The data for interday precision for Bortezomib is shown in table 7.3. The % R.S.D for intraday precision was found to be 0.30-1.57 % for Bortezomib

Mcg/ml	25	50	75
	207689	381580	574389

	205567	384567	573321
	201345	381456	570934
MEAN	204867	382534.33	572881.33
± SD	3239.40	1861.44	1768.96
RSD	1.58	0.47	0.31

Intra -day precision

The data for intra-day precision for Bortezomib is shown in table 7.4. The % R.S.D for intraday precision was found to be 0.12-0.56 %.

Mcg/ml	25	50	75
	206589	395476	574489
	204378	395807	573209
	204879	392657	573278
MEAN	205282	394646.6667	573658.6667
± SD	1159.28	1731.03	719.91
RSD	0.56	0.43	0.12

Accuracy

Accuracy of the analytical method has been performed by spiking of sample with the standard. Spiking of the placebo was performed at 50, 100 and 150 % of the target concentration

Table 12 Recovery data

curacy level	Amount of drug in sample (µg)	Amount of drug added (µg)	Total amount of drug (µg)	Total amount of drug found (µg)	%Recovery
80%	75	60	135	135.03	100.02
100%	75	75	150	151.83	101.22

LOD and LOQ

The limit of detection (LOD) and Limit of Quantification (LOQ) was found to be as per below:

LOD (µg/ml)	LOQ (µg/ml)
1.66	2.43

Selectivity

There is no interference in the mixture.

Robustness

Following parameters were altered one by one for determination of robustness of the method and

their effect was observed by comparing with the standard preparation. Mobile phase flowrate (± 0.2 mL/min), optimized flowrate was 2.0 mL/min. change in wavelength. Bortezomib = 25 μ g/mL for each alteration were carried out and RSD was measured.

Table 16 Robustness data

Condition	%RSD	%Assay	%difference in %assay	Retention time (mins)
Change in the mobile phase composition (± 2 ml in organic phase)				
Normal condition	0.47	99.2	-	4
Change in organic phase (+2ml)	0.78	98.9	0.3	4.29
Change in organic phase (-2ml)	0.64	99.3	0.1	4.15
Change in detection wavelength (± 2 nm)				
Normal condition	0.47	99.2	-	4
+2nm	0.66	98.5	0.7	3.58
-2nm	0.59	99.5	0.3	4.17
Change in flow rate				

Analysis of marketed product

A quantity of topical solution equivalent to about 100 mg of Bortezomib was weight accurately and it was transferred to a 100 ml volumetric flask. Mobile phase was added and the solution was sonicated for 10–15 minutes to extract the drug. The mixture was cooled and diluted up to volume with mobile phase. It was filtered through 0.45 μ m membrane filter and diluted further to obtain ~ 100 μ g/mL.

Table 17 Analysis of marketed formulations

Sr no	Amount of drug in sample (μ g)	Amount of drug found (μ g)	Amount of drug obtained%
1	75	74.33	99.10
2	75	74.63	99.5
3	75	74.12	98.8

Validation parameters			
Parameter	Limit	Result	Conclusion
		Bortezomib	
Linearity and Range	R ² > 0.995	0.999 (25-125 μ g/mL)	Method was linear
Repeatability	RSD<2	0.479	Method was repeatable
LOD	-	1.66	Detectable peak
LOQ	-	2.43	Quantifiable peak

Intra-day Precision	RSD<2	0.30.-1.57	Method was precise
Inter-Day Precision	RSD<2	0.12-0.56	Method was precise
%Recovery	98-102%	100.02 – 100.83%	Method was accurate

V. SUMMARY OF METHOD VALIDATION

Optimized chromatographic Condition	
Stationary Phase	C-18 (id 4.6 x 150 mm, 5 µm)
Mobile Phase	Methanol: Water (0.05% OPA + 0.05% TEA) (60:40 %v/v)
Detection wave Length	280 nm
Flow rate	1 ml/minute
Run time	10 minutes
Retention Time	4.5 min

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