



Research Article

HPLC METHOD DEVELOPMENT AND VALIDATION FOR THE DETECTION OF UNKNOWN IMPURITIES IN CETIRIZINE HYDROCHLORIDE DROPS

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ABSTRACT

Cetirizine hydrochloride oral liquid formulations require stability-indicating impurity profiling to ensure quality and safety. To develop and validate a robust RP-HPLC method for detection of unknown impurities. Separation achieved on Intersil ODS 3V C18 (4.6 × 250 mm, 5 μm) using acetonitrile: 1-heptanesulphonate sodium buffer: sulfuric acid (25:75:0.3 v/v/v), flow rate 1.0 mL/min, detection at 230 nm. Validation performed as per ICH Q2(R2) guidelines. Excellent linearity ($r^2=0.9999$) from 1.25-150%. Significant degradation under oxidative (10.837%) and photolytic (6.445%) conditions. Precision (%RSD<2%), recovery (98.91-100.41%), LOD (0.0524 μg/ml), LOQ (0.1587 μg/ml), robustness and stability met acceptance criteria. The method is stability-indicating and suitable for routine quality control and stability studies.

Keywords: Method validation, Related substances, Stability-indicating method, HPLC, Forced degradation.

INTRODUCTION

Cetirizine hydrochloride is a piperazine derivative belonging to the diphenyl methyl class of second-generation antihistamines. Chemically, it is described as: (±)-2-(2-(4-((4-chlorophenyl) phenylmethyl) piperazin-1-yl) ethoxy) acetic acid dihydrochloride. The structure consists of: A diphenyl methyl moiety, with one phenyl ring substituted at the para position by chlorine. piperazine ring, responsible for antihistaminic activity. An ethoxy acetic acid side chain is attached to the piperazine nitrogen. Present as a dihydrochloride salt, enhancing water solubility. Cetirizine exists as a racemic mixture of L- and D-enantiomers, where levocetirizine represents the pharmacologically active L-enantiomer (British Pharmacopoeia Commission, 2023; (European Pharmacopoeia Commission, 2002). Cetirizine is commonly administered orally in various dosage forms including tablets, capsules, syrups, and oral drops. Following oral administration, the drug is rapidly absorbed

and typically begins to produce therapeutic effects within approximately 30 minutes, while its pharmacological action persists for nearly 24 hours. Compared with first-generation antihistamines such as diphenhydramine, cetirizine demonstrates improved selectivity for peripheral H1 receptors and produces relatively fewer central nervous system effects due to its limited penetration across the blood-brain barrier (Pharmaceutical Press, 2018; American Society of Health-System Pharmacists, 2019). Nevertheless, mild sedation may still occur in certain individuals. Other commonly reported adverse reactions include headache, dry mouth, gastrointestinal discomfort, and mild drowsiness (Slater *et al.*, 1999). From a pharmacokinetic perspective, cetirizine exhibits dose-proportional behaviour within the therapeutic range of approximately 5-60 mg. After oral administration, the drug reaches peak plasma concentration within about one hour regardless of the dosage form. The reported oral bioavailability of cetirizine is approximately 70%, whereas its active enantiomer, levocetirizine, demonstrates slightly

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higher absorption efficiency (Portnoy & Dinakar, 2004; Current Medicinal Chemistry, 2008; Simons & Simons, 1999). Structurally, cetirizine exists as a racemic mixture consisting of two stereoisomers, namely the L- and D-forms. Levocetirizine represents the biologically active L-isomer responsible for most of the antihistaminic activity. Cetirizine belongs to the diphenylmethylpiperazine group of antihistamines, which also includes structurally related compounds such as hydroxyzine and cyclizine (Zhang *et al.*, 2013). Various analytical techniques have been reported for the determination of cetirizine hydrochloride in bulk drug substances and pharmaceutical formulations. Conventional approaches include acid-base titrimetric analysis as well as spectroscopic techniques such as UV spectrophotometry and spectrofluorimetric. Other analytical methods including calorimetric analysis, ion-selective electrode techniques, thin-layer chromatography (TLC), and high-performance thin-layer chromatography (HPTLC) have also been employed for the estimation of cetirizine (Parfitt, 1999; Haraguchi & Nothenberg, 1998; European Pharmacopoeia Commission, 2002; Suryanarayana *et al.*, 1992; Portnoy & Dinakar, 2004; El-Walily *et al.*, 1998; Zarapkar *et al.*, 1998; Jelinska *et al.*, 2000; Wen *et al.*, 2001; Paw *et al.*, 2002; Parthasaradhin *et al.*, 1993; Garg *et al.*, 1995; Melwanki *et al.*, 2001; Gazy *et al.*, 2002; Basavaiah & Srilatha, 1999; Prakash *et al.*, 2000; Gowda *et al.*, 2001; Shoukry *et al.*, 1999; Misztal & Paw, 2001; Makhija & Vavia, 2001). Among these methods, high-performance liquid chromatography (HPLC) has become the most widely applied analytical technique due to its high sensitivity, accuracy, reproducibility, and suitability for

pharmaceutical quality control. Several reported HPLC methods for cetirizine analysis utilize reversed-phase C18 columns with mobile phases containing acetonitrile, sodium n-heptane sulfonate, and strongly acidic aqueous buffers, with ultraviolet detection typically performed at approximately 230 nm. Although these methods provide satisfactory chromatographic separation, the use of highly acidic mobile phases may lead to rapid deterioration of chromatographic columns and reduced analytical stability during routine laboratory analysis. Despite the availability of multiple analytical methods, many previously reported procedures lack sufficient robustness for long-term routine quality control applications. In particular, the use of extremely acidic mobile phases can significantly shorten column life and increase operational costs. Furthermore, some reported methods do not adequately address impurity separation or stability-indicating capability under stress conditions. Consequently, there remains a need for a more reliable and stable chromatographic method that can provide accurate quantification of cetirizine hydrochloride while maintaining column integrity and analytical reproducibility. Therefore, the present study was undertaken to develop and validate a simple, robust, and stability-indicating reversed-phase high-performance liquid chromatography (RP-HPLC) method for the determination of cetirizine hydrochloride in pharmaceutical formulations. The proposed method aims to achieve effective separation of the drug and its potential impurities while improving chromatographic stability and ensuring suitability for routine quality control analysis.

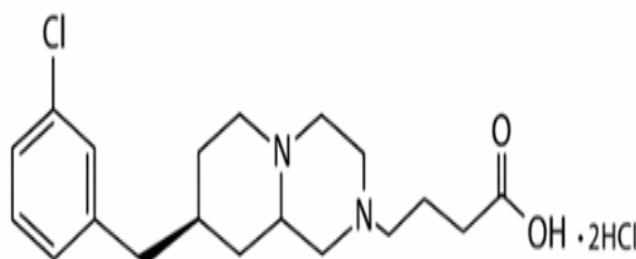


Figure 1. Cetirizine Dihydrochloride.

MATERIALS AND METHODS

Materials

The Cetirizine hydrochloride drops API WS/CET/01/24 (Purity 99.66%), Marketed formulation cetirizine hydrochloride drops (Maxtra) ZD/448/24 (Purity 99.66%) and placebo sample ZD/450/24 (Purity 99.43%) was supplied by Zuventus Healthcare private Limited company.

Chemicals

Analytical-grade or HPLC-grade acetonitrile, sulfuric acid, 1-heptane sulfonate acid sodium and water were used. All

aqueous preparations employed Milli-Q HPLC-grade water to avoid interference in chromatographic separations.

Instrumentation

The analysis was performed using Shimadzu and Waters Corporation HPLC systems equipped with UV and PDA detectors. Stability studies were conducted in a Newtronics photostability chamber, while pH and moisture were measured using a Lab India pH meter and Metalab LOD oven. Chromatographic separation was achieved on an Inertsil ODS-3V C18 Column.

METHOD DEVELOPMENT

Optimized Chromatographic Conditions

Analyses were performed under isocratic conditions using an Intersil ODS-3V column (4.6 × 250 mm, 5 µm). The optimized two mobile phase consisted of acetonitrile:1-heptanesulphonate sodium buffer:sulfuric acid (25:75:0.3, v/v/v) and 100% Acetonitrile delivered at 1.0 mL/min. Samples (20 µL) were detected at 230 nm. Under these conditions, retention times of related substances were approximately three times the main analyte.

Preparation of buffer solution

0.01 M solution was made by dissolving 1.8822 g of 1-heptane sulfonate sodium in 1,000 mL of distilled water. 0.1 M sulfuric acid was used to accurately adjust the pH to 3.0, and the solution was properly mixed to guarantee homogeneity. It acted as a buffering and ion-pairing agent.

Preparation of Mobile Phase A

The mobile phase consisting of 1-heptane sulfonate sodium buffer: acetonitrile: sulfuric acid (25:75:0.3 v/v/v) was prepared, filtered, and degassed before use.

Preparation of Mobile Phase B

100% Acetonitrile was used.

Preparation of Reference Stock solution

About 10 mg of cetirizine hydrochloride standard was accurately weighed and transferred into a 100 mL volumetric flask. About 70 mL of diluent was added and sonicated to dissolve, and the volume was made up to the mark with mobile phase and mixed well.

Preparation of Reference solution:

2 mL of the reference stock solution was transferred into a 100 mL clean and dry volumetric flask. The volume was made up with diluent and mixed well.

Preparation of Sample solution

A 100 mL volumetric flask was filled with 2 g of cetirizine hydrochloride after it had been weighed. To guarantee dissolution, the mixture was sonicated for ten minutes with sporadic shaking after 70 mL of diluent was added. After that, the solution was properly mixed and diluted to volume using more diluent. Lastly, a 0.45 µm nylon membrane filter was used to filter the sample, discarding the first 5 mL of filtrate prior to collection.

Preparation of Placebo solution

2 g of placebo was weighed into a 100 mL volumetric flask, followed by the addition of 70 mL of diluent. The mixture was sonicated for 10 minutes with intermittent shaking, then diluted to volume and mixed well. The solution was filtered through a 0.45 µm nylon membrane filter, discarding the first 5 mL of the filtrate.

METHOD VALIDATION

The HPLC method was validated according to ICH Q2(R2) guidelines.

Specificity

The specificity of the HPLC method was determined by complete separation of unknown impurities along with other parameters like retention time, capacity factor, tailing factor and asymmetric factor, etc.

Linearity and range

The linearity of the HPLC method for cetirizine hydrochloride was evaluated over a range of 0.025-2.990 ppm (1.25-150% of the specification limit). Eleven standard solutions were injected in triplicate.

Accuracy

The accuracy of the analytical method was established by performing recovery studies at four levels: LOQ, 50%, 100%, and 150% of the specified concentration. At each level, three replicate samples were spiked with a known amount of Cetirizine Hydrochloride and analyzed as per the validated HPLC method.

Precision

Precision reflects the closeness of repeated individual measurements of an analyte under the same conditions (repeatability) and varying conditions (intermediate precision). Six replicate injections of the standard solution yielded results within limits for precision, theoretical plates, and tailing. This confirms the HPLC system is reliable and repeatable for routine analysis.

Limit of Detection and Quantification

LOD and LOQ were determined through linear regression and signal-to-noise ratio methods. The LOD for Cetirizine Hydrochloride was found to be 0.1 ppm, and the LOQ was 0.2 ppm, corresponding to 0.5% and 10% of the standard concentration, respectively.

Robustness

Robustness was evaluated by making small changes in flow rate (±0.1 mL/min), mobile phase pH (±0.2), and wavelength (±2 nm).

Solution Stability

At room temperature for 72 hours, at intervals of 12 hours, the stability of reference and test solutions was quantitatively evaluated. Testing was conducted hourly until compliance if the reference solution's cumulative RSD was ≤ 2% after 24 hours. In order to make sure cumulative RSDs fulfilled accuracy requirements, the test solution was simultaneously checked for the biggest unknown and total impurities. Throughout, system appropriateness was confirmed to preserve analytical validity.

Forced Degradation Studies

The forced degradation study exposed cetirizine HCl and controls (plus blank) to acid, base, oxidative, hydrolytic,

thermal, moisture, and photolytic stress, requiring $\approx 10\%$ degradation in at least one condition.

Table 1. Forced Degradation Studies.

| S.No. | Condition | Degrading Agents/Conditions | Exposure period |
|-------|--------------------------------|---|---|
| 1 | As such, a sample | N.A. | N.A. |
| 2 | Acid degradation | 10 ml 0.1M HCl | For 60 minutes @ 70°C in the water bath |
| 3 | Alkali degradation | 10 ml 0.1M NaOH | For 60 minutes @ 70°C in the water bath |
| 4 | Oxidative degradation | 10 ml 30 % H ₂ O ₂ | For 60 minutes @ 70°C in the water bath. |
| 5 | Hydrolysis degradation | 10 ml Water | For 60 minutes @ 70°C in the water bath |
| 6 | Heat degradation (solid state) | 70° C | For 24 hours |
| 7 | Humidity degradation | 40°C/75% RH | For 24 hours |
| 8 | Photolytic degradation | 1.2 million lux hours and near UV at 200-watt hrs./m ² | 1.2 million lux hours and near UV at 200-watt hrs./m ² |

RESULTS AND DISCUSSION

Main API peak was obtained sharp and well resolved at 25.175 drug A, with good symmetry, indicating method suitability for quantification, Baseline Stability. Specificity was established by peak purity analysis. Single point threshold should be less than the peak purity index. (Table 2) Reference solutions spanning 0.625%-150% of the target concentration established the method's sensitivity: LOD at LOD (0.0524 $\mu\text{g/ml}$), LOQ (0.1587 $\mu\text{g/ml}$). Six injections at the LOQ confirmed precision, and the calibration curve up to 150% showed a correlation coefficient of 0.9999 with all system suitability criteria met, confirming the method's robust quantitative performance. (Table 2). Accuracy was evaluated using unspiked and spiked cetirizine HCl samples at LOQ, 50%, 100%, and 150% levels. Recoveries ranged from 108.25-109.43% at LOQ (RSD 0.55%) and 98.91-100.41% for 50-150% levels (RSD 0.63%), showing good accuracy and precision of the method. (Table 2). Six

injections of the standard yielded a % RSD of 0.51%, indicating excellent instrument reproducibility. Six individual sample preparations had identical impurity values (0.00%), with % RSD of 0.51%, demonstrating consistency in sample preparation and method reproducibility. Intermediate Precision results remained consistent across different analysts, instruments, and columns, confirming that the method is rugged and not operator-dependent. (Table 2). The LOD for cetirizine hydrochloride was 0.1 ppm, while the LOQ was 0.2 ppm, equivalent to about 0.5% and 10% of the standard concentration, respectively. The method satisfies ICH Q2(R1)-based validation requirements and shows excellent trace-level quantitation capability: the LOQ of 0.2 ppm is measured with %RSD $\leq 1\%$, confirming precise and accurate impurity detection. With a signal-to-noise ratio >10 , the method is robustly sensitive for impurity profiling in cetirizine HCl formulations. (Table 2).

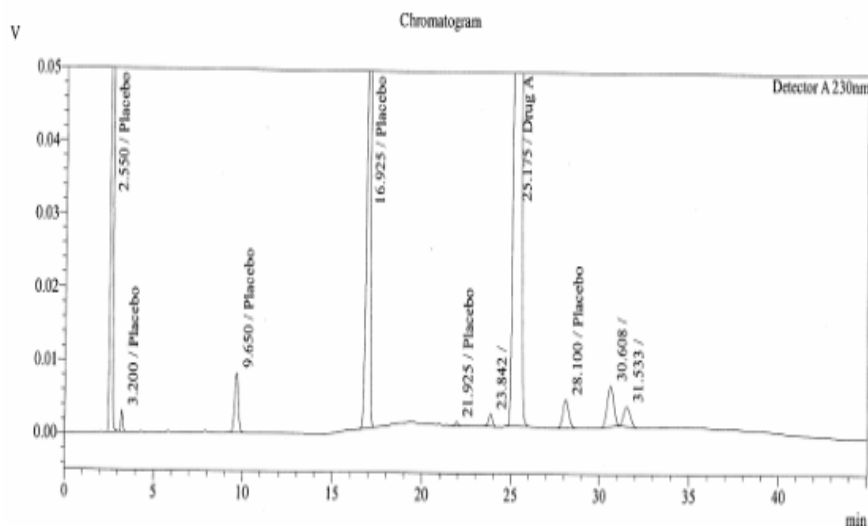


Figure 2. Optimized HPLC method.

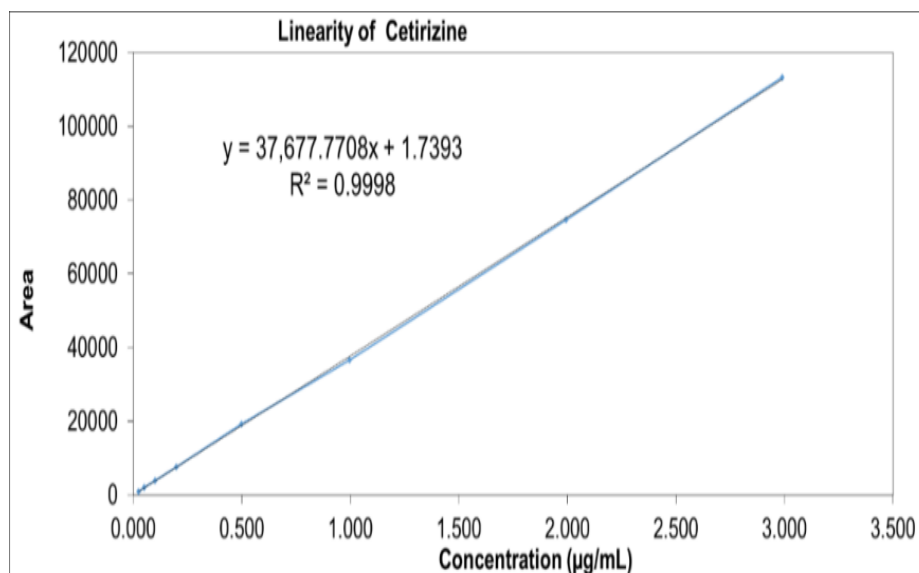


Figure 3. Linearity of Cetirizine Hydrochloride.

Table 2. Method Validation data.

| Parameters | | Cetirizine Hydrochloride drops |
|---|------------------------|--------------------------------|
| Specificity | Single point Threshold | 0.179000 |
| | Peak purity index | 0.239000 |
| Linearity Range µg/ml | | 0.625% -150% |
| Accuracy | LOQ | 108.88 ± 0.62, 0.55 |
| (%Recovery) | 50% | 100.34 ± 0.62, 0.06 |
| ±SD, %RSD | 100% | 99.27 ± 0.62, 0.40 |
| | 150% | 99.47 ± 0.62, 0.67 |
| Intermediate | Interday | ±470.47, 0.6028 |
| Precision(n=3) | Intraday | ±978.61, 1.2592 |
| ±SD, %RSD | | |
| Limit of detection (µg/ml) | | 0.0524 |
| Limit of quantification (µg/ml) | | 0.1587 |
| Robustness (total impurity, ±SD, % RSD) | | 0 ± 0, 0 |
| Change in Wavelength (±2) | | 0 ± 0, 0 |
| Change in flow rate (± 0.1 mL/min) | | 0 ± 0, 0 |

The LOQ precision of 3.60% RSD at 2 ppm is acceptable for such a low concentration. Despite the inherent variability at this level, the signal-to-noise ratio confirms that the method remains sensitive and reliable for quantification. Robustness testing assessed slight variations in wavelength (228-232 nm), buffer pH (2.8-3.2), and flow rate (0.9-1.1 mL/min). These variations did not significantly affect retention time, peak area, or impurity levels, indicating that the method is robust. No new contaminants were found, the results satisfied system suitability requirements, and the percentage RSD stayed within acceptable bounds. This demonstrates the HPLC method's stability and dependability even in the face of minor fluctuations. (Table 2).

Solution stability was evaluated to ensure the analyte and its impurities remained chemically unchanged during the

analysis. The cetirizine hydrochloride standard solution remained stable for up to 72 hours at 5°C (with a %RSD < 1.25%), while the sample solution was stable for up to 50 hours at the same temperature. No increase in unknown impurities was observed. Using a PDA detector, the cetirizine peak was cleanly resolved from degradation products in all cases, with minor impurities observed only under oxidative and photolytic stress, yet the primary analyte remained fully separated and free from placebo interference, thus validating the method's specificity and stability-indicating capability. Peak purity results under all stress conditions showed that the purity angle was lower than the threshold, confirming that the Cetirizine Hydrochloride peak is spectrally pure. This indicates no interference from degradants and confirms that the method is specific and stability-indicating.

Table 3. Peak Purity results for Cetirizine Hydrochloride.

| Stress Conditions | Highest Unknown Impurity (%) | Total Unknown Impurity (%) | Peak Threshold (%) | Peak purity | Peak purity Angle (%) |
|--------------------------------------|------------------------------|----------------------------|--------------------|-------------|-----------------------|
| As such sample | 0 | 0 | 0.279 | | 0.139 |
| Acid degradation | 0 | 0 | 0.283 | | 0.147 |
| Alkali degradation | 0 | 0 | 0.286 | | 0.145 |
| Oxidation degradation | 9.786 | 10.837 | 0.236 | | 0.072 |
| Hydrolysis degradation (solid state) | 0 | 0 | 0.284 | | 0.148 |
| Heat degradation (solid state) | 0 | 0 | 0.249 | | 0.097 |
| Humidity degradation | 0 | 0 | 0.281 | | 0.150 |
| Photolytic degradation | 4.029 | 6.445 | 0.317 | | 0.194 |

The proposed HPLC method successfully separated Cetirizine hydrochloride from its impurities with high specificity and no interference from excipients. Forced degradation studies confirmed that the method is stability-indicating, with oxidative and photolytic stress identified as the major degradation pathways. The validation results showed excellent linearity ($r = 0.9999$) along with high precision. The method also demonstrated good sensitivity with low LOD and LOQ values. Compared with previously reported methods, it provides improved performance and reliability. Therefore, the method is suitable for routine quality control, impurity profiling, and long-term stability studies of oral drop formulations.

CONCLUSION

In accordance with the ICH Q2(R2) Guideline on Validation of Analytical Procedures, the developed HPLC technique for the identification of related chemicals in Cetirizine hydrochloride oral drops was successfully validated. The technique successfully separated the medication from its breakdown products and demonstrated good specificity with no interference from blank or placebo. With a correlation coefficient of 0.9999, good linearity was achieved over the range of 1.25-150%. With a LOD of 0.0524 $\mu\text{g/mL}$ and a LOQ of 0.1587 $\mu\text{g/mL}$, the technique showed good sensitivity and acceptable accuracy at the LOQ level. The method's dependability and repeatability were validated by precision, accuracy, and robustness. The method is appropriate for regular quality control and stability testing because stability experiments also demonstrated that standard and sample solutions stay stable for prolonged periods of time at 5 °C.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL

Not applicable

FUNDING

This study received no specific funding from public, commercial, or not-for-profit funding agencies.

AI TOOL DECLARATION

The authors declares that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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