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MANAGEMENT OF QUALITY BY DESIGN (QBD) IN CLEANING METHOD DEVELOPMENT: ENSURING COMPLIANCE AND EFFICIENCY IN THE QUANTIFICATION OF CINACALCET API USING UV-SPECTROSCOPY AND REVERSE PHASE-HPLC

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ABSTRACT

Cinacalcet Hcl[CIN] is used to treat hyperthyroidism and hypercalcisim. QbD approach used to assess risk and develop cleaning method for Cinacalcet HCl .The method operable design region (MODR) was obtained by CCD concluded from surface and contour plot Analytical Target Profile defined with 15 variables verified for quality.The contour diagram displays the anticipated and optimized data, which includes the composition of the eluent phase consisting of potassium dihydrogen ortho Phosphate buffer with a pH of 3.5 and acetonitrile (CH_3CN) in a ratio of 20:80 v/v. The flow rate was set at 1 mL/min for a duration of 10 minutes. The analysis was performed using a Kinetex C_{18} column at a temperature of 25 °C, and the wavelength chosen for detection was 279 nm. After injecting swabbed samples from SS plate(10*10 cm), sharp and resolved peak of CIN at 2.8 minutes of retention [RT] , was observed. The set method had a LOQ of 0.740 µg mL−1 and a LOD of 0.244 µg mL−1.The measured linearity of the calibration curve ranges from 0.25 to 12.5 gmL^{-1}, with a r^2 of 0.999. All validation parameter findings fell within the permitted range.% RSD of system suitability 0.03 %, inter-day and intra-day precision % RSD value 1.07&0.95%, respectively, and accuracy (0.059–0.189)%. QbD approach is applied effectively to optimize HPLC method for CIN estimation in formulation and API manufacturing.

Keywords: Cinacalcet, central composite design, MODR, Cleaning method, Analytical target profile; method validation ,QbD.

INTRODUCTION

Cinacalcet plays a role as a calcimimetic and a P450 inhibitor[1] and improves the sensitivity of calcium receptors on parathyroid cells to reduce parathyroid harmone levels and hence decrease serum calcium levels. It also has a role in hypercalcemia and kidney disease (CKD) in persons with parathyroid cancer[2].

Cinacalcet Hcl has the chemical formula C22H22F3N.HCl and a molecular weight of 357.41 g/mol as a freebase and 393.87 g/mol as a salt of HCl.[3]It is a white to off-white, crystalline solid that is somewhat soluble in water, methanol, and 59% ethanol. Cinacalcet Hcl has a pKa value of 8.72 (Strongest Base: 10.3) and a melting point between 175 and 177 °C [4]

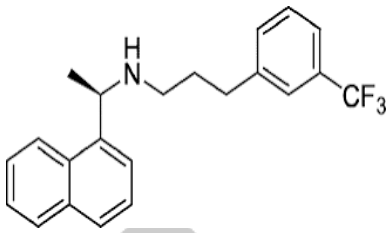


Fig 1:Chemical structure of Cinacalcet

Validating cleaning method is a process used to show that a cleaning method successfully removes impurities or residues from surfaces or equipment[5]. It guarantees that the cleaning technique can reliably and consistently achieve the specified level of cleanliness[6]. QbD in method development focuses on the analytical methods used to ensure the quality of pharmaceutical prod ucts.[7] In order to design methods using the Quality by Design (QbD) approach, Critical Method Parameters must be identified. (CMPs) one of the parameters that can impact the data's level of quality generated by the method.After been found, these CMPs need to be optimised using a Design of Experiments (DOE) methodology. The DOE methodology enables scientists to examine the impact of the CMPs on method performance and ensures the strength and reliability of the procedure.QbD encompasses the optimisation of CMPs as well as the formulation of a control strategy for the approach. This control strategy should include appropriate acceptance criteria for the method, such as the accuracy and precision of the data, as well as the linearity and range tested for the method. This control strategy allows scientists to guarantee that the method performance meets the desired specifications. Finally, a risk-based approach should be taken when developing the control strategy to make sure that the method is fit for its intended design.As a part of the QbD approach to method development, critical method parameters (CMPs) are identified which influences the data's level of quality generated by the method.In order to ensure the reliability and robustness of the method, the CMPs are optimized using a design of experiments

approach (DOE).Parallel to a process QbD, AQbD results are well understood, adequate for their intended use, and robust throughout one's lifecycle. The analytical quality-by-design (AQbD) idea, which has been extensively explored in the scientific literature, can be used to analytical techniques to assure controlled risk-based method development with quality assurance. Manjula A, *et al*[8] stated The molar absorptivity (ε) was 4.2 x 10'1/molcm^{-1}.Reddy PS, et al. Concluded a sensitive, stability-indicating, and rapid gradient reversed-phase ultra-performance liquid chromatography method has been developed to quantify Cinacalcet HcL impurities in active pharmaceutical components and pharmaceutical formulations. An Acquity BEH Shield RP18 column, measuring 100 x 2.1 mm and 1.7 um, was employed to achieve a highly efficient chromatographic separation. Acetonitrile and phosphate buffer with a pH of 6.6 comprised the mobile phase.Yang C, et al. define the current method as the Chiral separation of Cinacalcet HcL, its starting material, and an intermediate using high-performance liquid chromatography[9-10]. Addressing the hypothesesH1: Implementing QbD in cleaning validation significantly reduces operational costs associated with non-compliance,H2: A QbD approach leads to higher managerial satisfaction due to improved efficiency and reduced risk in cleaning validation.The core challenge in pharmaceutical manufacturing lies in ensuring the effective and consistent removal of residues from equipment and facilities to prevent cross-contamination and maintain product quality.Key challenges in achieving efficient, compliant, and cost-effective cleaning validation include:

- Complex Manufacturing Processes:
  - Diverse range of products with varying residue characteristics
  - Multiple equipment types with unique cleaning requirements
  - Frequent changeovers and cleaning cycles
- Regulatory Stringency:

Strict regulatory standards (e.g., FDA, EMA) for cleaning validation

  - Increasingly rigorous documentation and data analysis requirements
- Cost and Resource Constraints:
  - Limited budgets for cleaning validation activities.
  - Need to balance cleaning costs with product quality and regulatory compliance.
- Subjective Cleaning Verification Methods:
  - Reliance on visual inspection and swab testing, which can be subjective and prone to human error.
- Lack of Proactive Approach:
  - Reactive approach to cleaning validation, often triggered by quality issues or regulatory observations.

Limited use of scientific and risk-based approaches to cleaning method

development and validation.Hence the research is critical from a managerial perspective, addressing how effective cleaning validation contributes to product quality, regulatory compliance, and operational sustainability.This studywill be helpful to QA managers thereby can make well-informed decisions regarding cleaning procedure validation by combining the principles of Quality by Design (QbD) with HPLC.A robust cleaning validation program can significantly impact operational costs and compliance risks within the pharmaceutical industry. Few are mentioned below:

- **Operational Costs:**

Reduced Downtime: Effective cleaning validation ensures that equipment is cleaned efficiently and thoroughly, minimizing downtime between production runs. This can lead to increased production capacity and reduced operational costs.

Optimized Cleaning Procedures: By understanding the critical cleaning parameters and optimizing cleaning cycles, companies can reduce the consumption of cleaning agents, water, and energy, leading to cost savings.

Reduced Product Losses: A well-validated cleaning process minimizes the risk of cross-contamination, preventing product spoilage and recalls. This can significantly reduce financial losses.

Improved Equipment Lifespan: Effective cleaning practices can extend the life of equipment by preventing premature wear and tear caused by residual contaminants.

- **Compliance Risks:**

Regulatory Compliance: A robust cleaning validation program helps ensure compliance with regulatory requirements, such as GMP (Good Manufacturing Practices) and FDA regulations. This reduces the risk of regulatory actions, fines, and product recalls.

Product Quality: Effective cleaning validation guarantees the removal of residues and contaminants, ensuring the quality and safety of products. This helps maintain brand reputation and customer trust.

Patient Safety: By preventing cross-contamination and ensuring product purity, robust cleaning validation contributes to patient safety. This is crucial in the pharmaceutical industry, where product quality directly impacts human health.

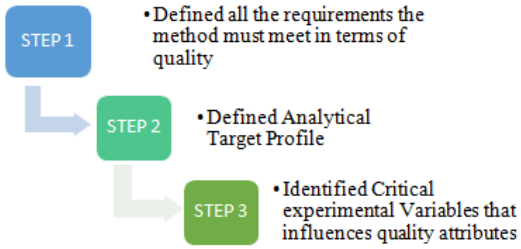


Figure 2: Steps in Analytical QbD

Overall, the QbD approach to analytical method development helps sure that any potential sources of variability are discovered and managed, and that the methods used to evaluate the quality of pharmaceutical goods are precise, dependable, and robust. Pharmaceutical businesses can increase the overall quality of their goods and optimize their analytical processes by applying QbD concepts.The UV spectroscopy method can be developed to reach the necessary level of sensitivity, selectivity, and accuracy required for the analysis of a specific sample by tuning these and other CMPs.Figure2. Diagram towards left hand side showing the steps required for fulfilling Analytical Quality bydesign(AQbD)requirements&onright andSideshowing the five key steps involved in establishing an AnalyticaltargetProfile(ATP) for cleaning method development. The investigation into the literature found that only a few testing methods, such as UV[11-15], HPLC[16-30], LC-MS[31-36] , were reported for drug estimation. An effort was made to implement the analytical quality by design approach in the proposed investigation and we rigorously followed ICH Q2 [R 1] for the screening, selection, and optimization of numerous parameters that impact the development and authenticity of the method.Risk assessment, Design of Experiment (DoE), Analytical Target Profile (ATP), and Critical Quality Attributes (CQA) were among the methodologies implemented.

Following earlier reports, we optimized the chromatographic conditions for the creation and validation of a reliable and accurate approach, as well as for its use in quantitative analysis. We opted [CCD] central composite design in stat ease 12.0(software)Here, we provide a QbD-based HPLC technique that makes use of a UV spectrophotometer detector. The procedure described here uses acetonitrile, and potassium dihydrogen ortho Phosphate buffer pH 3.5.Cinacalcet is completely dissolved by acetonitrile in tablet samples, allowing for the direct injection of the samples into HPLC after filtration.Another benefit of using the QbD methodology with HPLC is that it requires fewer tests to provide more reliable findings, which saves time and resources during the method development stage. Additionally, as far as we are aware, no Qbd-Assisted cleaning method of Cinacalcet by HPLC-UV method using the QbD methodology has published. As a result, a quick, accurate, and straight forward HPLC process was created using the QbD concept. Here chromatographic settings were improved by QbD methods using central composite design.

EXPERIMENTAL WORK

MATERIALS AND METHODS

Dr Reddys supplied the reference standard for Cinacalcet HcL. The tablet dosage form of Cinacalcet HcL is PTH 30 tablet by Intas pharmaceuticals. Potassium dihydrogen ortho Phosphate ,orthophosphoric acid were acquired from SD fine chemical tech. Methanol of HPLC grade from Rankem chemicals.Acetonitrile HPLC grade from Finar chemicals.A Waters HPLC system (Waters 1525, For HPLC analysis,, a binary pump, and UV-Visible detector 2487 were utilized. Separation was accomplished in an analytical C18 kinetex column with internal diameter measurements of (100 × 4.6 × 5) µm (internal diameter).Double Beam UV-visible spectrophotometer(LabIndia UV-3200),cyclomixer (CM 101)made by Remi Equipments,swabs(polypropylene sticks) by Himedia Lab,stainless steel plate (10× 10 ×2mm) thickness,Analytical balances Make by Shimadzu, sonicator by Soltec(2200MH).

METHODOLOGY

OPTIMIZATION WITH QbD

QbD was used to design trials that varied in the interaction of factors on dependent variables. A CCD study was planned with two independent components (mobile phase composition and buffer pH) and three dependent response factors (retention time, tailing factor, and resolution). Eleven runs were performed to optimize the independent variables and evaluate the dependent variables.Implementing QbD in a pharmaceutical organization requires a strategic approach and strong management oversight. Here are some key insights for effective QbD management:

- Leadership Commitment:

Strong leadership commitment was essential requirement to drive QbD adoption and ensure its integration into the organization's culture.

Adequate resources, including budget and personnel, were allocated to support QbD initiatives.

- Cultural Change:

A culture of continuous improvement and scientific inquiry was fostered.

Comprehensive training was provided on QbD concepts, tools, and techniques.

- Robust QbD Framework:

The Quality Target Product Profile (QTPP) was clearly defined to establish the desired quality attributes of the product.

Thorough risk assessments were conducted to identify potential risks and develop mitigation strategies.

The design space was defined to understand the acceptable ranges of critical process parameters (CPPs) and critical material attributes (CMAs).

A robust control strategy was established to ensure product quality and consistency.

- Data Management and Analytics:

Robust data management practices were implemented to ensure data accuracy and reliability.

Statistical tools and data analytics were used to identify trends, patterns, and correlations in process data.

Knowledge gained from QbD initiatives was documented and shared to facilitate continuous improvement.

➢ Collaboration and Communication:

Cross-functional teams were fostered to ensure a holistic approach to QbD.

Clear communication channels were established to share information and address concerns.

➢ Regulatory Compliance:

The organization stayed updated on regulatory expectations and guidelines related to QbD.

Proactive engagement with regulatory authorities was undertaken to discuss QbD approaches and obtain early feedback.

➢ Continuous Improvement:

QbD documents and procedures were regularly reviewed and updated.

Process deviations and failures were analyzed to identify opportunities for improvement.

A culture of innovation and experimentation was encouraged to drive continuous improvement.

By effectively managing these aspects, Pharmaceutical organizations can realize the full potential of QbD, leading to improved product quality, reduced costs, and enhanced regulatory compliance.

Expected Outcomes and Implications

Management Implications of QbD:Quality by Design (QbD) offers a multitude of benefits for pharmaceutical manufacturers, leading to enhanced compliance, cost savings, and streamlined quality control processes. Here are some key management implications:

➢ Enhanced Compliance:

✧ Proactive Risk Management: QbD enables proactive identification and mitigation of potential risks, ensuring compliance with regulatory standards.

✧ Strong Scientific Basis: A QbD-based approach provides a strong scientific foundation for regulatory filings and inspections.

Consistent Product Quality: By designing robust processes, QbD helps to ensure consistent product quality, reducing the risk of product recalls and regulatory actions.

➢ Cost Savings:

✧ Efficient Resource Allocation: QbD focuses on critical quality attributes and parameters, allowing for efficient allocation of resources.

✧ Reduced Re-work and Waste: By understanding the design space, manufacturers can minimize process variations and reduce the need for re-work.

✧ Optimized Process Development: QbD-based approaches can accelerate product development timelines by reducing the number of experimental trials.

➢ Streamlined Quality Control Processes:

✧ Risk-Based Quality Control: QbD enables a risk-based approach to quality control, focusing on critical

control points and reducing unnecessary testing.

- ✧ Improved Product Quality: By designing robust processes, QbD helps to ensure the consistent production of high-quality products.
- ✧ Enhanced Data Analysis: QbD promotes the use of data analytics to monitor process performance and identify trends, leading to proactive problem-solving.

➢ Practical Applications of QbD in Decision-Making and Operational Efficiency:

- ✧ Informed Decision-Making: QbD provides a data-driven approach to decision-making, enabling managers to make informed choices about process parameters, formulation changes, and manufacturing strategies.
- ✧ Optimized Process Design: By understanding the impact of different factors on product quality, QbD can help optimize process parameters, such as temperature, pressure, and mixing time.
- ✧ Reduced Time to Market: QbD can accelerate product development and launch by minimizing the number of experimental trials and regulatory interactions.
- ✧ Enhanced Problem-Solving: By identifying root causes of process deviations, QbD enables effective problem-solving and corrective actions.
- ✧ Improved Product Quality: QbD helps to ensure consistent product quality by minimizing variability and maximizing product performance.
- ✧ Cost Reduction: By optimizing processes and reducing waste, QbD can contribute to significant cost savings.

By implementing QbD principles, pharmaceutical manufacturers can achieve a more efficient, compliant, and profitable operation.

Table 1: Matrix Design according to central composite design (CCD) for Cinacalcet HcL HPLC technique optimization

R	Run Order	Coded Factor Level	
		FA	FB
1	8	65	3.5
2	6	80	3.25

R	Run Order	Coded Factor Level	
		FA	FB
3	7	65	3
4	2	80	3
5	4	80	3.5
6	10	65	3.25
7	9	65	3.25
8	1	50	3
9	3	50	3.5
10	5	50	3.25
11	11	65	3.25

Influence of factor Level

Parameter	Low (−1)	Intermediate (0)	High (+1)
A: Acetontrile	50	65	80
B: Buffer PH	3	3.25	3.5

R- run; FA- factor A; FB-factor B

Table 2:Analyzing experimental findings and choosing the final method conditions

		F- 1	F- 2	R-1	R-2	R- 3
Std	Run	A: Acetonitrile(%)	B:Buffer pH	Retention time (Min)	Tailing Factor	Resolution
8	1	65	3.5	4.6	1	2
6	2	80	3.25	2.4	0.7	2.8
7	3	65	3	3.1	1.3	1.7
2	4	80	3	2	0.9	2.2
4	5	80	3.5	2.8	0.4	3.4
10	6	65	3.25	3.5	1.1	1.9
9	7	65	3.25	3.5	1.1	1.9
1	8	50	3	5.1	2	1.4
3	9	50	3.5	5.7	1.5	1.7
5	10	50	3.25	5.4	1.8	1.5
11	11	65	3.25	3.5	1.1	1.9

F– factor;R–response

SAMPLE PREPARATION

Preparation of standard stock solution: 5mg of Cinacalcet HCl was weighed and placed in a 5mL volumetric flask. It was then diluted with acetonitrile up to the mark,(1000 microgm mL^{-1}) (stock solution 1). 1 mL of this solution was made to the 10mL graduation with acetonitrile (100 microgm mL^{-1})(stock solution 2). Further serial dilutions were made from stock solution 2 to obtain concentrations of 1, 1.25, 2, 2.5, 5, 10, 15, 20, 25, 30, 50, 75, and 100 microgm mL^{-1}.

Buffer preparation:Weigh accurately 3.4 grams of potassium dihydrogen phosphate and transfer into 500 ml volumetric flask,Make up to the mark with distilled water,With the help of ortho phosphoric adjust the pH 3.5,Similarly adjust the solution to the required pH ,3,3.25and 3.5.,Filter the final solution by using membrane filter 0.45and then sonicated the solution for 10 min.

Mobile Phase Preparation: Acetonitrile of HPLC grade is taken in a chromatographic bottle and sonicated for 10 min,The prepared Buffer and Acetonitrile was taken in a required ratio and together used as a mobile phase.

CLEANING METHOD

SAMPLING PROCEDURES: Direct surface sampling (swab method):

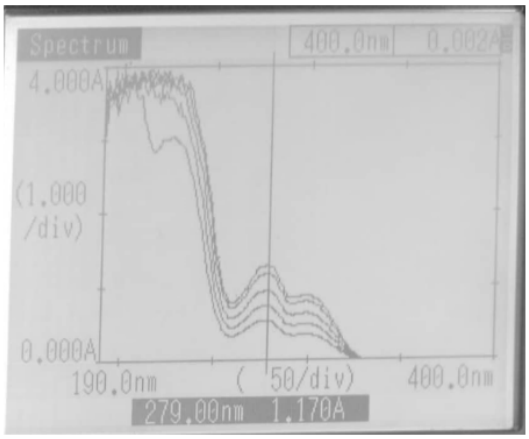
The most common sampling method involves swabbing a surface methodically with a probe, also known as a "swab,"SS plate(stainless steel plate) was taken and gently wiped with choosen solvent(Acetonitrile), then pipetted out 1 ml of solvent and spread drop wise on ss plate ,dried the ss plate by using hair dryer ,then with the help of rinsed swab stick (swab stick was placed in a solvent and sonicated for 5 min)collect the sample left on ss plate by horizontal,vertical and diagonal strikes then enclose the swab in test tube with solvent selected and mix in cyclomixer for 4 min and made up the solution upto 10ml with Acetonitrile and measure its RT and absorbance,consider this as blank, now repeat the same with different concentrations (2,4,5,6,8,10,15,20,25,30,35,40,45,50,75,100) ppm, the same is applied on the manufacturing equipment to detect the traces left from the previous batch production.

RESULTS AND DISCUSSIONS

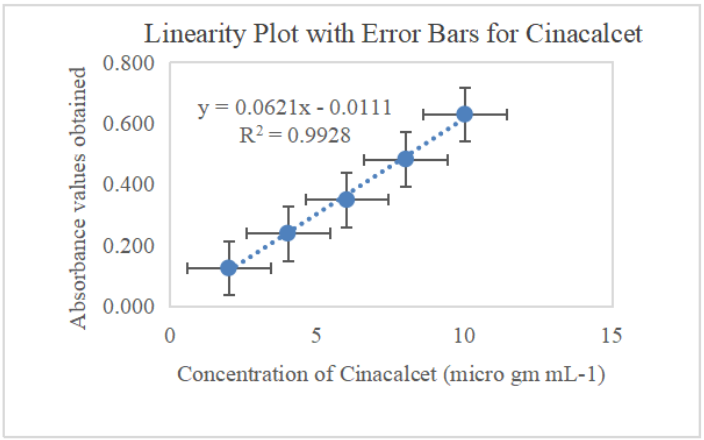
UV-Spectroscopic Method Validation

The plot Figured as 3 (a) & (b) values in Table 3 exhibits strong linear relationship between Cinacalcet concentration and absorbance, as evidenced by the high R^2 value of 0.9928. This indicates that the method used for quantification is suitable within the tested concentration range.The error bars associated with each data point are relatively small, suggesting good precision in the measurements. This is crucial for accurate quantification and method reliability.The y-intercept value of -0.0111 suggests a minimal baseline signal or background interference. This is generally desirable as it indicates a low level of noise in the measurements.The observed linearity and precision of the

method are essential for accurate and expand the quantification



(a)



(b)

reliable quantification of Cinacalcet. The data suggests that the analytical method used is suitable for the intended purpose within the specified concentration range. The linearity of the method can be assessed at higher concentrations to range.Additional validation parameters (accuracy, precision, limit of detection, limit of quantification,Robustness) shown in Table 4 found to be fit for comprehensive assessment of the method's performance.

Table 3: Linearity study of Cinacalcet Hcl

Concentration (micro gram mL^{-1})	**Absorbance±SD$^{\#}$**
2	0.125±0.061
4	0.239±0.0122
6	0.341±0.0166
8	0.472±0.0197
10	0.629±0.0609

$^{\#}$Standard Deviation(n=3)

Fig 3: (a)Visual representation in the form of Spectra obtained from an UV-instrument; (b) Relationship between the concentration of Cinacalcet in a preparation and peak area

Table 4 : Validation parameters for UV-Spectroscopy

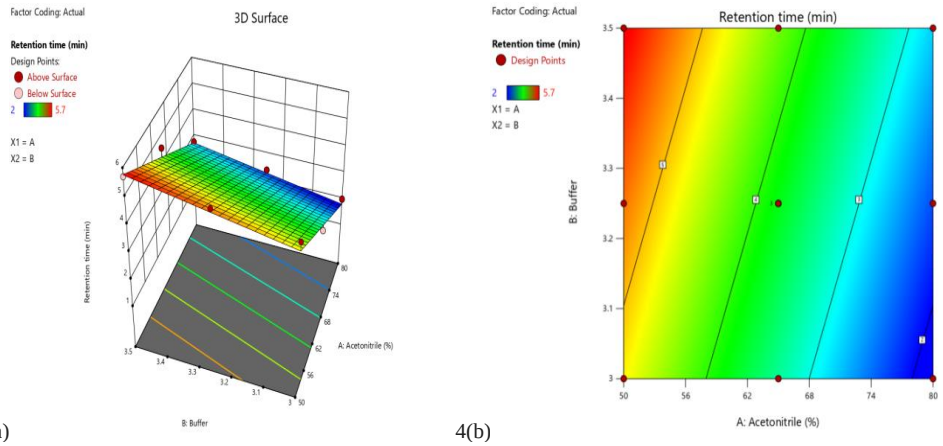
VALIDATION PARAMETERS	OBSERVED VALUES		
Precision	%RSD		
Intra-day	0.122602		
Inter-day	0.097362		
Accuracy	98.99-100.44%		
LOD	0.300 µg/mL		
LOQ	0.909 µg/mL		
Robustness	Wavelength[!]	Shimadzu[!]	Lab India[!]
	280	0.036017	0.22602
	279	0.008375	0.35421
	278	0.210299	0.35927
Ruggedness[@]	0.109947		

[!]magnitude of the observed %RSD values across all three wavelengths for two instruments

OPTIMIZATION

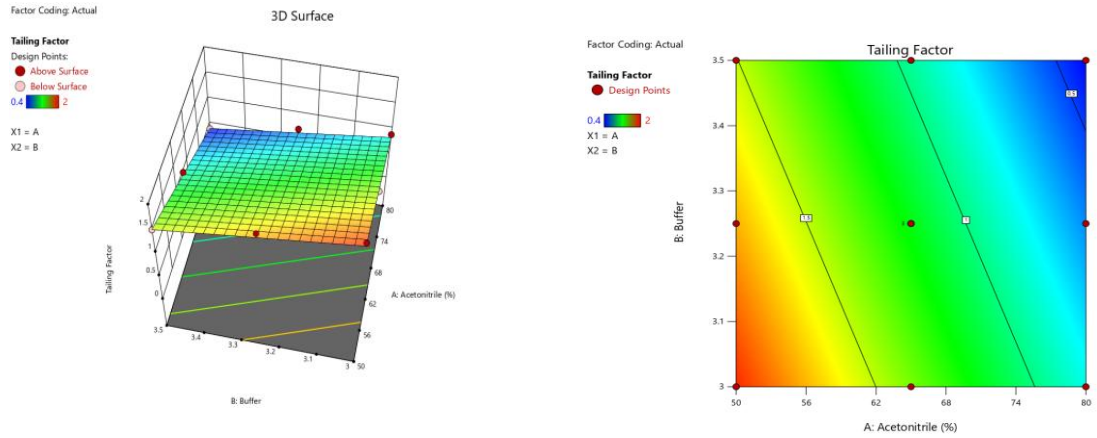
Experimental design optimization can develop a mathematical model to identify ideal chromatographic parameters.

Retention time : Utilizing three independent factors and a significant analytical model (p-values < 0.0500), CCD was able to optimize the retention duration effectively(Fig 4). Due to the fact that the signal-to-noise ratio of 28.846 suggests that there is adequate signal, the model can be utilized to navigate the design space.



4(a) 4(b)

Fig 4(a). 3D- response surface effects of an independent element on the retention time (b) A contour plot showing how the independent component affects retention time



5(a) 5(b)

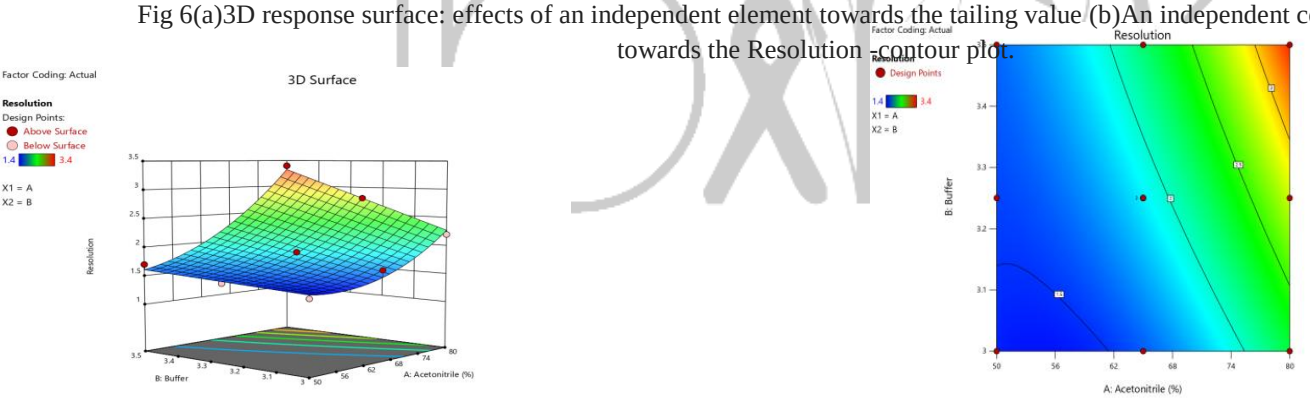
Fig 5:(a)The influence of an independent component on the tailing factor in the three-dimensional response surface; (b)The influence that an independent component has on the contour plot of the tailing factor

Tailing factor: Utilizing CCD surface response and ANOVA for the linear model, the tailing factor was optimized.The model was significant (p-values < 0.0500) and the signal-to-noise ratio of 39.082 indicates an adequate signal. This model can be used to navigate the design space(Fig 5).

Resolution: Optimization of resolution for the simplified quadratic model (Fig 6 a & b) was accomplished by the utilization of CCD surface response and ANOVA. The model was found to be statistically significant (p-values were < 0.0500), and the signal-to-noise ratio of 25.246 shows that the signal is sufficient.

6(a) 6(b)

Fig 6(a)3D response surface: effects of an independent element towards the tailing value (b)An independent component impact towards the Resolution -contour plot.



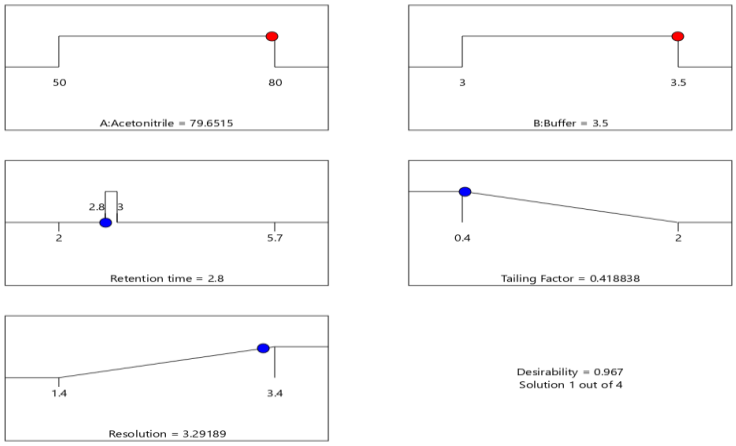


Fig 7:Optimized QbD parameters

HPLC VALIDATION PARAMETERS

System suitability

Numerical values displayed in Table 5 details on the compatibility of HPLC system with the method developed,considering standard deviation as 348.600 for 6 injections of CIN,its calculated relative % obtained as 0.30.

Table 5: System suitability study for Cinacalcet Hcl

Sl.No	Rt	Area	Theoretical plate	Tailing factor
1	2.884	115040	6005	1.187
2	2.884	117427	6007	1.18
3	2.884	116630	6009	1.179
4	2.884	117264	6907	1.187
5	2.884	117337	6.000	1.186
6	2.884	117230	6007	1.187
Mean	2.884	117232.342		
STDEV		348.600		
%R.S.D		0.30		

Linearity

Beginning with a lower concentration as depicted in Table 6,swabbed sample of CIN was proved for its regression which is projected in Figure 8a,where its corresponding Overlain is figured in Figure 8b.Tested five concentrations has showed good results.

Table 6 :Linearity study of Cinacalcet Hcl by HPLC

Concentration (µg/ml)	Retention time	Area
2.5	2.876	48157
5	2.876	117504
7.5	2.876	189850
10	2.876	262807
12.5	2.876	328756

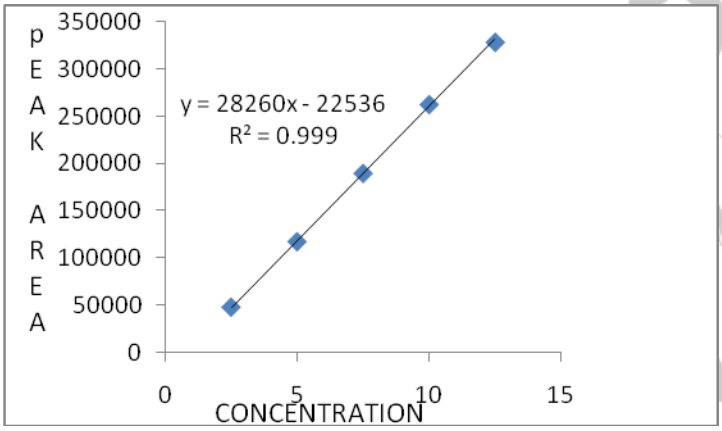


Fig 8a Linearity by HPLC

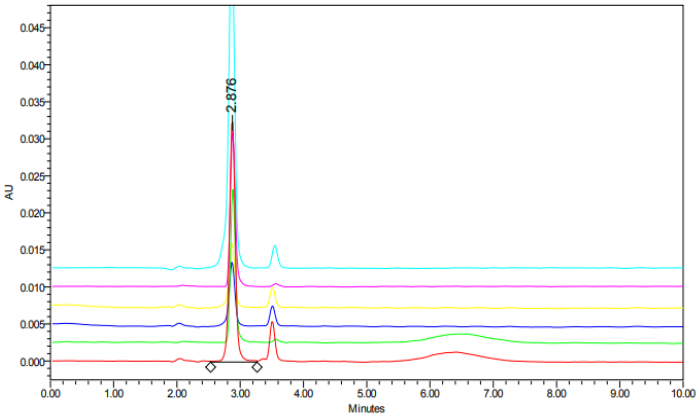


Fig 8b overlay chromatogram obtained for swabbed CIN

Precision

Having considering lower concentration,CIN counterpart was eluted at 2.871 min & 2.865 min respectively for Intra-day as well as Inter-day.Mean response for the same was down through the limit, seen as 1.07% and 0.95%. Table 7 narrates the results.

Table 7 :Precision of Cinacalcet Hcl by HPLC

	INTRA-DAY		INTER-DAY	
Concentration	**Retention time**	**Area**	**Retention time**	**Area**
2.5µg/ml	2.871	56043	2.865	63519
2.5µg/ml	2.871	56946	2.865	63307
2.5µg/ml	2.871	55618	2.865	63307
2.5µg/ml	2.871	57234	2.865	64849
2.5µg/ml	2.871	56116	2.865	63307
2.5µg/ml	2.871	56391	2.865	63519
Mean	2.871	56391.307	2.865	63634.651
STDEV		602.1		604.033
%R.S.D		1.07		0.95

Accuracy

Specified concentration in Table 8,swabbed CIN attained mean % recovery getting through the limits.Its % relative standard deviation was acquired as 0.090,0.189,0.059 respectively at each spike level.

Table 8 :ACCURACY study of Cinacalcet Hcl by HPLC

Level	Amnt of pure drug	Amnt of sample	Total CONC	% Recovery	Mean recovery	%R.S.D
50%	2.5 µg/ml	5 µg/ml				
	22765	97337	120027	99.67		
	22767	96597	119249	99.49	99.57	0.090
	22993	97964	120853	99.54		
100%	5 µg/ml	5 µg/ml				
	117337	97337	213773	99.23		
	117427	97427	213513	98.85	99.05	0.189
	117264	97264	213427	99.06		

	7.5 µg/ml	5 µg/ml				
	222990	98742	321033	99.68		
150%	223299	97726	320490	99.76	99.69	0.059
	224820	97737	321756	99.64		

Robustness

Parameters evaluated under this heading were just beyond the developed method rather staying in the prescribed limits,collected into Table 9.

Table 9 : Robustness study of Cinacalcet Hcl by HPLC

PARAMETER	VALUE	TAILING FACTOR	RETENTIONTIME	AREA
FLOW RATE	**0.9ml/min**	1.19	3.319	162729
	1.1ml/min	1.05	2.741	148631
MOBILE PHASE	**+5%**	1.1	2.850	108486
	-5%	1.08	2.880	120027
WAVELENGTH	**278**	1.4	3.540	34171
	280	1.08	3.022	12371

Ruggedness

Mean responses procured by inserting CIN in different components were expressed in Table 10.% relative standard deviation on day 1& 2 confirms the set boundaries.

Table 10 :Ruggedness study of Cinacalcet by HPLC

	COLUMN 1 [kinetex 5µm C18 ,250 x 4.6 mm]			COLUMN 2 [luna 5µm C18 ,250 x 4.6 mm]]	
	DAY-1			DAY-2	
		ANALYST-1		ANALYST-2	
	CONCENTRATION	RT	AREA	RT	AREA
LOD and LOQ	2.5PPM	2.871	56043	2.872	56946
	2.5PPM	2.872	56946	2.871	57234
	2.5PPM	2.870	55618	2.872	56794
	2.5PPM	2.871	57234	2.870	57934
	2.5PPM	2.872	56116	2.871	56391
	2.5PPM	2.870	56391	2.871	55661
	MEAN	2.871	56391.307	2.871	56826.67
	SD		602.1		768.8
	%RSD		1.07		1.35

Applying the formula, detectable and quantifiable amount of CIN gained is illustrated in Table 11.

Table 11: LOD and LOQ study of Cinacalcet by HPLC

DRUG NAME	LOD	LOQ
CINACALCET HCL	1.1 µg/ml	0.03 µg/ml

Assay of Cinacalcet by HPLC

Formula:

$$\frac{\text{Sample area}}{\text{STD area}} \times \frac{\text{wt. of STD}}{\text{dilution of STD}} \times \frac{\text{dilution of sample}}{\text{wt. of sample}} \times \frac{\text{purity}}{100} \times \frac{\text{wt. of tablet}}{\text{label claim}} \times 100$$

$$= \frac{217311}{217470} \times \frac{10.1}{1000} \times \frac{1000}{10.2} \times \frac{99.9}{100} \times \frac{152}{150} \times 100$$

$$= 101.166\%$$

CONCLUSION

An AQbD approach was used to develop, optimize, and validate a method for estimating cinacalcet in bulk and formulation. The method meets ICH requirements and is robust, linear, accurate, specific, sensitive, and precise.The criticality of each targeted parameter was determined, and risk-bearing parameters were carefully evaluated. The method was optimized, and the design space was established using a central composite design.To show how the mobile phase composition and the retention factor are related, design expert software was used to create contour plots and 3-D response surface graphs.For the examination of bulk and formulation quality control samples of Cinacalcet in the pharmaceutical industry, the developed method is suitable. On Analyzing CCD design obtained from QbD it is observed that the effect of buffer Ph is inversely proportional to the tailing factor and effect of buffer Ph and acetonitrile is directly proportional to the retention time and Resolution.

CONFLICT OF INTEREST

The authors do not declare any conflicts of interest.

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