RESEARCH ARTICLE

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Stability Indicative Assay Development and Validation of Cinacalcet HCl

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ABSTRACT

The current study presents development and successive validation of simple, rapid, stability indicative HPLC method for quantitative assay of Cinacalcet Hydrochloride. with known process impurities namely, ethnamine impurity, mesylate impurity, and dehydro impurity. The isocratic mixture of acetonitrile and phosphate buffer pH 3.0 (1:1 v/v) and the YMC pack C4 column was used for elution. Flow rate was set to 1ml/ min and detection was carried out at 215nm. The specificity of method was demonstrated in presence of process impurity viz Impurity A, Impurity B, Impurity Cas well as by carrying out forced degradation. The method linearity was established in range of 40 ppm to 150 ppm with regression coefficient > 0.999. The % accuracy was 99.2 to 100.1. All other validation parameters comply ICH requirement.

Key Words: cinacalcet hydrochloride, assay, forced degradation, impurity 1, impurity 2, impurity 3, stability indicative.

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INTRODUCTION

Cinacalcet Hydrochloride (Cinacalcet HCl) iscalcimimc drug. In certain disorders like cancer of parathyroid gland or kidney disease - hyperparathyroidism, uncontrolled amount of calcium is observed in patient's blood. Cinacalcet controls the production of parathyroid hormone which in turn limits the level of Calcium in blood. It is used in adults and children aged 3 tears and above. (*Cinacalcet accordpharma-European Medicines Agency*, 2020).

The chemical name of Cinacalcet is (R)-N-[1-(1-naphthyl) ethyl]-3-[3-(trifluoromethyl) phenyl] propan-1-amine. Chemical Structure can be seen in Figure 1.

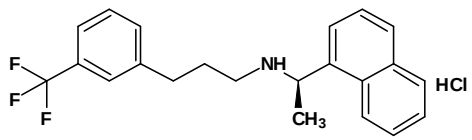

Figure 1 : Structure of Cinacalcet HCl

Table 1 shows some of the process impurities in Cinacalcet HCl.

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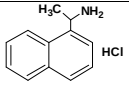
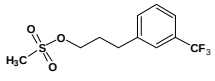
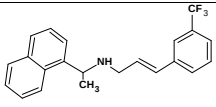
Conflict of interest : None

Table-1: Process Impurities of Cinacalcet Hydrochloride

Structure	Name of Impurity
	Impurity 1 1-(naphthalen-1-yl) ethan-1-amine
	Impurity 2 3-(3-(trifluoromethyl)phenyl) propyl methanesulfonate.
	Impurity 3 (E)-N-(1-(naphthalen-1-yl) ethyl)-3-(3-(trifluoromethyl) phenyl) prop-2-en-1-amine.

The estimation or assay of active pharmaceutical ingredient (API) is one of the key quality attributes. It has enormous significance on account of community health, patient safety, efficacy, and economy of society. (Misiuk W.,2010).Since stability related concerns of drugs are widely discussed in various publications (Xu, Q. A., 2008), the analytical method should be capable to address such challenges.

Cinacalcet HCl is not official in leading pharmacopeia like IP, EP or USP. The various literature depicts uv-spectroscopicestimation of Cinacalcet in Bulk drug or formulation. (Darwish et. Al., 2012; Loni et. Al., 2012; Rao & Gowrisankar, 2016) However, UV spectroscopic methods are non-specific and inefficient to resolve potential challenges arises due to stability.

The objective was to develop simple, fast stability indicative assay method specific to Cinacalcet and its process impurities mentioned above as well as degradation impurities. The ruggedness, accuracy, robustness to be demonstrated by successive validation of method as per regulatory expectations (ICH Q2 R1, 2005).

MATERIALS AND METHODS

Cinacalcet HCl sample was received from Mehta Chemicals Private Limited, Mumbai. All standards were received as a gift from Daicel Lab, Telangana. The solvents and chemicals namely Acetonitrile, KH_2PO_4,and o-phosphoric acid were of analytical grade (Make: Merck). The development and validation were done on Dionex HPLC (3000 series) with variable wavelength detector operated by Chromelon 21 CFR compliant software.

Development trails were done using various combinations of mobile phase including water or buffer pH 3, methanol / acetonitrile and C18, C8, Cyano and C4 column. The good peak shape and good resolution at lower retention was achieved using equal volume of acetonitrile and 0.05 M KH_2PO4 buffer, pH adjusted to 3.0 with o-phosphoric acid. YMC Pack C4 (4.6 mm x 10 cm with internal diameter 3.0 µ) was maintained at 25^0 C and flow rate of 1.0 ml/min was used for elution. The estimation was carried out 215 nm. The injection volume was 10 microliters (µL). The Sample and Standards concentration of 100 ppm was used by appropriate weighing and dilution.

METHOD VALIDATION

Specificity & System suitability Specificity of method was checked by injecting Blank, Cinacalcet Hydrochloride, Impurity 1, Impurity 2, and Impurity 3.Standard was injected in six replicates. The theoretical plates, USP tailing, % RSD of peak response was calculated.

Linearity and RangeLinearity was demonstrated in range of 40 ppm to 150 ppm, i.e.,40 % to 150 % of working concentration.

Precision Repeatability was performed by six individual assay preparations. To demonstrate intraday precision, analysis was repeated with fresh preparation on alternate day.

Accuracy Accuracy was demonstrated by deferential weighing technique (each level in triplicate) and comparing with expected true value. Levels were selected 50%, 100 % and 150% of working concentration.

Robustness Column flow rate was changed to 0.9 ml/ min and 1.1 ml/ min from 1.0ml/min. In subsequent chapters, Acetonitrile concentration was changed to 450 ml and 550 ml instead of 500 ml, keeping buffer concentration same.

RESULTS AND DISCUSSION

Specificity and System Suitability

No interference from Blank or any known impurities are observed at RT of Cinacalcet Hydrochloride, Impurity 1, Impurity 2 and Impurity 3. In figure 2, API was spiked with impurities. System Suitability results are mentioned in Table 2.

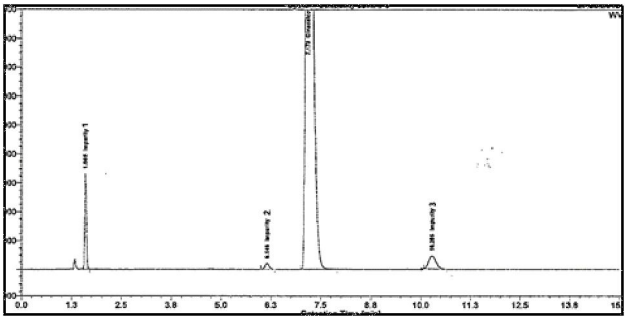


Figure 2 : Spiked chromatogram of Cinacalcet with Known Impurities

Table-2 : System Suitability for Cinacalcet Standard replicates

System Suitability Criteria	Results
% RSD (NMT 0.73)	0.17
Theoretical plates (NLT 2000)	8890
USP tailing factor: (NMT 2.0)	1.5

Linearity and Range

A liner detector response was observed for Cinacalcet in range of 40 ppm to 150 ppm.

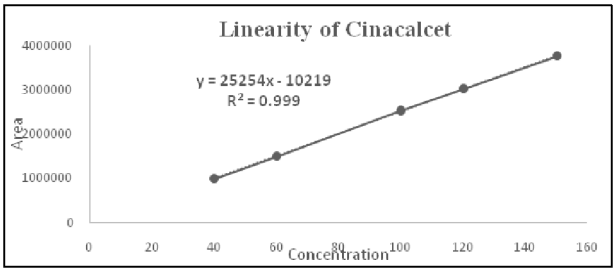


Figure 3: Calibration Curve for Cinacalcet Hydrochloride

Precision

% RSD of Assay value in both repeatability and intermediate precision was less than 2.0%. % Variation of assay value between Repeatability and Intermediate precision was 0.17%

Table-3: Repeatability and Intermediate Precision

	Repeatability % Assay	Int Precision % Assay
Mean	99.60	99.43
% RSD (NMT 2.0)	0.21	0.15

Accuracy

Accuracy for each preparation was found to be between 99.19% to 110.9%

Table-4: % Accuracy for Cinacalcet HCl

	Level 1	Level 2	Level 3
% Accuracy (Mean)	99.24	99.71	99.87

Robustness

% variation of assay value in each robustness study is less than 0.52.

Table-5: % Variation Between in Precision Study and Robustness Study

Study	% Mean Assay	% Variation
Precision	99.6	NA
Rob 1	99.53	0.07
Rob 2	99.08	0.52
Rob 3	99.26	0.35
Rob 4	99.95	0.35

CONCLUSION

A short, economical method was developed for quantitation of Cinacalcet Hydrochloride in bulk drug, which can also be used for assay or dissolution of Cinacalcet Tablet. The method is specific for process as well as degradation impurities. The method was validated and can be routinely employed for release and stability analysis.

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