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Quality by Design Approach in HPLC Method Development and Validation of Iptacopn Pharmaceutical Dosage Form

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ABSTRACT
A simple, precise, and robust reverse-phase high-performance liquid chromatography (RP-HPLC) method was developed and validated for the estimation of Iptacopan in bulk and pharmaceutical dosage forms in accordance with ICH Q2(R1) guidelines. Chromatographic separation was achieved using an Inspire C18 column (150×4.6 mm, 5 µm) with a mobile phase comprising acetonitrile and trifluoroacetic acid (35:65 v/v) at a flow rate of 1.0 mL/min, and detection was carried out at 230 nm. The method demonstrated excellent system suitability, with a USP plate count of 4932.41 and a tailing factor of 1.22. Linearity was observed in the concentration range of 10–50µg/mL with a correlation coefficient (R^2) of 0.999. Precision studies showed %RSD values of 0.7% for repeatability and 0.5% for intermediate precision, indicating high reproducibility. Accuracy, evaluated through recovery studies, yielded a mean recovery of 98.10%, within the acceptable range of 98–102%. The limit of detection (LOD) and limit of quantification (LOQ) were found to be 0.57 µg/mL and 1.98 µg/mL, respectively. Robustness studies confirmed that small deliberate changes in flow rate and mobile phase composition did not significantly affect method performance. The validated method meets all ICH criteria and is suitable for routine quality control analysis of Iptacopan in bulk and dosage forms, offering high sensitivity, reproducibility, and cost-effectiveness.

Keywords: Iptacopan, RP-HPLC method development, Method validation, ICH Q2(R1), Trifluoroacetic acid, mobile phase, Linearity, Precision, Accuracy, Sensitivity, Limit of detection (LOD), Limit of quantification (LOQ), Robustness, System suitability, Quality control analysis, Pharmaceutical dosage forms.

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

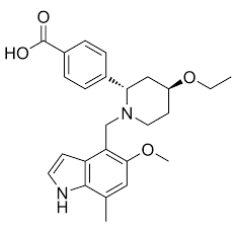

Fig.1: Iptacopn

Table.1: Iptacopn

Molecular Formula	C38H50N6O5
Molecular Weight	670.86 g/mol
IUPAC Name	(2S)-N-[(2S,3R)-4-[(3S)-3-(tert-butylcarbamoyl)-3-pyridin-2-ylpropyl]-3-hydroxy-1-phenylbutan-2-yl]-2-(quinolin-2-ylcarbonylamino)butanediamide
Chem Spider ID	4449

Density	1.23 g/cm3
Boiling Point	720.4°C
Vapour Pressure	1.15E-13 mmHg
Flash Point	386.4°C
Refractive Index	1.56
Polar Surface Area	173.2 Å2
LogP	4.7 (Octanol/Water)
Generic Name	Iptacopn
Brand Names	Invirase, Fortovase
Drug category	HIV Protease Inhibitor
Indications	Treatment of HIV-1 infection in combination with other antiretroviral agents
Pharmacology	Inhibition of HIV-1 protease, preventing viral replication
Potency	High potency against HIV-1 protease
Tolerability	Generally well-tolerated, but may cause gastrointestinal disturbances, diarrhea, nausea
Contraindications	Hypersensitivity to Iptacopn or any component of the formulation
Adverse Effects	Gastrointestinal disturbances, diarrhea, nausea, vomiting, abdominal pain
Availability	Prescription-only medication, available in oral capsules or tablets
Mechanism of Action	1. Binding to HIV Protease: Iptacopn binds to the active site of the HIV protease enzyme, which is essential for the maturation of viral particles. 2. Inhibition of Proteolytic Cleavage: By binding to the active site, saquinavir prevents the protease enzyme from cleaving viral polyprotein precursors into functional proteins, such as gag, pol, env. 3.Prevention of Viral Maturation: The inhibition of proteolytic cleavage prevents the maturation of viral particles, thereby inhibiting the replication of HIV. 4. Reduction of Viral Load: The reduction in viral replication leads to a decrease in viral load, which slows down the progression of HIV disease.

2. Materials and Methods

Table.2: List of Instrument Used

S.No	Instrument	Model
1	HPLC	WATERS, software: Empower, 2695 separation module.2487 UV detector.
2	UV/VIS	LABINDIA UV 3000+
3	pH meter	Adwa – AD 1020
4	Weighing machine	Afcoset ER-200A
5	Pipettes and Burettes	Borosil
6	Beakers	Borosil

Table 3: Chemicals used

S.No	Chemical	Brand
1	IPTACOPAN	Supplied by MSN LAB
2	KH_2PO_4	FINAR chemical LTD
3	Water and Methanol	Standard solutions Ltd
4	Acetonitrile	Standard solutions Ltd
5	HCl, H_2O_2, NaOH	MERCK

Optimized chromatographic conditions:

Instrument used : High performance liquid chromatography equipped with
Auto Sampler and PDA detector
Temperature : Ambient
Column : INSPIRE (150X4.6mm 5µm)
Mobile phase : (35: 65) ACN: Trifluoro acetic acid
Flow rate : 1ml/min
Wavelength : 230nm
Injection volume : 20 µl
Run time : 10 min.

Preparation of buffer and mobile phase:

Preparation of TFA pH 3:

To prepare TFA solution, by adding 1ml TFA in a 1000ml water. Adjust this solution to pH 3 by using acid / base based on the ph of the resulted solution.

Preparation of mobile phase:

Mix a mixture of above CAN 650ml (65%), 350 ml TFA (35%) and degas in ultrasonic water bath for 5 minutes. Filter through 0.45 µ filter under vacuum filtration.

Diluent Preparation:

Acetonitrile: TFA (65:35) ratio.

System Suitability:

Tailing factor for the peaks due to Iptacopan in Standard solution should not be more than 2.0

Theoretical plates for the Iptacopan peaks in Standard solution should not be less than 2000

Calculation: (For Iptacopan)

$$\%\ Assay = \frac{AT}{AS} * \frac{WS}{DS} * \frac{DT}{WT} * \frac{Average\ weight}{Label\ Claim} * \frac{P}{100} * 100$$

Where:

AT = average area counts of sample preparation. AS = average area counts of standard preparation. WS = Weight of working standard taken in mg.

P = Percentage purity of working standard LC = Label Claim mg/ml.

Results:

System Suitability Results:

- Tailing factor Obtained from the standard injection is 1.16
- Theoretical Plates Obtained from the standard injection is 3338

Validation parameters:

1. Assay:

Standard Solution Preparation:

Accurately weigh and transfer 20 mg of Iptacopan working standard into a 20 ml clean dry volumetric flask add Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution). Further pipette 0.3ml of the above stock solution into a 10ml volumetric flask and dilute up to the mark with Diluents.

Sample Solution Preparation:

Accurately weigh and transfer 20 mg of Iptacopan working standard into a 20 ml clean dry volumetric flask add Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution). Further pipette 0.3ml of the above stock solution into a 10ml volumetric flask and dilute up to the mark with Diluents.

Procedure: Inject 10 µL of the standard, sample into the chromatographic system and measure the areas for the Iptacopan peaks and calculate the % Assay by using the formulae.

2. Linearity:

Preparation of stock solution: Accurately weigh and transfer 20 mg of Iptacopan working standard into a 20 ml clean dry volumetric flask add Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)

Preparation of Level – I (10ppm of Iptacopan):

0.1 ml of stock solution has taken in 10ml of volumetric flask dilute up to the mark with Diluents.

Preparation of Level – II (20ppm of Iptacopan):

0.2 ml of stock solution has taken in 10ml of volumetric flask dilute up to the mark with Diluents.

Preparation of Level – III (30ppm of Iptacopan):

0.3 ml of stock solution has taken in 10ml of volumetric flask dilute up to the mark with Diluents.

Preparation of Level – IV (40ppm of Iptacopan):

0.4 ml of stock solution has taken in 10ml of volumetric flask dilute up to the mark with Diluents.

Preparation of Level – V (50ppm of Iptacopan):

0.5ml of stock solution has taken in 10ml of volumetric flask dilute up to the mark with Diluents. Procedure: Inject each level into the chromatographic system and measure the peak area. Plot a graph of peak area versus concentration (on X-axis concentration and on Y-axis Peak area) and calculate the correlation coefficient.

3. Precision:

Preparation of stock Solution:

Accurately weigh and transfer 20 mg of Iptacopan working standard into a 20 ml clean dry volumetric flask add Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution). Further pipette 0.3ml of the above stock solution into a 10ml volumetric flask and dilute up to the mark with Diluents.

Procedure:

The standard solution was injected for six times and measured the area for all five injections in HPLC. The %RSD for the area of five replicate injections was found to be within the specified limits.

4. Intermediate Precision/Ruggedness:

To evaluate the intermediate precision (also known as Ruggedness) of the method, Precision was performed on different day within the laboratory.

Preparation of stock solution:

Accurately weigh and transfer 20 mg of Iptacopan working standard into a 20 ml clean dry volumetric flask add Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution). Further pipette 0.3ml of the above stock solution into a 10ml volumetric flask and dilute up to the mark with Diluents.

Procedure:

The standard solution was injected for five times and measured the area for all Six injections in HPLC. The %RSD for the area of five replicate injections was found to be within the specified limits.

5. Accuracy:

For accuracy determination, three different concentrations were prepared separately i.e. 50%, 100% and 150% for the analyte and chromatograms are recorded for the same.

Preparation of Standard stock solution:

Accurately weigh and transfer 20 mg of Iptacopan working standard into a 20 ml clean dry volumetric flask add Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution). Further pipette 0.3ml of the above stock solution into a 10ml volumetric flask and dilute up to the mark with Diluents.

Preparation Sample solutions:

For preparation of 50% solution (With respect to target Assay concentration): Accurately weigh and transfer 10 mg of Iptacopan working standard into a 20 ml clean dry volumetric flask add Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution). Further pipette 0.3ml of the above stock solution into a 10ml volumetric flask and dilute up to the mark with Diluents.

For preparation of 100% solution (With respect to target Assay concentration): Accurately weigh and transfer 20 mg of Iptacopan working standard into a 20 ml clean dry volumetric flask add Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution). Further pipette 0.3ml of the above stock solution into a 10ml volumetric flask and dilute up to the mark with Diluents.

For preparation of 150% solution (With respect to target Assay concentration): Accurately weigh and transfer 30 mg of Iptacopan working standard into a 20 ml clean dry volumetric flask add Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)**.** Further pipette 0.3ml of the above stock solution into a 10ml volumetric flask and dilute up to the mark with Diluents.

Procedure:

Inject the standard solution, Accuracy -50%, Accuracy -100% and Accuracy -150% solutions. Calculate the Amount found and Amount added for Iptacopan and calculate the individual recovery and mean recovery values.

6. Limit of Detection:

Preparation of Iptacopan solution:

Preparation of 0.57µg/ml solution: Accurately weigh and transfer 20 mg of Iptacopan working standard into a 20 ml clean dry volumetric flask add Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)**.** Further pipette 0.3ml of the above stock solution into a 10ml volumetric flask and dilute up to the mark with Diluents. Further pipette 0.19ml of the above stock solution into a 10ml volumetric flask and dilute up to the mark with Diluents.

7. Limit of Quantification:

Preparation of Iptacopan solution:

Preparation of 1.98µg/ml solution:

Accurately weigh and transfer 20 mg of Iptacopan working standard into a 20 ml clean dry volumetric flask add Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution). Further pipette 0.3ml of the above stock solution into a 10ml volumetric flask and dilute up to the mark with Diluents. Further pipette 0.66ml of the above stock solution into a 10ml volumetric flask and dilute up to the mark with Diluents.

8. Robustness:

As part of the Robustness, deliberate change in the Flow rate, Mobile Phase composition, Temperature Variation was made to evaluate the impact on the method.

- The flow rate was varied at 0.8 ml/min to 1.2 ml/min.
- Standard solution 30 µg/ml of Iptacopan prepared and analyzed using the varied flow rates along with method flow rate.
- The Organic composition in the Mobile phase was varied from 58.5% to 71.5%

Standard solution 30 µg/ml of Iptacopan was prepared and analyzed using the varied Mobile phase composition along with the actual mobile phase composition in the method.

Table 4: Development by QBD Optimization

		Factor 1	Factor 2	Factor 3	Response 1	Response 2
Std	Run	A: Mobile Phase Ratio	B: Buffer PH	C: Flow Rate	Retention time mins	tailing factor
6	1	70.00	4.00	1.00	7.477	1670
1	2	50.00	3.00	1.10	3.694	95
10	3	60.00	3.00	1.20	11.347	1386
13	4	60.00	4.00	1.10	7.126	1403
5	5	50.00	4.00	1.00	13.487	1603
8	6	70.00	4.00	1.20	6.163	1615
15	7	60.00	4.00	1.10	7.126	1403
11	8	60.00	4.00	1.10	7.126	1403
7	9	50.00	4.00	1.20	10.596	1400
4	10	70.00	5.00	1.10	10.495	1229
2	11	70.00	3.00	1.10	9.962	1559
9	12	60.00	5.00	1.00	2.445	9
14	13	60.00	4.00	1.10	7.126	1403
12	14	60.00	4.00	1.10	7.126	1403
3	15	50.00	5.00	1.10	3.791	440
6	1	70.00	4.00	1.00	7.477	1670

Table 5: Software Information

Study type	**Respone surface**	**RUNS**	**15**
Initial design	Box-behnken	**BLOCKS**	No blocks
Design model	Quadratic		

Table 6: Factors

Factor	**Name**	**Units**	**Types**	**Minimum**	**Maxmium**	**Low coded**	**High coded**	**Mean**	**Std.dev**
A	**Mobile phase ratio**		Numeric	50.00	70.00	-1.000	1.000	60.000	7.303
B	**Buffer PH**		Numeric	3.00	5.00	-1.000	1.000	4.000	0.632
C	**Flow rate**	ml/min	Numeric	1.00	1.20	-1.000	1.000	1.100	0.063

Table 7: Responses

Response	**Name**	**Units**	**Observation**	**Minimum**	**Maximum**	**Mean**	**Std.dev**	**Ratio**
R1	Rt	Min	15	2.445	13.487	7.672	2.956	5.516
R2	Plate count		15	528.077	185.556	9.000	1670.000	1201.400

3. Results and Discussion

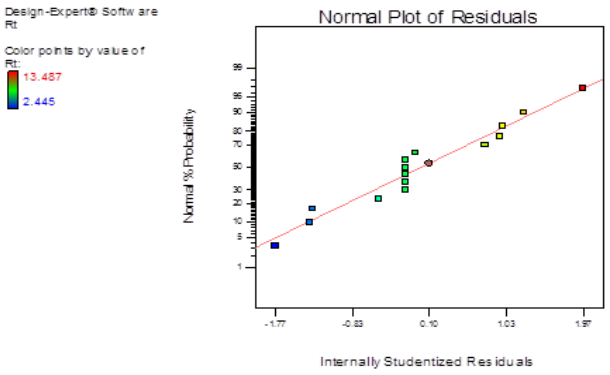

Fig.2: Normal plot of Residuals for Iptacopan

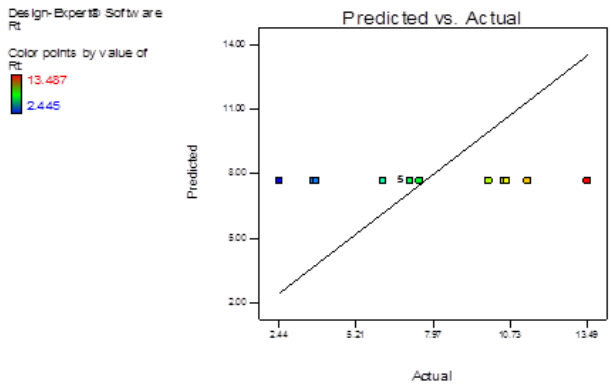

Fig.3: Predicted vs. Actual for Iptacopan

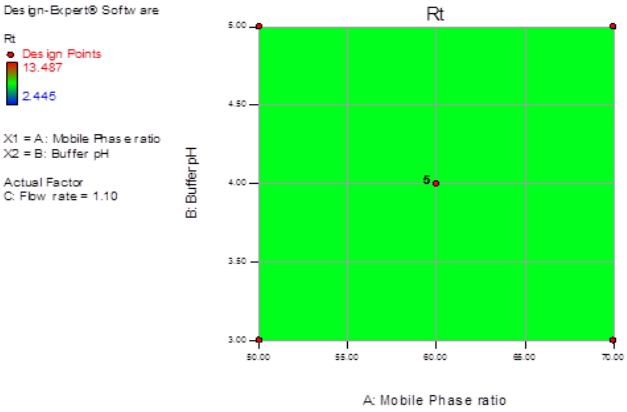

Fig.4: Retention time for Iptacopan

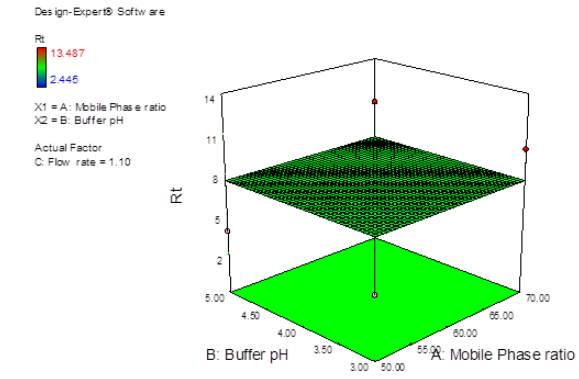

Fig.5: 3D Suface for Iptacopan

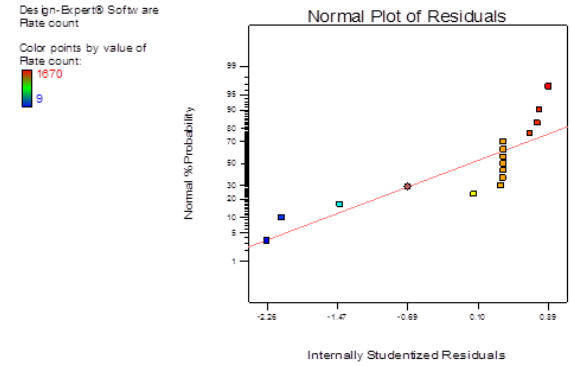

Fig.6: Normal plot of Residuals for Iptacopan

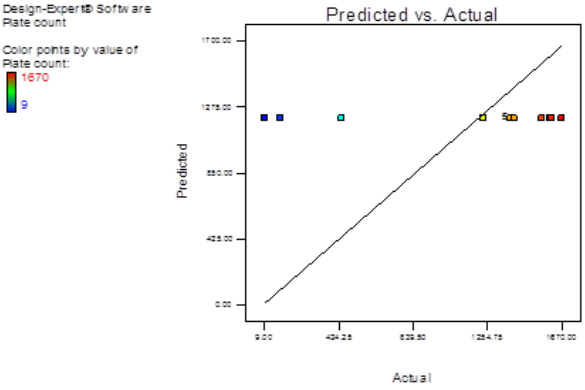

Fig.7: Predicted vs. Actial for Iptacopan

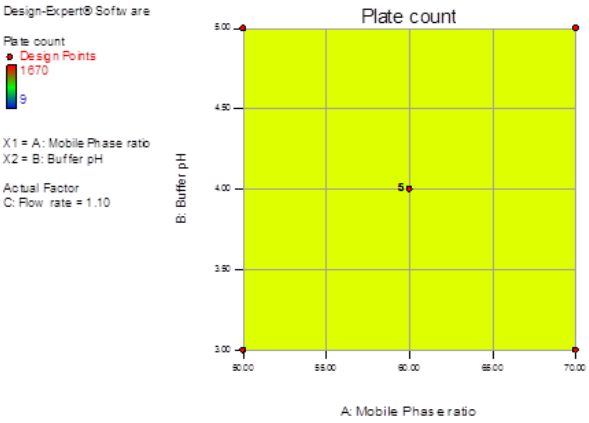

Fig.8: R tailing factor for Iptacopan

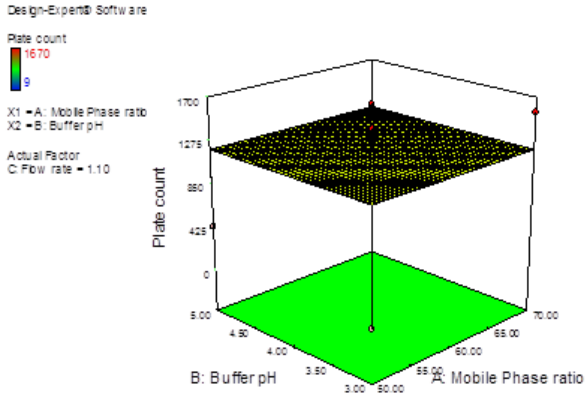

Fig.9: 3D Surface for Iptacopan

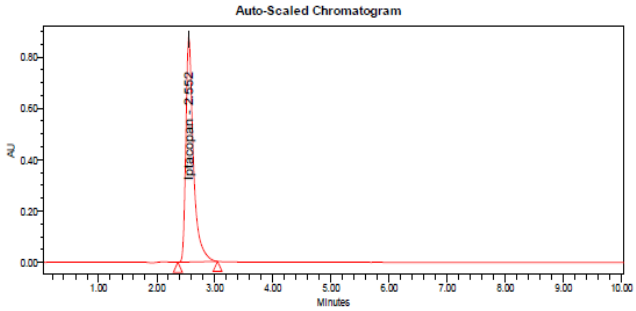

Fig.10: Chromatogram for system suitability

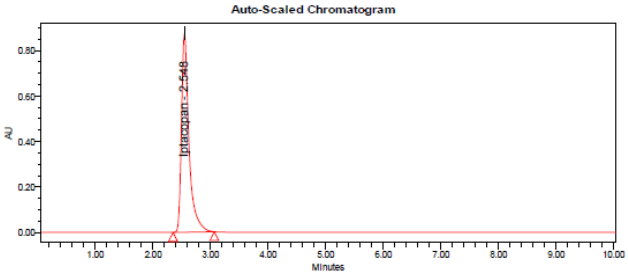

Fig.11: Chromatogram for Sample

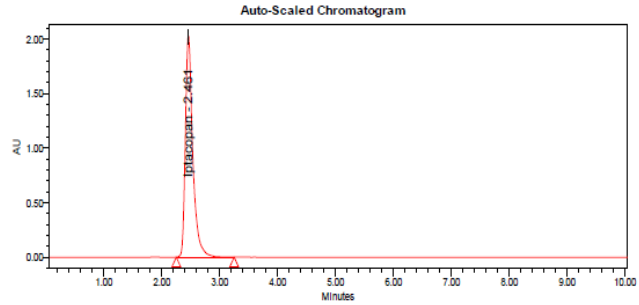

Fig.12: Chromatogram for linearity-5

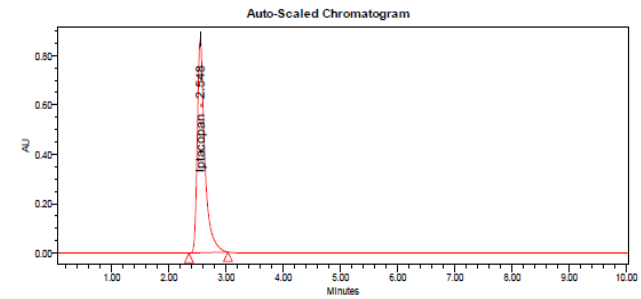

Fig.13: Chromatogram for Precision -6

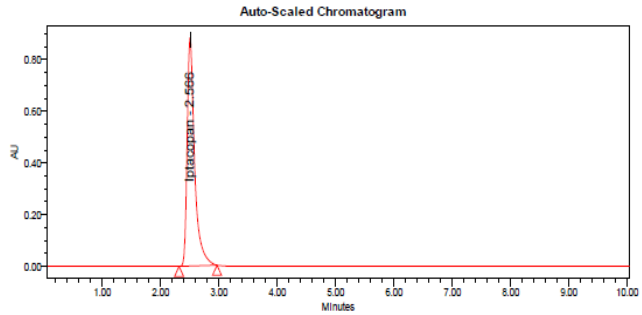

Fig.14: Chromatogram for ID Precision -6

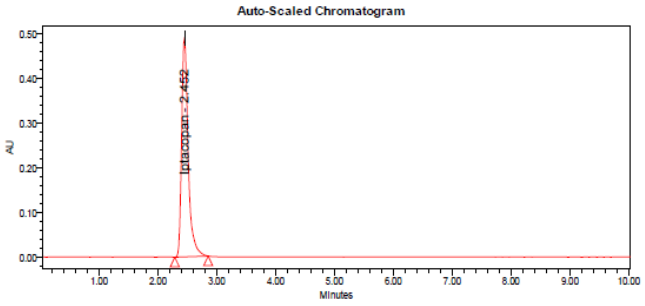

Fig.15: Chromatogram for Accuracy 50%-3

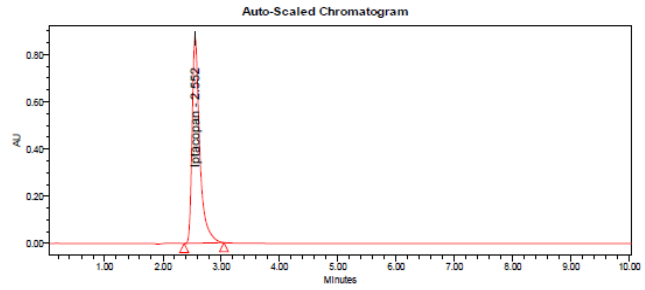

Fig.16: Chromatogram for Accuracy 100%-3

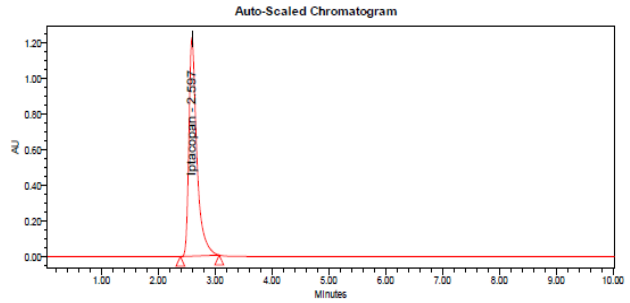

Fig.17: Chromatogram for Accuracy 150%-3

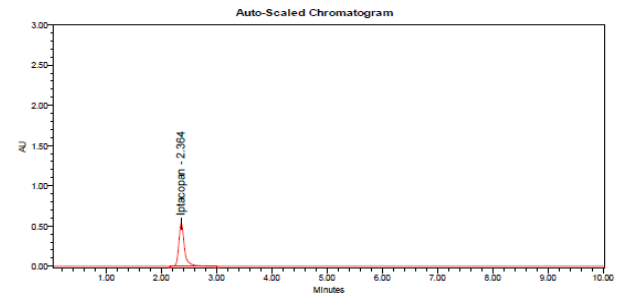

Fig.18: Chromatogram of Iptacopan showing LOD

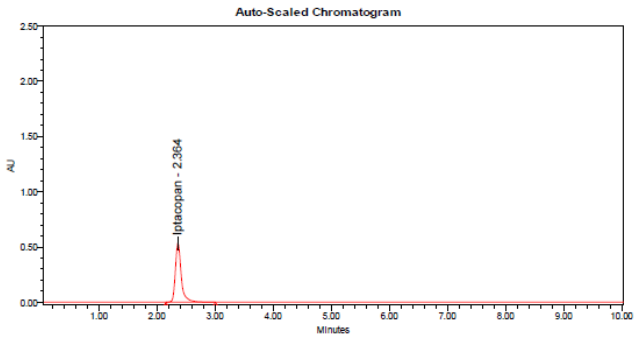

Fig.19: Chromatogram of Iptacopan showing LOQ

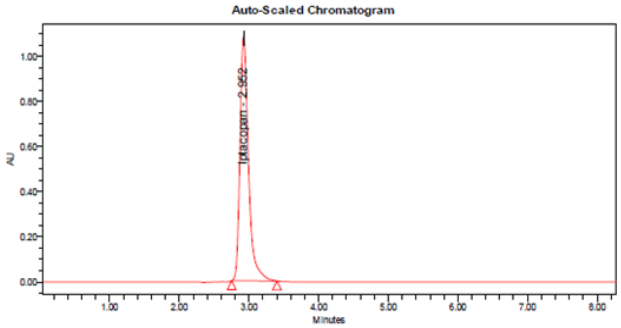

Fig.20: Chromatogram showing less organic composition

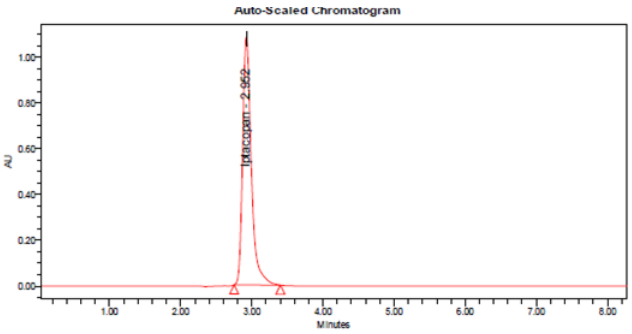

Fig.22: Chromatogram showing less flow

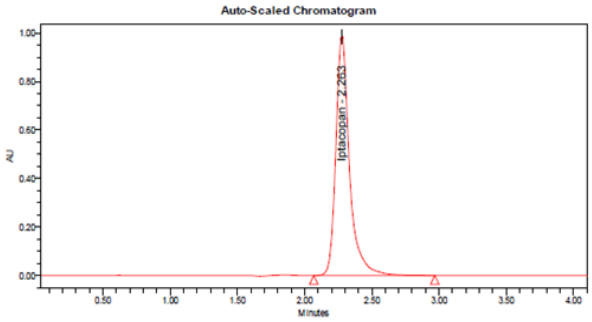

Fig.21: Chromatogram showing more organic composition

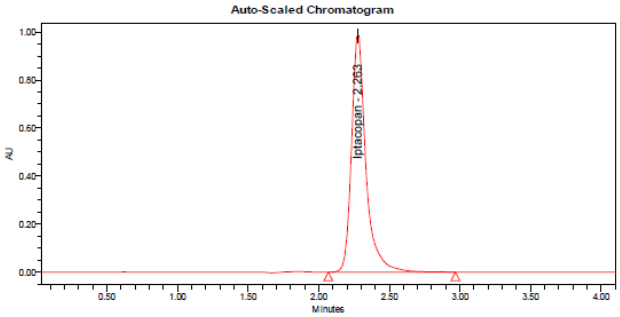

Fig.23: Chromatogram showing more flow

Table 8: Response-1 Retention Time of Iptacopan FIT Summary

Source	Sequential p-value	Adjusted R^2	Predicted R^2	
Linear	< 0.0001	0.9071	0.8520	
2FI	0.9786	0.8815	0.6607	
Quadratic	< 0.0001	0.9943	0.9602	Suggested
Cubic		1.0000		Aliased

ANOVA for Quadratic model **Table 9:** Response: 1 RT

Source	Sum of squares	DF	Mean square	F value	P value Prob>F	
Mean vs total	883.00	1	883.00			
Linear vs mean	12.91	3	4.30	0.40	0.7555	Suggested
2FI vs linear	2.06	3	0.69	0.047	0.9854	
Quadratic vs 2FI	15.56	2	7.78	0.46	0.6495	Aliased
Cubic vs quadratic	100.57	2	50.28	6.366E+007	<0.0001	Aliased
Residual	0.000	4	0.000			
Total	1014.10	15	67.61			

Table 10: Response 2: tailing factor

source	Sum of squares	DF	Mean square	F value	P value Prob>F	
Mean vs total	2.165E+007	1	2.165E+007			
Linear vs mean	1.195E+006	3	3.985E+005	1.47	0.2770	Suggested
2FI vs linear	7.053E+005	3	2.351E+005	0.82	0.5165	Suggested
Quadratic vs 2FI	1.224E+006	2	6.120E+005	3.47	0.0997	Aliased
Cubic vs quadratic	1.058E+006	2	5.291E+005	6.366E+007	< 0.0001	Aliased
Residual	0.000	4	0.000			
Total	2.583E+007	15	1.722E+006			

Table 11: Results of LOD

Drug name	Baseline noise(µV)	Signal obtained(µV)	S/N ratio	Conc
Iptacopan	59	171	2.90	0.57µg/ml

Table 12: Results of LOQ

Drug name	Baseline noise(µV)	Signal obtained(µV)	S/N ratio	Conc
Iptacopan	59	589	9.98	1.98µg/ml

4. Conclusion

A simple, precise, and robust RP-HPLC method was developed and validated for the estimation of Iptacopan in bulk and pharmaceutical dosage forms as per ICH Q2(R1) guidelines. Chromatographic separation was achieved on an Inspire C18 column (150 × 4.6 mm, 5 µm) using a mobile phase of acetonitrile and trifluoroacetic acid in the ratio of 35:65 v/v, at a flow rate of 1.0 mL/min, with detection at 230 nm. The method demonstrated excellent system suitability with a USP plate count of 4932.41 and a tailing factor of 1.22, meeting all acceptance criteria. Linearity was observed over the range of 10–50 µg/mL, with a correlation coefficient (R^2) of 0.999. Precision studies yielded %RSD values of 0.7% for repeatability and 0.5% for intermediate precision, indicating high reproducibility. Accuracy studies showed mean recovery of 98.10%, well within the acceptable range of 98–102%. The LOD and LOQ were determined to be 0.57 µg/mL and 1.98 µg/mL, respectively, demonstrating good sensitivity. Robustness results confirmed that small variations in flow rate and mobile phase composition did not significantly affect method performance. The developed RP-HPLC method is accurate, specific, precise, and robust, fulfilling all ICH Q2(R1) validation requirements. The method provides consistent results with good peak symmetry, high sensitivity, and short retention time, making it suitable for routine quality control of Iptacopan in bulk and dosage forms. Its reliability under varying chromatographic conditions ensures its applicability in analytical laboratories for both regulatory compliance and batch release testing. The simplicity, reproducibility, and cost-effectiveness of the method make it an ideal choice for routine analysis in pharmaceutical industries.

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