Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(5), 1653-1663 | ISSN:2251-6727

Application of Qbd Principles to Develop and Validate a Method for Cinacalcet Determination in Api and Its Dosage Form

[1]A.Srinija,[2] Sneha Takur,[3]R.Prasanthi,[3]Buggana Siva Jyothi,[4*]R.Swetha Sri

[1]Research student,[3]Department of Pharmaceutical Quality Assurance, [4]Department of Pharmaceutical Analysis
[1,3,4]Sarojini Naidu Vanita Pharmacy Maha Vidyalaya, Secunderabad, India
[2]Department of Pharmacognosy,St.Paul's College of Pharmacy,Hyderabad,India

(Received: 11 June 2024 Revised: 16 July 2024 Accepted: 10 August 2024)

KEYWORDS

Cinacalcet, central composite design, MODR, Cleaning method, Ana lytical target profile; met hod validation ,QbD.

ABSTRACT:

Introduction: Cinacalcet Hcl [CIN] is used to treat hyperthyroidism and hypercalcisim. 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.

Objectives: QbD approach used to assess risk and develop cleaning method for Cinacalcet HCl.So far no methods were reported for estimation of the same

Methods: 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.

Results: 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)%. Percentage purity was found as 101.16.

Conclusion: QbD approach is applied effectively to optimize HPLC method for CIN estimation in formulation and API manufacturing.

1. 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]

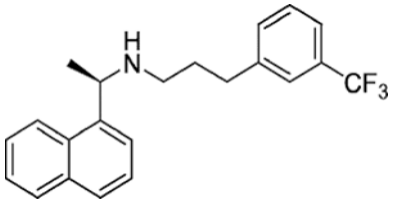


Fig 1: Chemical structure of Cinacalcet

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(5), 1653-1663 | ISSN:2251-6727

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 th e analytical methods used to ensure the quality of pharm aceutical products.[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]. In a review written by the authors talked about the idea of analytical quality by design (AQbD) and how it may be applied as a tool for robust analytics and regulatory flexibility.The paper also gives instances of how AQbD has been successfully used for development and validation of the method in the pharmaceutical business.

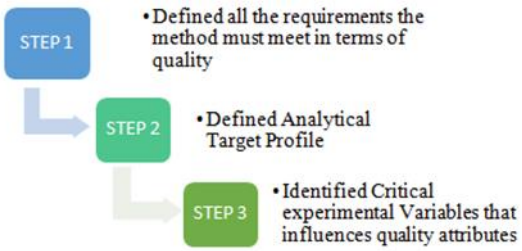


Fig 2: Steps in Analytical QbD

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 by design(AQbD)requirements&on right and Side showing the five key steps involved in establishing an A nalytical target Profile(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

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(5), 1653-1663 | ISSN:2251-6727

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 13.0(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.

2. Objectives

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

3. 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(Lab India 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).

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.

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
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	

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(5), 1653-1663 | ISSN:2251-6727

R	Run Order	Coded Factor Level	
		FA	FB
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 micro gm mL^{-1}) (stock solution 1). 1 mL of this solution was made to the 10mL graduation with acetonitrile (100 micro gm 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 micro gm 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.

4. Results

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

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(5), 1653-1663 | ISSN:2251-6727

data point are relatively small, suggesting good precision in the measurements.

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 Dev#Standard Deviation(n=3)

5. Discussion

UV-Spectroscopic Method Validation

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 expand the quantification 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.

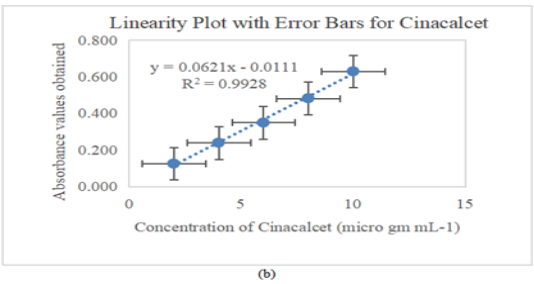


Fig 3: (a)Visual representation in the form of Spectra obtained from an UV-instrument; (b) Relationship between the concentration of Cinacalcet in a preparation and peak area

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

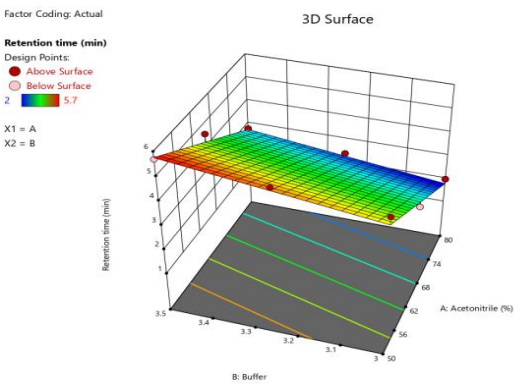
!magnitude of the observed %RSD values across all three wavelengths for two instruments

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.

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).

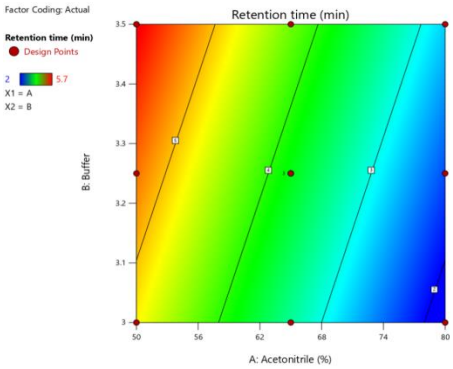


4(a)

Journal of Chemical Health Risks

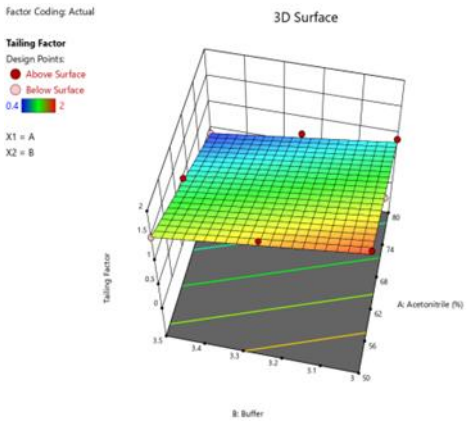
www.jchr.org

JCHR (2024) 14(5), 1653-1663 | ISSN:2251-6727

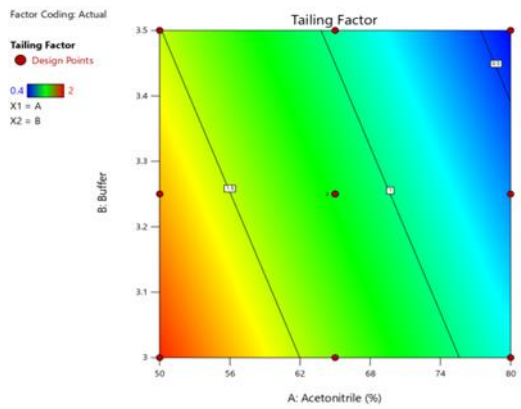


4(b)

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)

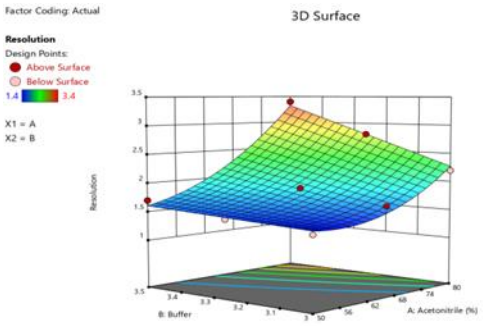
Fig 5:(a)The influence of an independent component on the tailing factor in the three-dimensional response surface; (b)The influence that an independent component has on the contour plot of the tailing factor

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.

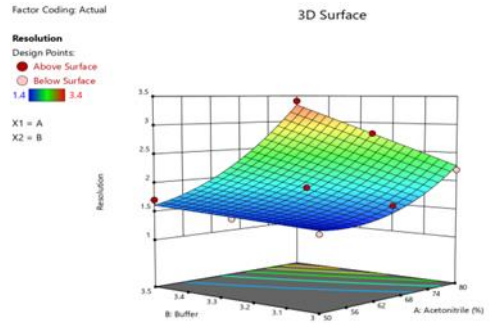
HPLC VALIDATION PARAMETERS

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.



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.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(5), 1653-1663 | ISSN:2251-6727

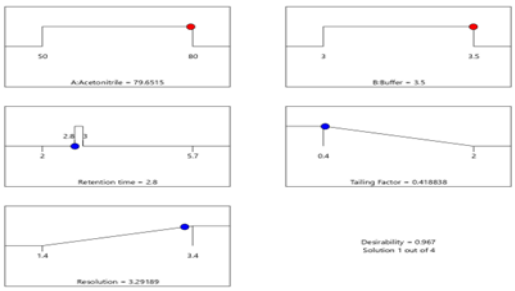


Fig 7:Optimized QbD parameters

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	1.186
6	2.884	117230	6007	1.187
Mean	2.884	117232.34		
STDEV		348.6		
%R.S.D		0.3		

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

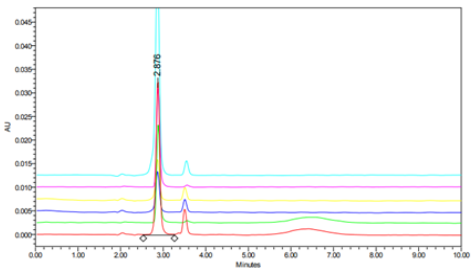


Fig 8a Linearity by HPLC

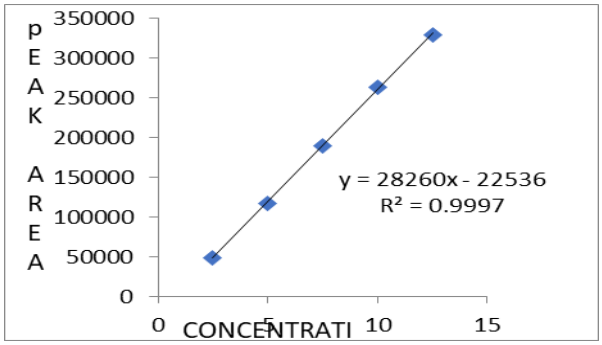


Fig 8b overlay chromatogram obtained for swabbed CIN

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.

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 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

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(5), 1653-1663 | ISSN:2251-6727

%R.S.D	1.07	0.95

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 22765 22767 22993	5 µg/ml 97337 96597 97964	120027 119249 120853	99.67 99.49 99.54	99.5	0.09
100 %	5 µg/ml 117337 117427 117264	5 µg/ml 97337 97427 97264	213773 213513 213427	99.23 98.85 99.06	99.0	0.18
150 %	7.5 µg/ml 222990 223299 224820	5 µg/ml 98742 97726 97737	321033 320490 321756	99.68 99.76 99.64	99.6	0.05

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(ml/min)	TAILING FACTOR	RETENTION TIME	AREA
FLOW RATE	**0.9**	1.19	3.319	162729
	1.1	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.

LOD and LOQ

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

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
2.5PPM	2.871	56043	2.872	56946
2.5PPM	2.872	56946	2.871	57234
2.5PPM	2.87	55618	2.872	56794
2.5PPM	2.871	57234	2.87	57934
2.5PPM	2.872	56116	2.871	56391
2.5PPM	2.87	56391	2.871	55661
MEAN	2.871	56391.307	2.871	56826.67
SD		602.1		768.8
%RSD		1.07		1.35

Table 11: LOD and LOQ study of Cinacalcet by HPLC

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

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

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(5), 1653-1663 | ISSN:2251-6727

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.

CONFLICTS OF INTEREST

The authors do not declare any conflicts of interest.

AKNOWLEDGEMENT

The Cinacalcet Hcl API was provided by Dr. Reddy's, and the authors would like to express their gratitude to them for their assistance in carrying out the project.

References

1. Padhi D, Harris R. 2009.Clinical pharmacokinetic and pharmaco dynamic profile of cinacalcet hydrochloride. Clinical pharmacokinetics,48(5):303-11.DOI: 10.2165/00003088-200948050-00002.
2. National Center for Biotechnology Information. "PubChem Compound Summary for CID 156418, Cinacalcet hydrochloride".
3. Mostafa GA, Al-Badr AA.2007. Cinacalcet Hydrochloride. In Profiles of Drug Substances, Excipients and Related Methodology ,1; 42:1-90. Academic Press.
4. Sensipar (Cinacalcet) - Side Effects, Interactions, Uses, Dosage, Warnings | Everyday Health.
5. Abhishek, Raj . (2014). “Cleaning Validation In Pharmaceutical Industries” J.Atoms and Molecules, 4(4); 779– 783.
6. S. Lakshmana, Prabhu.(2010). Cleaning validation and its importance in pharmaceutical industry; pharma times;42(7); 21-25.
7. Khushbu Patel, Ujashkumar A. Shah, Hirak V. Joshi, Jayvadan K. Patel, Chhaganbhai N. Patel. QbD Stressed Development and Validation of Stability-Indicating RP- HPLC Method for the Simultaneous Estimation of Linagliptin and Metformin HCl in Pharmaceutical Dosage Form. Research Journal of Pharmacy and Technology. 2022; 15(5):1917-3. doi: 10.52711/0974-360X.2022.00319
8. Manjula A, ChandanaDeepthi G, Vijayaraj S. 2012. Spectrophotometric determination of cinacalcet hydrochloride in bulk. Int. J. Pharm. Rev. Res,2(2): 111-118
9. Farnoudian-Habibi A, Jaymand M. 2017.Development and validation of a quantitative assay for the determination of cinacalcet and its main metabolites in human plasma using RP-HPLC method. Microchemical Journal, 130: 377-83.DOI: https://doi.org/10.1016/j.microc.2016.10.017.
10. Panda SS, Rath J, Bera VVRK. QbD Driven Development and Validation of UV Spectrophotometric Method for Estimation of Paliperidone in Extended Release Tablet Dosage Form. Anal Chem Lett. 2018;8(4):510-518. doi: 10.1080/22297928.2018.1446845.
11. Maruthi R, Chandan R.S, Barath M, G Naveen Datta, Merryl D’Silva, Kajal Kumari M, Farhan Ahmad, Geetha R. Analytical Method Development and Validation of Teneligliptin by UV Spectroscopy. Research J. Pharm. and Tech. 2021; 14(1):75-78. doi: 10.5958/0974-360X.2021.00014.7
12. Dinesh Kumar D, Nallagatla VR, Vagolu S, et al. Analytical method development and validation for the estimation of cinacalcet hydrochloride in bulk and tablet dosage form by UV spectroscopy. International Journal of Pharmaceutical Sciences and Research. 2012;3(7):2304-2308.
13. K.R Sreejith, P.L Rajagopal, K Premaletha. Analytical Method Development and Validation of Anostrozole in Pure and Tablet Dosage Form by UV Spectroscopy. Research J. Pharm. and Tech. 2017; 10(4): 1015-1019. doi: 10.5958/0974-360X.2017.00183.4
14. M. Sumithra, P. Yuvanesh, Anamika Mistry. Analytical method development and validation of ambroxol hydrochloride by UV spectroscopy and forced degradation study and detection of stability. Research J. Pharm. and Tech. 2016; 9(7):794-800 . doi: 10.5958/0974-360X.2016.00152.9
15. Sagar Suman Panda, Jagrutirani Rath & Venkata Varaha Ravi Kumar Bera (2018) QbD Driven Development and Validation of UV Spectrophotometric Method for Estimation of Paliperidone in Extended Release Tablet Dosage

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(5), 1653-1663 | ISSN:2251-6727

Form, Analytical Chemistry Letters, 8:4, 510-518, DOI: 10.1080/22297928.2018.1446845

16. Soni P, Patel D, Patel H, Patel M. Development and validation of RP-HPLC method for simultaneous estimation of cinacalcet hydrochloride and calcium carbonate in pharmaceutical dosage form. Journal of Analytical Science and Technology. 2015;6:20. doi:10.1186/s40543-015-0067-1
17. Chandrasekhar KB, Rao JR, Kumar BG, Rao JV. Development and validation of a stability-indicating HPLC method for cinacalcet hydrochloride and its related impurities in bulk drug and pharmaceutical dosage forms. Journal of Liquid Chromatography & Related Technologies. 2015;38(16):1608-1615. doi:10.1080/10826076.2015.1061885
18. Ashish A. Gawai, Kishor Charhate, Faisal Shaikh, Amir Khan, Aniruddha Chaubey, K. R. Biyani. RP-HPLC method development and validation for hyperlipidemic agent atorvastatin in pharmaceutical dosage form. Research J. Pharm. and Tech. 2017; 10(6): 1780-1787.
19. Rituraj Singh Chundawat, Y.S. Sarangdevot, R.P.S. Rathore, Dharmendra Singh Sisodiya, Udaibhan Singh Rathore. Method Development and Validation for Simultaneous Estimation of Montelukast and Fexofenadine in Pharmaceutical Dosage Form by HPLC Method. Research J. Pharm. and Tech. 6(10): October 2013; Page 1102-1106.
20. Anisha Naik, Celina Nazareth, Sarvada Naik Gaonkar. Cleaning Method Development and Validation for the Simultaneous Estimation of Olmesartan and Atorvastatin by HPLC. Research J. Pharm. and Tech 2020; 13(5):2125-2128. doi: 10.5958/0974-360X.2020.00382.0
21. Aswini Kumar Parida, K. Srinivasa Rao , Ajay Kumar Patnaik. A Novel Validated RP-HPLC Method for the estimation of Ticagrelor in Bulk and Pharmaceutical Dosage Forms. Research J. Pharm. and Tech. 2018; 11(3): 867-872. doi: 10.5958/0974-360X.2018.00161.0
22. Murugan S, Chandra Sekhar R. Method Development and Validation of Fingolimod in Bulk and Tablet Dosage Form by RP-HPLC. Research J. Pharm. and Tech. 2017; 10(8): 2573-2576. doi: 10.5958/0974-360X.2017.00456.5
23. Nandini R. Pai, Seema S. Sawant. Development and validation of RP-HPLC method for estimation of olmesartan medoxomil in tablet dosage form. Research J. Pharm. and Tech. 2013; 6(11): 1279-1284.
24. A. Tanuja, S. Ganapaty, Varanasi S N Murthy. Stability Indicating RP-HPLC Method Development and Validation for the Determination of Solifenacin Succinate in Bulk and its Pharmaceutical Formulation. Research Journal of Pharmacy and Technology. 2021; 14(7):3509-4. doi: 10.52711/0974-360X.2021.00608
25. Santosh. . Waghmare & M. Sumithra (2021) QbD Based Development and Validation of RP-HPLC Method for Nintedanib Esylate: Application to Bioanalytical and Stability Study in Plasma, Analytical Chemistry Letters, 11:3, 392-408, DOI: 10.1080/22297928.2021.1930581
26. Barrawaz Aateka Yahya, Abubakar S. Bawazir, Jaiprakash N. Sangshetti, Shahajan S. Baig & Sana S. Shaikh (2021) QbD-Based Development and Validation of an Efficient RPHPLC Method for Estimation of Abiraterone Acetate in Bulk, Tablet, and In-House-Developed Nano-Formulation, Analytical Chemistry Letters, 11:1, 112-130, DOI: 10.1080/22297928.2021.1888794
27. T.S.S. Jagan Mohan, Hitesh A Jogia & Khagga Mukkanti (2020) A Stability Indicating UHPLC Method for the Simultaneous Estimation of Perindopril, Indapamide in Presence of Potential Impurities: An Application of QbD for Robustness Study, Analytical Chemistry Letters, 10:4, 477-497, DOI: 10.1080/22297928.2020.1817776
28. Sachin Nashik Sanap, Amol Chhatrapati Bisen, Abhijit Deb Choudhury, Sarvesh Kumar Verma, Mukesh Kumar & Rabi Sankar Bhatta (2022) A Qbd Driven Approach for Development and Validation of an RP-UHPLC Method for Simultaneous Estimation of Ofloxacin and Fluconazole: An Application to Pharmaceutical Analysis, Analytical Chemistry Letters, 12:3, 310-321, DOI: 10.1080/22297928.2022.2063069
29. Amitkumar J. Vyas, Dhruvanshi A. Gol, Ajay I. Patel, Ashok B. Patel, Nilesh

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(5), 1653-1663 | ISSN:2251-6727

K. Patel, JayantR. Chavda, Arvind Lumbhani & Al pesh Chudasama (2021) Implementing Analytical Quality by Design (AQbD) Approach for Simultaneous Estimation of Tadalafil and Macitentan by RP-HPLC Method, Analytical Chemistry Letters, 11:4, 539-552, DOI: 10.1080/22297928.2021.1938215

30. Ramalingam P, Bhadraya K, Reddy YP. Analytical Quality by Design: A Tool for Regulatory Flexibility and Robust Analytics. Int J Anal Chem. 2015;2015:868727. doi: 10.1155/2015/868727
31. Thota N, Chowdary KP, Kanumula NV, Naveen Kumar M, Kantevari S. Development and validation of an LC-MS/MS method for the quantification of cinacalcet in human plasma and its application to pharmacokinetic study. Biomedical Chromatography. 2015;29(5):795-802. doi:10.1002/bmc.3342
32. Sahu RK, Kumar S, Kumar A, et al. Development and validation of an LC-MS/MS method for the quantification of cinacalcet in rat plasma: Application to a pharmacokinetic study. Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences. 2015;1000:71-77. doi:10.1016/j.jchromb.2015.07.038
33. Reddy NB, Reddy KG, Reddy KJ, Srinivas NR. Rapid and sensitive determination of cinacalcet in human plasma by LC-MS/MS method: Application to a bioequivalence study. Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences. 2012;897:128-133. doi:10.1016/j.jchromb.2012.03.033
34. Tegegne HA, Raju KVSN, Reddy PVGK, Kumar MK, Annapurna MM. Development and validation of a rapid and sensitive LC-MS/MS method for the quantification of cinacalcet in human plasma. Biomedical Chromatography. 2018;32(4):e4134. doi:10.1002/bmc.4134
35. Tella SR, Mohan GM, Ravi TK, Reddy PV, Reddy PV. Development and validation of LC-MS/MS method for the determination of cinacalcet in rat plasma and its application to pharmacokinetic studies. Latin American Journal of Pharmacy. 2013;32(10):1548-155
36. Prasad Kancherla, Keesari Srinivas, Pallavi Aleget e & Saeed. S. Albaseer (2020) LC-MS/MS Characterization of Forced Degradation Products of Repaglinide Quality by Design Approach for Stability-Indicating LC Method Development and Validation for Degradation Products, Analytical Chemistry Letters, 10:6, 740-757, DOI: 10.1080/22297928.2020.1861975