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A QUANTITATIVE DETERMINATION OF CHLOROACETIC ACIDS IN CETIRIZINE HYDROCHLORIDE API BY GAS CHROMATOGRAPHY

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ABSTRACT

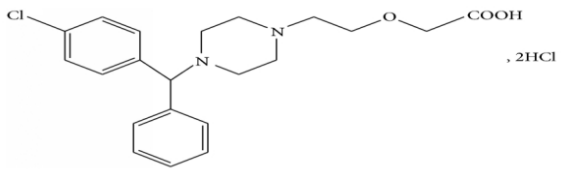
A gas chromatographic procedure has been developed for the determination of chloroacetic acid in cetirizine hydrochloride API. Due to the high polar acidic in nature of chloroacetic acid, compound was not eluted properly in Gas chromatograph column. Therefore derivatizating technique need, Compound was derivatised using reagent N, O-Bist (trimethylsilyl) trifluoroacetamide (BSTFA) in presence of methyl tert-butyl ether solvent prior to their analysis via gas chromatogram coupled with a flame ionization detector (GC-FID). The derivatised chloroacetic acid was well separated on HP-5 column, 30 m, 0.32 mm ID, 0.25µm film thickness. The oven program was 40°C initial temperature hold time 8.0 minute, then 20°C ramp per min upto 200°C then hold to 4.0 minute. This analytical method was validated as per international conference on harmonization guideline for parameter specificity, linear, accuracy, precision and limit of detection and limit of quantitation. The obtained recovery of chloroacetic acid was found to be 90% to 110% and detection and quantitation limit was 0.0081% and 0.025% with respective to cetirizine hydrochloride API. The linearity was ranging from 0.08 to 0.23% with respective to cetirizine hydrochloride API and the observed correlation coefficients was 0.9990. The repeatability was evaluated against limit concentration and at LOQ level concentration, which were obtained as 1.82% and 2.05%.

KEYWORDS: Cetirizine hydrochloride API, Gas chromatograph, Chloroacetic acid, Derivative, Method development, Validation.

1. BACKGROUND OF THE INVENTION

Chloroacetic acid play an important roles in chemical and pharmaceutical industries, most of time it is used in industrial processes such as production of dyes, insecticides and active pharmaceutical ingredients. The chloroacetic acid was difficult to analyze by Gas chromatography method due to their highly polar acidic in nature, therefore need to prepare derivative of chloroacetic acid to improve the volatility and peak shapes on a chromatographic column. The BSTFA (N, O-bis (trimethylsilyl) trifluoroacetamide) was one of the preferred reagent for derivatizating of trimethylsilylation of alcohols, alkaloids, amines, biogenic amines, carboxylic acids, phenols, and steroids. The BSTFA (N, O-bis (trimethylsilyl) trifluoroacetamide) will readily silylate a wide range of non-sterically hindered functional groups. TMCS is a silylation catalyst, rarely used alone with analytical applications but typically mixed with other silylation reagents to increase their reactivity in derivatization.

In synthesis of cetirizine hydrochloride API at intermediate stage, sodium 2-chloroacetate one of the chemical used in manufacturing process, this chemical sodium 2-chloroacetate gets converted into chloroacetic acid in the manufacturing process, therefore need to control those chloroacetic acid in intermediate stage as well as final finished product. To control this chloroacetic acid we have to develop a gas chromatographic method. Base on the nature of compound and solubility of product we developed the method and validate as per ICH guideline. The cetirizine hydrochloride API, prominently marketed under the brand name Zyrtec among others, is a potent second-generation antihistamine used in the treatment of hay fever, allergies, angioedema and urticaria. It acts as a selective antagonist of the histamine H1 receptor. Because the symptoms of itching and redness in these conditions are caused by histamine acting on the H1 receptor, blocking those receptors temporarily relieves those symptoms.Cetirizine is also commonly prescribed to treat acute and (in particular cases) chronic urticaria, more efficiently than any other second-generation antihistamine. The structure of cetirizine hydrochloride is as follows.



Chemical / IUPAC name: 2-(2-(4-((4-chlorophenyl) (phenyl) methyl) piperazin-1-yl) ethoxy) acetic acid Dihydrochloride

Figure 1: Structure of Cetirizine.

2.0 MATERIALS

2.1 Reagent and Chemicals

The chemicals and reagent used for development and validation are N,O-Bis(trimethylsilyl) trifluoroacetamide (BSTFA), Chloroacetic acid AR grade procure from Sigma-Aldrich, Sulphuric acid AR and Methyl tertiary butyl ether AR grade (MTBE) procure from Merck, Cetirizine hydrochloride API provides by analytical research and development of Indoco Remedies Limited, Rabale.

2.2 Instrumentation

PerkinElmer, Clarus 500, Gas Chromatograph (GC) with Flame Ionisation Detector and Turbomatrix 40 headspace autosampler, a thermostatic column compartment, 2 ml sample vials with PTFE septa. Agilent HP-5 column 30 m * 032 mm ID * 0.25µm or equivalent. Data acquisition and calculations were carried out using Total chrome navigator software version 6.3.2.0646 and Sartorius (Germany) analytical balance was used for weighing standards and samples.

3.0 METHODOLOGY

3.1 Method optimization

Chlroacetic acid play as an important roles in chemical and pharmaceutical industries. It is very difficult to analyze by gas chromatography method due to their highly polar acidic in nature, therefore method development need to control chloroacetic acid impurity in different stages of manufacturing process. For development we required different instrumental technique also. In developmental trial, initial we check the solubility of cetirizine hydrochloride product in different solvent like DMSO, DMF and NMP. Whichever the best solubility of cetirizine hydrochloride API, those solvents used for further development. First product was dissolved in NMP solvent and then injected into a gas chromatograph with available column and observed the raw data outcome. The cetirizine hydrochloride API with chlroacetic acid peaks were not eluted in gas chromatograph due to the non-volatility nature. Then we tried with head space technique, in headspace technique approx. 1500 ppm of chloroacetic acid working standard was dissolved in NMP and incubate for 30 minute with static pressure, then generated gases was transfer to detector end and observed the peaks. The data shows that there was no any peak observed at retention time of chlroacetic acid. The chlroacetic acid molecule was high boiling point about 189.3°C, due to the higher boiling point of chlroacetic acid may not be transfer to detector end therefore further trial was taken with increasing an

autosampler temperature and thermo statistic time with different diluent solvent, but still no improvement in chlroacetic acid standard peak was observed. Base on avaible raw data and study we conclude that it is very difficult to quantify chlroacetic acid with headspace technique.

Then we tried with extraction technique, in extraction technique we use different solvent like Methylene dichloride, Toluene, Ether and Methyl tert-butyl ether (MTBE) for solubility purpose. Base on solubility of chlroacetic acid standard and cetirizine hydrochloride API with above solvent. We take best solubility solvent as MDC and MTBE solvent. We select first those solvents for extraction then tried for development. In extraction technique first cetirizine hydrochloride was dissolve in water further added 10% H_2SO_4 and MDC for extraction, shake well, then extract. The organic layers and aqueous layer were separated, the organic layers was collected in to 10 ml volumetric flask then added derivatizating reagent and make to volume with same diluent. The water layer should be discard. The derivatised sample was kept to 40 min and then injected directly into the injector of gas chromatogram. The derivatised chloroacetic acid peak was observed, then check with specificity for peak separation. To verify the analytical method we did one of the accuracy level, but the accuracy was not found within limit therefore we take another solvent as MTBE and perform the same experiment and check the specificity and accuracy. The results shows well separation in peak and good recovery. Hence we concluded that MTBE was best solvent for extraction. For whole development purpose we used HP-5 column, 30 m, 0.32 mm ID, 0.25 µm film thickness. The developed method was validated as per ICH guideline for all other parameter.

Diluent

Methyl tert-butyl ether AR grade (MTBE).

Blank solution

Transfer 5 mL 10% H_2SO_4 in to 250 ml separating funnel then add 5 mL MTBE shake well and take upper MTBE layer. Transfer the upper layer in to a 10 mL volumetric flask then added 0.5 mL BSTFA reagent make upto volume by diluent, keep it at 40^{o}C for 15 min,cool then inject derivatised blank.

Standard stock solution

Weigh accurately about 0.50 g of Chloroacetic acid working standard into a 100 mL volumetric flask and make upto volume with diluent. Transfer 0.3 mL solution into a 10 mL volumetric flask and make upto volume with diluent.

Standard solution

Transfer 1 mL standard stock solution into 10 mL volumetric flask then add 0.5mL BSTFA reagent and make upto mark with diluent, keep it at 40^{o}C for 15 min. cool then inject derivatised standard.

Test solution

Weight about 0.5 g sample into 250 ml separating funnel add 5 mL 10% H_2SO_4, shake to dissolve it, then add 5 mL MTBE shake well, keep for some time for separation of layer. Transfer the upper MTBE layer into a 10 mL volumetric flask, add 0.5 mL BSTFA reagent and make up to volume then keep it at 40^{o}C for 15 min. Cool then inject derivatised test solution.

Chromatographic Conditions

Equipment	**Gas Chromatograph**
Model	Perkin Elmer, Clarus 500 with head space
Column	HP-5 30 m * 032 mm ID * 0.25mm or equivalent.
Detector	Flame Ionization Detector
Oven temperature	Initial 40°C, hold for 8.0 minutes
	Increase @ 20°C per minute to 200°C
	Hold at 200°C for 4.0 minutes
Detector Temperature	220°C
Injector Temperature	200°C
Attenuation	- 6
Split Ratio	10:01
Carrier Gas	Nitrogen
Carrier Gas Flow	1.50 mL/min
Run time	35 min
Range	01

Injection sequence

Sl#	**Description**	**No. of Injections**
1	Blank	2
2	Standard solution	6
3	Blank	2
4	Test solution-1	1
5	Test solution-2	1

Procedure

Condition the column at 200°C for two hours and equilibrate the column at 40°C.

Evaluation of blank

Place blank solution in the magazine. Inject blank solution and record the chromatogram. Make blank correction if necessary.

Evaluation of standard solution

Inject the standard solution into the magazine and inject six replicate and record the chromatograms. Ensure that system suitability parameters are satisfied.

System suitability

Acceptance criteria

Number of Theoretical plates

The number of theoretical plates calculated for the six replicate injections of standard solution should not be less than 5000.

% RSD: The % RSD for six replicates of areas should not be more than 15.0 in standard solution.

Procedure

Inject blank solution, standard solution then test solution in duplicate and record the chromatograms. The retention time of standard solution should match as given below.

SI#	Solvents	Retention Time (About in min)
1	Chloroacetic acid	10.8

Calculations

Calculate chloroacetic acid content form Test solution-1 and Test solution-2 and report the average content by using the following formula:

$$\text{Content of chloroacetic acid (\%)} = \frac{AT \times WS \times 0.3 \times 5}{AS \times WT \times 100 \times 10} \times P$$

Where,

AT is peak area of test solution.

AS is average peak area of standard solution.

WS is weight in g of standard solution.

WT is weight in g of sample soution.

P is purity of working standard.

4.0 Analytical Method Validation

The developed method is subjected to analytical method validation, which is conducted according to the International Council for Harmonisation (ICH) guidelines.[5-10] The parameter which was taken for analytical method validation are specificity, limit of detection, limit of quantitation, linearity, accuracy, precision and robustness.

5.0 RESULTS AND DISCUSSION

5.1 System suitability

The system suitability test represents as an integral part of the method and used to ensure adequate performance of the chromatographic system. To check the system suitability, inject mixture of standard solution and observed the peak tailing factor, number of theoretical plates and percentage relative standard deviation for replicate injections. The relative standard deviation, theoretical plate and tailing factor were recorded in Table 2. The percentage relative standard deviation should be less than 15.0, tailing factor should not be more than 2.0 and the theoretical plate should not be less than 5000. The system suitability was checked before each validation parameters.

Table 2: System suitability data.

Sr No.	Name of standard	Retention Time	Theoretical plates	Tailing factor
1	Chloroacetic acid	10.8	372312	1.56

5.2 Specificity

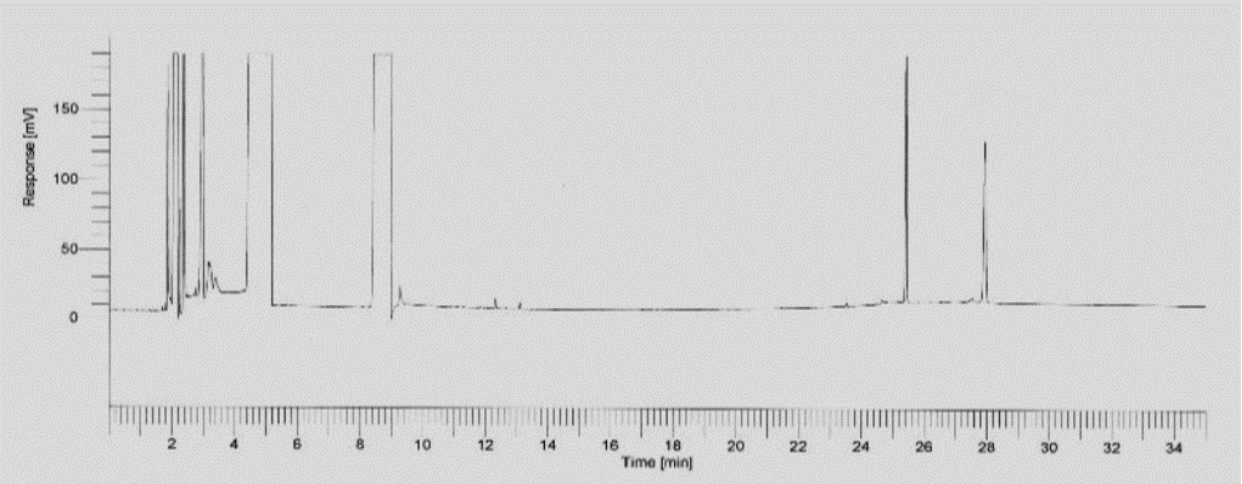
Specificity is the capability of the method to measure the response of standard in presence of drug substance and its impurities. Figure 1 shows the typical chromatograms of the blank as methyl tertiary butyl ether (MTBE), Chloroacetic acid Standards, Test sample, and sample mixed with Chloroacetic acid standard. The results indicated that standard chloroacetic acid peak was well separated under the optimized chromatographic conditions from all other impurities and API. There was no interference of peaks due to blank solution and the samples solution within the retention time of chloroacetic acid peak obtained. The retention times of chloroacetic acid refer Table No.03.

Table 03: Retention time of Solvent.

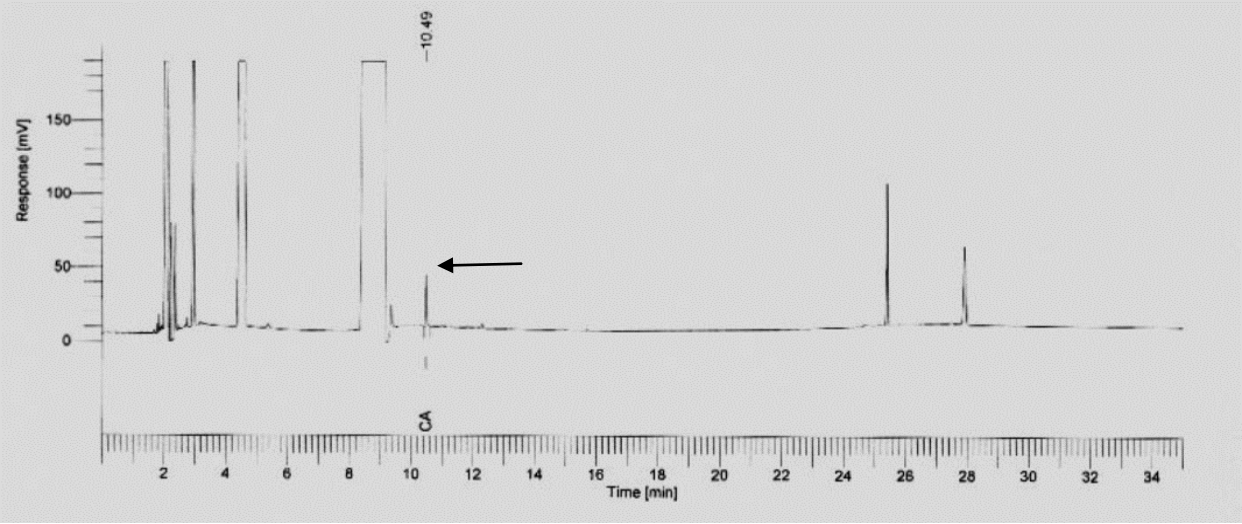
Sr No.	Name of standard	RT
1	Chloroacetic acid	10.8

Typical chromatogram

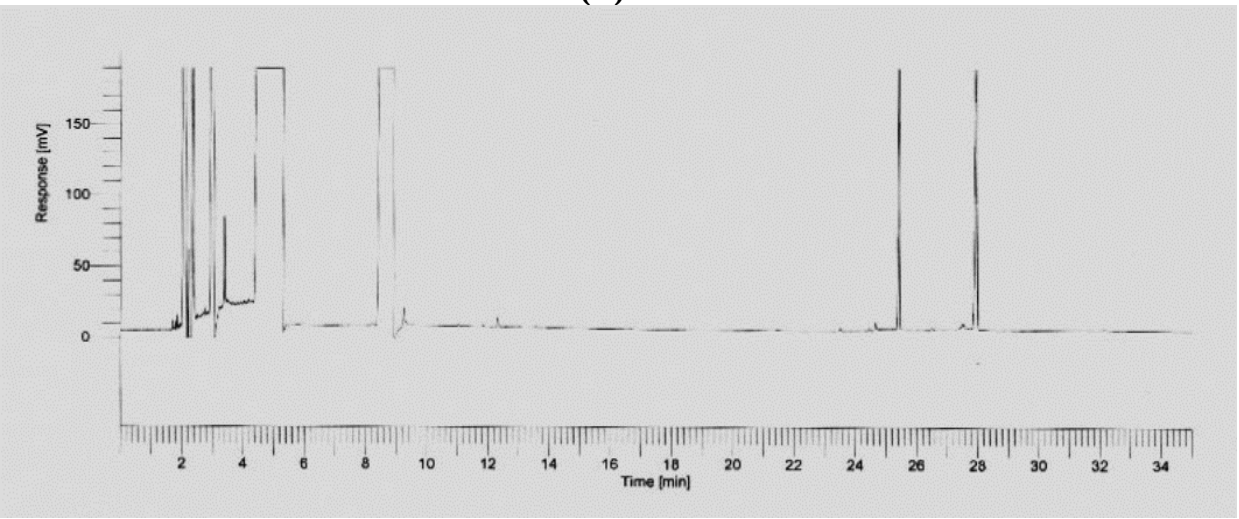
(A)



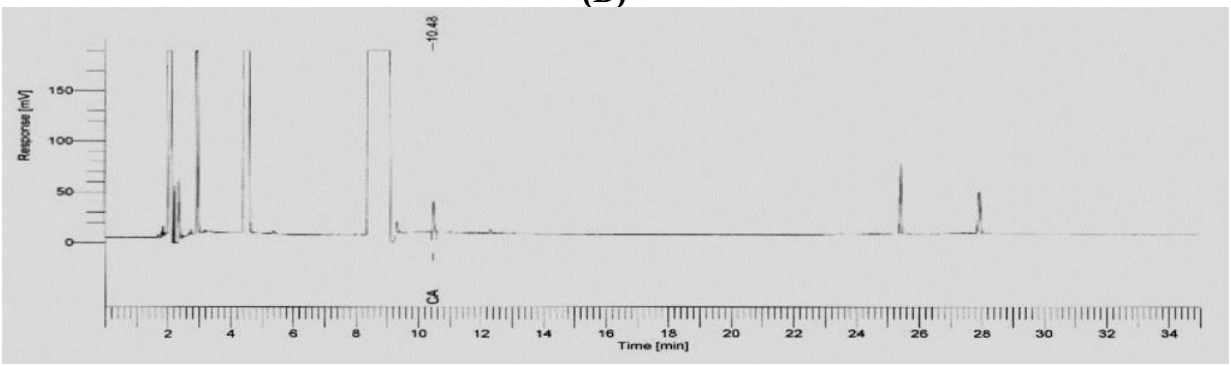
(B)



(C)



(D)



A) Diluent, B) Chloroacetic acid Standards, C) Cetirizine hydrochloride Sample, D) Sample with Chloroacetic acid Standards.

Figure 2: Specificity.

5.3 Limit of detection and limit of quantitation

A serial concentration of chloroacetic acid working standard were injected in system and calculate the signal to noise ratio based on residual standard deviation (STE_{YX}) as and slope as per ICH guidline. The calculated Limit of detection (LOD) and Limit of Quantitation (LOQ) should be within limit and it show 0.0081% as LOD and 0.025% as LOQ (Table 04).

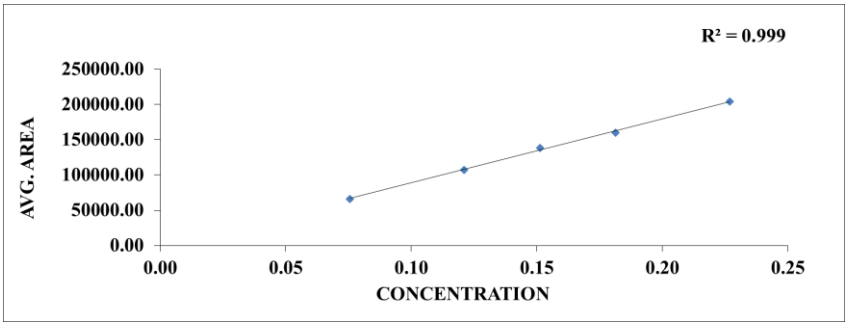
Table 04: Limit of detection and quantitation.

Sr. No	Standard	RT	LOD in %	LOQ in %
01	Chloroacetic Acid	10.855	0.0081	0.025

5.4 Linearity

A serial dilution of chloroacetic acid standard solution were prepared from 50% to 150% of target concentration. The linearity curves were drawn by plotting the peak response of Chloroacetic acid working standard against its corresponding concentration. The plotted graph of area against test concentration and calculate the regression coefficient, slope and % y intercept and report the result in Table 05. The calculated regression coefficient should be greater than 0.999 and % y intercept was less than 5.0%.

Table 05: Linearity figures and Results.



Slope : 994599.09

Intercept : -1595.18

%y-Intercept : -1.15498

Regression coefficient (R^2) : 0.9990

5.5 Precision

System precision was an integral part of instrument and its shows instrument was working satisfactory. System precision test was carried out by injecting six replicate of chloroacetic acid standard solutions at limit level concentration, where as in LOQ precision parameter, expected LOQ concentration was injected in replicate and check the relative standard deviation. The relative standard deviation for chloroacetic acid standard solution was found to be 1.82% and for LOQ level was below 2.05% (Table 06).

Table 06: System precision and precision at LOQ.

Sr. No	Parameter	%RSD
01	System Precision	1.82
02	LOQ Precision	2.05

5.6 Accuracy

Accuracy of the method was established by carrying out the recovery of impurity in test sample. The test sample was spiked with chloroacetic acid standard at specified limit level concentrations 50%, 100% and 150%. Each spiked test solution was analyzed for recovery study and observed the percentage recovery. Recovery obtained for doped working standard should be between 80% to 120% (Table-07, 08 and 09).

Table 07: Recovery of Impurities-50%.

Sr #	Standard Name	Standard Area	Sample Area	Standard Wt (g)	Sample Wt (g)	% Recovery
1	Chloroacetic Acid	126921.71	66271.32	0.5041	0.5033	104.6
2		126921.71	66321.12	0.5041	0.5089	103.5
3		126921.71	65874.17	0.5041	0.5092	102.8

Table 08: Recovery of Impurities-100%.

Sr #	Standard Name	Standard Area	Sample Area	Standard Wt (g)	Sample Wt (g)	% Recovery
1	Chloroacetic Acid	126921.71	138113.03	0.5041	0.5023	109.2
2		126921.71	137524.12	0.5041	0.5074	107.6
3		126921.71	131453.23	0.5041	0.5089	102.6

Table 09: Recovery of Impurities-150%.

Sr #	Standard Name	Standard Area	Sample Area	Standard Wt (g)	Sample Wt (g)	% Recovery
1	Chloroacetic Acid	126921.71	178138.6	0.5041	0.508	92.9
2		126921.71	178453.5	0.5041	0.5078	93.1
3		126921.71	177453.4	0.5041	0.5005	93.9

6.0 CONCLUSION

A derivatised selective Gas Chromatographic method was developed and validated for the quantitate determination of chloroacetic acid present in cetirizine hydrochloride bulk drug through an understanding of the synthetic process, nature of impurity and nature of stationary phases of columns. The method was shown to be specific, liner, accurate and precise for Cetirizine hydrochloride API and was applied successfully to monitor and control of chlroacetic acid on a manufacturing level. The method was found to be applicable for the routine analysis of the cetirizine hydrochloride API in pharmaceutical industry.

7.0 ACKNOWLEDGMENT

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