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Determination of 3-Trifluoromethyl benzaldehydegenotoxic impurity in Cinnacalcet drug substances

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ABSTRACT

A new simple, sensitive HPLC method developed and validated for the determination of 3- Triflouromethyl benzaldehyde in Cinacalcet. 3- Triflouromethyl benzaldehyde was separated on Inertcil ODS-3V analytical column with water and acetonitrile used as mobile phase at a flow rate 1.0ml/min. The effluent was monitored by UV detection at 240nm. Column temperature maintained at 35ºC, injection volume 25µl. Calibration plots were linear in the range of LOQ to 150% level and LOQ and LOD were 0.06 and 0.02.The high recovery and low relative standard deviation confirm the suitability of the method for routine quality control determination of 3-Triflouromethyl benzaldehyde in Cinnacalcet.

INTRODUCTION

Cinacalcet is chemical named (R)-N-[1-(1-naphthyl)ethyl]-3-[3-(trifluoromethyl) phenyl] propan-1-amine. It is a novel and typical drug used for the treatment of secondary hyperparathyroidism (elevated parathyroid hormone) which is the common. Cinacalcet is a drug that acts as calcimimetic (i.e.it mimics the action of calcium on tissues) by allosteric activation of the calcium-sensing receptor that is expressed in various human organ tissues. Based on the route of synthesis there were many intermediate and raw material used for the synthesis of cinacalcet drug substance.

In pharmaceutical industry, drug development demands several physical and chemical properties to evaluate in the drug substance to satisfy the FDA and ICH regulations. Among those properties, the genotoxic impurity control and determination is essential and most important significant factor. Though different analytical techniques are available to determination of content of cinacalcetand its potential process and degradation productsby Spectrophotometric (1) and by HPLC(2-10), there was no method available to determination of 3- Triflouromethyl benzaldehyde genotoxic impurity in Cinacalcet bulk drug.

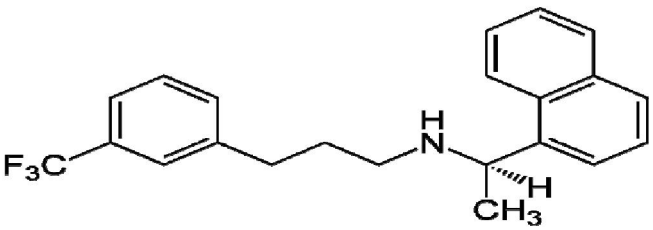

Figure 1 : Cinacalcet

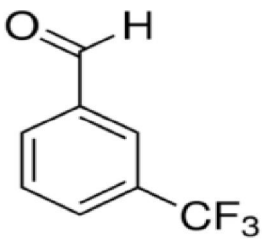

Figure 2 : 3- Triflouromethyl benzaldehyde

MATERIAL AND METHODOLOGY

Chemicals and reagents

Milli-Q water is used in all reagent preparations. Acetonitrile are analytical grade chemicals purchased from Rankem. All pure drug substance and impurities are used for research in Macleods Pharmaceuticals Ltd.

Chromatographic conditions

A Shimadzu (LC-2010CHT) HPLCs equipped with PDA Detector were used for analysis. Milli Q water and acetonitrile are used for mobile phase preparation. A Inertsil ODS 3V, 250mm X 4.6mm) 5µ Column and gradient mixture of Milli Q water and Acetonitrile used as stationary and mobile phase respectively. The gradient program (Time / % Acetonitrile) was fixed as (0.01/50),(15.0/50),(20.0/70),(25.0/70),(30.0/50),(35.0/50). Milli Q Water and acetonitrile (in the ratio of 1:1) used as diluent. The column oven maintained at 35°C with 1.0ml/minute flow rate. An Injection volume 25µL was used. The elution compounds were monitored at 240nm.

Preparation of standard and sample solutions

A stock solution of 3-Trifluoromethyl benzaldehyde impurity was prepared by dissolving the appropriate amount of 3-Trifluoromethyl benzaldehyde impurity in diluent. Working concentration of 0.25ppm impurity solution were prepared from the stock solution and used as standard solution. The sample solutions (60000ppm) were prepared by weighing 600mg of drug substance and transferred to 10mL of Volumetric flask.

RESULT AND DISCUSSIONS

Method development optimizations

The main target of chromatographic method was to achieve the separation of genotoxic impurity of 3-Trifluoromethyl benzaldehyde impurity from other process and degradent impurities and main components. The maximum absorption wavelength of 3-Trifluoromethyl benzaldehyde impurity was 240nm, which was obtained from UV-Spectrum. Hence 240nm was selected for the quantification of this impurity in the cinacalcet drug Substances. After many trial of different gradient composition, the 3-Trifluoromethyl benzaldehyde was separated from other process and degradent impurities and main peak. Based on the above experimental date the chromatographic separation was finalized by the following gradient program Time / % Solution B(0.01/50),(15.0/50),(20.0/70),(25.0/70),(30.0/50),(35.0/50) by using Milli Q water and acetonitrile. The flow rate of mobile phase was 1.0ml per minute with column temperature at 35°C and detection wavelength 240nm. The injector volume was 25µl. In this condition the genotoxic impurity was separated from main peaks and there was no interference from process and degradant impurities. The system suitability results are shown in TABLE-1.

ANALYTICAL METHOD VALIDATION

The described LC Method has been validated for genotoxic impurity determination in cinacalcet as per ICH guidelines:

System suitability

The standard solution was prepared and injected in six replicate into HPLC System before starting every validation parameter. The % RSD of the peak due to 3-Trifluoromethyl benzaldehyde impurity in diluted standard solution was reported.

Specificity

Specificity is the ability to assess unequivocally in the presence of its potential impurities which may be expected to be present. Spiked studies were performed on cinacalcet contains 3-Trifluoromethyl benzaldehyde genotoxic impurity to provide an indication of the stability –indicating property and specificity of the proposed method.

Precision

Six Individual measures of 3-Trifluoromethyl benzaldehyde impurity in cinacalcet were performed with 0.005%w/w of impurity spiked in cinacalcet drug substance of target concentration. The content of gentoxicity impurity of 3-Trifluoromethyl benzaldehyde was determined for each of the preparations and method precision was evaluated by calculating

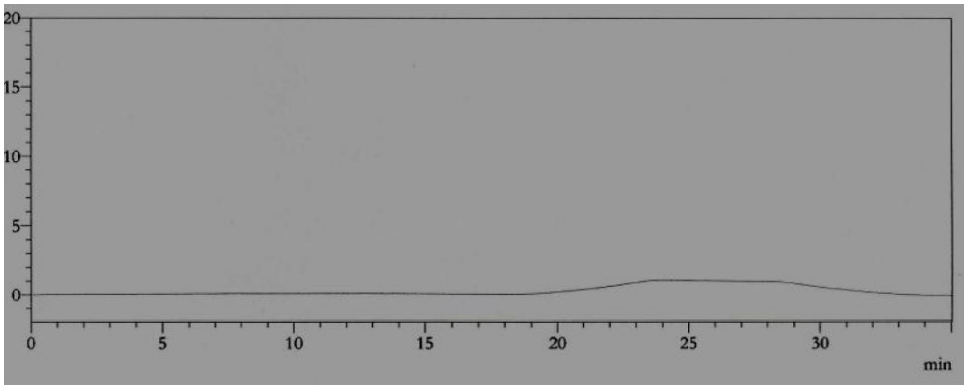

Figure 3 : Blank

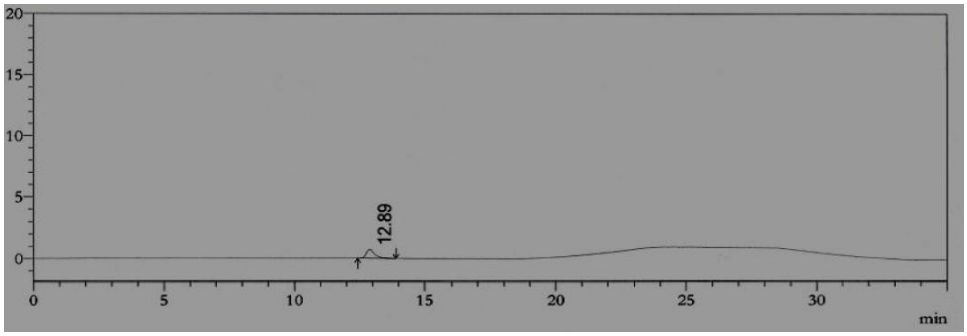

Figure 4 : Standard

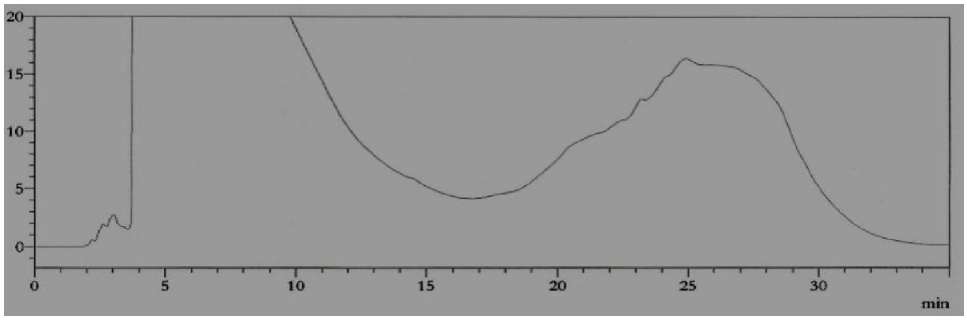

Figure 5 : Sample

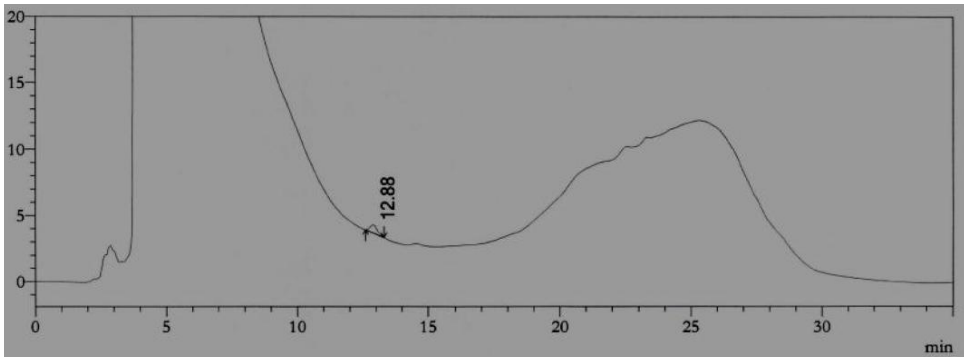

Figure 6 : Spiked

percentage RSD of the impurity content in six preparations. Experiment with a different analyst, column and instrument in the same laboratory were performed in order to ascertain the intermediate precision of the developed method. From TABLE 1, the %RSD for the content of 3-Trifluoromethyl benzaldehyde impurity were less than 5.30%, confirming the high precision of the method. The results are

TABLE 1 : Validation results

Sr. No.	Parameters	Experiment	Acceptance Criteria	Results
1	Specificity	Blank	No interference	Complies
		Impurities	No interference	Complies
2	LOD & LOQ	Limit of detection And Quantitation		3-Trifluoromethyl benzaldehyde impurity
			LOD conc. in% w/w	0.02
			LOQ conc. in % w/w	0.06
			% RSD at LOQ level should NMT 15.0	1.45
3	Linearity & Range			3-Trifluoromethyl benzaldehyde impurity
		Slope	Record Results	70090.89552
		Intercept	Record Results	829.66368
		Correlation Coefficient	Minimum 0.99	0.99
		Range (µg/mL)	Record Results	0.06 µg/mL to 0.38 µg/mL
4	Precision	System Precision		3-Trifluoromethyl benzaldehyde impurity
			RSD NMT 10.0 %	1.43
		Repeatability	RSD NMT 10.0 %	5.30
		Intermediate Precision	RSD NMT 10.0%	6.14
5	Accuracy	LOQ	Recovery should be 80.0% to 120.0 %	95.0%-96.7%
		50%		85.7% - 107.1%
		100%		87.3% - 88.5%
		150%		97.6% - 98.8%
6	System Suitability	Diluted Standard solution to be injected before starting every validation parameter	% RSD of peak due to 3-Trifluoromethyl benzaldehyde impurity, should be NMT 10.0	Complies

shown in TABLE 1.

Limit of detection and limit of quantification

The LOD and LOQ for 3-Trifluoromethyl benzaldehyde was determined at Slop linearity method by injecting a series of dilute solutions with known concentrations. Precision study was also carried out at LOQ level by injecting six individual preparations and calculating the %RSD of the area. The limit of detection of 3-aminophenol impurity was 0.02 (of analyte concentration mg/ml). Under the same conditions, the LOQ was 0.06. The precision of 3-Trifluoromethyl benzaldehyde at LOQ Concentration level was less than 1.45%. The results are shown in TABLE 1.

Linearity and range

The linearity of the method was estabilished at a low level as performed by preparing six different solutions from the LOQ to 150% (LOQ, 50,80,100,120 and 150%) of 3-Trifluoromethyl benzaldehyde impurity with respect to target analyte concentrations. The peak area versus concentration data was plotted for linear regression analysis. The linear calibration plot for the method was obtained over the calibrations ranges tested from LOQ to 150% for 3-Trifluoromethyl benzaldehyde impurity. The correlation coefficient obtained was greater than 0.99 for genotoxic impurity of 3-Trifluoromethyl benzaldehyde. The result are shown in TABLE 1.

Accuracy

The accuracy of the genotoxic impurity, method was evaluated at four concentration levels of LOQ, 50%,100% and 150%. Recovery was calculated for 3-Trifluoromethyl benzaldehyde added concentration. The percentage recovery of 3-Trifluoromethyl benzaldehyde impurity was calculated by consider-

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ing the amount of the impurity spiked. The recovery is further calculated by using formula and the results were found to upto the mark and tabulated in TABLE 1. The recovery of the 3-Trifluoromethyl benzaldehyde impurities in cinacalcet ranged from 85.7 to 107.1 %. The results are shown in TABLE 1 and it is observed that the method is accurate within the determined range.

CONCLUSION

A simple, new specific, linear, precise, sensitive and accurate RP-HPLC method has been developed and validated for quantitative determination of 3-Trifluoromethyl benzaldehyde genotoxic impurity in cinacalcet bulk drug substances. The method was stability indicating and can be used for routine analysis for quality control.

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