ORIGINAL ARTICLE

Comparison of Stability of Cetirizine Dihydrochloride in Solid and Liquid Dosage Forms by HPLC Analytical Method

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Abstract

Aim: The objective of the present study was to compare the stability of cetirizine (CTZ) dihydrochloride in different formulations of tablet and syrup dosage form by long-term and accelerated stability studies conducted according to an international conference on harmonization (ICH) guidelines. **Materials and Methods:** Both the dosage forms were formulated with the help of various excipients. The pharmaceutical analysis was performed for the quality attributes, and both formulations were kept for long-term stability studies at 30 ± 2°C and 65 ± 5 RH for 36th months and 6th months for accelerated stability studies at 40 ± 2°C and 75 ± 5 RH. The estimation of CTZ was done by high-performance liquid chromatography (HPLC) by recommended USP method that was previously calibrated and validated as per the ICH guideline. **Results:** The content analysis of tablet and syrup formulation was found to be 99.63–97.59% after 36th months of long-term stability conditions, respectively, whereas after completion of 6th months of accelerated stability studies, percentage content was 99.95–98.73%, respectively. **Conclusion:** It was concluded that CTZ is more stable in tablet dosage form as compared to syrup dosage form. It was also verified that the HPLC analytical method, present in USP, is useful for content analysis of CTZ in tablets and syrup dosage form.

Key words: Accelerated stability study, cetirizine HCl, high-performance liquid chromatography method, long-term stability study, pharmaceutical quality evaluation

INTRODUCTION

Cetirizine (CTZ) dihydrochloride is also known by the chemical name (±) - [2- [4- [(4-chlorophenyl) phenyl methyl] -1- piperazinyl] ethoxy] acetic acid, dihydrochloride with molecular weight of 461.82.[1] It is a piperazine derivative and metabolite of hydroxyzine, is an antihistamine, reported to be a long acting and with some mast-cell stabilizing activity.[2] It is used for the symptomatic relief of hypersensitivity reactions including rhinitis and chronic urticarial.[3] CTZ is rapidly absorbed from the gastrointestinal tract after oral administration, peak plasma concentration being attained in about 1 h.[2] It is highly bounded to plasma proteins and has an elimination half-life of about 11 h.[4] CTZ has been detected in breast milk and excreted primarily in the urine mainly as unchanged drug. CTZ has several antiallergic properties that suggest a potential effect on the development of airway inflammation and asthma in infants with atopic dermatitis.[3] The new H1-receptor antagonist, CTZ, is eliminated primarily unchanged by renal excretion and is thus potentially useful for relief of pruritus in patients with hepatic dysfunction, in whom many H1-receptor antagonists are contraindicated.[5]

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There are many possibilities of chemical reaction with excipients and an active pharmaceutical moiety that may result in degradation of drug causes decrease therapeutic effect, or it can affect the drug safety. It was observed that many reactions of CTZ were reported with excipients in liquid dosage form, which can degrade the drug.[6,7]

According to an international conference on harmonization (ICH) guidelines,[8] it is considered a good practice to perform the stability study of drugs and their products.[9] It is considered as a vital part of the pharmaceutical development program and considered mandatory by regulatory bodies to establish the quality of products.[10] Information about the molecule stability gives an idea for the proper selection of formulation and packaging including their storage condition to attain optimum shelf life which is also a vital document to get registered by the regulatory authority.[11] To develop the procedure, a systemic approach should be made for presenting and evaluating the stability information, which should focus all the necessary aspects of quality, including chemical, physical, microbiological, biological, and others quality aspects. The main idea behind performing stability studies is to provide assurance that how the quality of drug will vary with the periods of time when different environmental factors are altered, namely temperature, humidity, and light.[8] This will then guide the manufacturer about the recommended storage conditions, retest periods and shelf lives of products.[8]

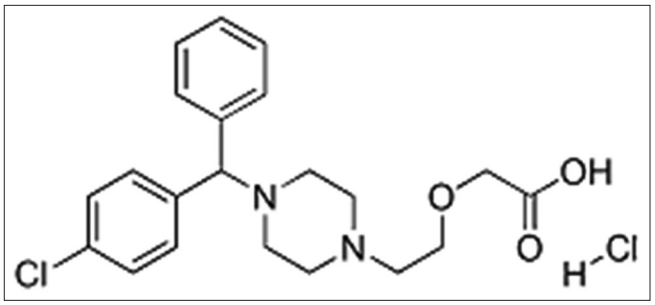
According to the guidelines it is very significant to perform the stability studies on two different conditions majorly, accelerated condition (40 ± 2°C–75 ± 5 RH) and long-term conditions (30 ± 2°C and 65 ± 5 RH). As per it, long-term stability studies performed from 0 to 36th month at a different time interval after the manufacturing date, while accelerated studies performed on 0 and 6th month.

The aim of the study was to design and develop two different dosage forms of CTZ dihydrochloride, i.e., tablet and syrup and to perform stability studies of the formulations. The focus of the study was to investigate the quality attributes of both formulations in the presence of adjuvant. It was evaluated by accelerated and long-term stability studies. In this study, the stability of the products was established by the determination of content analysis with high-performance liquid chromatography (HPLC) analytical method that is present in USP. The method was used after validation and calibration according to the equipment requirements [Scheme 1].

MATERIALS AND METHODS

Materials

CTZ dihydrochloride was a kind gift from platinum pharmaceutical limited, methylparaben and propylparaben (Sigma-Aldrich), Sorbitol 70% (Merck Millipore), disodium hydrogen phosphate anhydrous (Sigma-Aldrich), citric acid monohydrate (Merck Millipore), starch (Sigma-Aldrich), povidone K-30 (Sigma-Aldrich), magnesium stearate (Sigma-Aldrich), and lactose monohydrate (Merck Millipore).



Scheme 1: Chemical structure of cetirizine dihydrochloride

Preparation of prototype formulations

The two different dosage forms of CTZ hydrochloride equivalent to 10 mg tablet (net weight of compressed tablets = 120 mg) and 1 mg/mL syrup were formulated and analyzed for the accelerated and long-term stability studies under different conditions recommended by the ICH guidelines.[8] Table 1a and b showed a composition of excipients and percentage amount of each excipient in both formulations. The assay was performed to analyze the degradation of CTZ in both dosage forms recommended by USP.[12]

Pharmaceutical analysis of CTZ tablet and syrup formulation

The tablets were analyzed for quality attributes including weight variation, friability, disintegration, dissolution, and content assay testing. All attributes were performed according to USP and results were interpreted according to specified limits.[12] For syrup, pH and content assay were performed to determine the quality of the formulation.

Content analysis of CTZ

The chromatographic system consisted of Shimadzu LC20 was used to determine the CTZ in formulated tablets and syrup. In the case of syrup, the separation was achieved on the USP L10, 5 microns column at 50°C temperature. UV detection was performed at 233 nm with flow rate of 2 mL/min. Whereas the samples amount was introduced through an injector valve was 20 µL. On the other hand, the amount of CTZ in tablets was calculated on the USP L1, with 5 microns column at room temperature. UV detection was performed at 230 nm with flow rate 1.5 mL/min. The samples size that introduced into the injector was 10 µL.

HPLC analytical method

USP method was used to analyze CTZ HCl in both formulations. Before analysis, the feasibility and verification

Table 1a: Percentage composition of syrup (1 mg/mL)

Composition of syrup	Quantity %	For 5 L (in kg)
⁂Cetirizine dihydrochloride (USP)	0.12	0.0060
Methylparaben (USP)	0.0336	0.00168
Propylparaben (USP)	0.01666	0.00083
Sugar (BP)	34.4	1.72
Sorbitol solution 70% (BP)	52.6	2.63
Disodium hydrogen phosphate anhydrous (EP)	0.28	0.014
Citric acid monohydrate (USP)	0.1112	0.00556
Flavor and color	–	–
Purified water (BP)	12.44	0.622

⁂Mol. Wt - $C_{21}H_{25}ClN_2O_3$-461.808, Mol. Wt - $C_{21}H_{25}ClN_2O_3$ 2HCl - 534.808

Table 1b: Percentage composition of tablet (10 mg)

Composition of tablets	Quantity %	For 5 kg (in kg)
Cetirizine dihydrochloride (USP)	10.9	0.545
Starch (USP)	9.61	0.4805
Povidone-K 30 (USP)	4.297	0.2149
Magnesium stearate (USP)	0.554	0.0277
Lactose monohydrate (BP)	72.27	3.6135
Coating material	2.285	0.1143

of the method were done by different parameters as per the ICH guideline. Linearity, precision (repeatability and intermediate precision), and selectivity were done for the verification and reproducibility of the method.

Preparation of mobile phase for CTZ tablets

Preparation of solution A

2 N sulfuric acid mixed with distilled water in the ratio of 2:33 for the preparation of solution A.

Preparation of buffer

- Dilute 2.9 mL of sulfuric acid with 1000 mL of distilled water.
- Prepare a mixture of buffer and acetonitrile in the ratio of 700:300, filter through 0.45 micron filter and degas, use the solution as the mobile phase.

Preparation of diluent

Prepare diluents by mixing acetonitrile, solution A and distilled water in the ratio of 100:1:100.

Preparation of reference solution

Prepared standard stock solution of CTZ by dissolving 20 mg of CTZ into 100 mL of diluent (200 µg/mL), sonicated to dissolve, cool at room temperature.

Preparation of test solution

Crush 20 tablets in a mortar and pestle, weigh powder equivalent to 20 mg of CTZ and transfer to 100 mL of volumetric flask. Add 80 mL of diluents; sonicate to dissolve followed by stir through magnetic stirrer. Cool the solution and make up the volume with diluents, filter the solution through 0.45 micron filter, and use filtrate as the test solution.

Preparation of mobile phase for CTZ syrup

Preparation of solution A

Degassed acetonitrile was used as Solution A.

Preparation of solution B

Weigh and transfer 1.36 g of potassium dihydrogen phosphate to a 1000 mL beaker already containing 800 mL of distilled water, stir to dissolve and adjust pH to 3.5 with 2.0% solution of dilute phosphoric acid, make up the volume of solution up to the mark with distilled water, filter and degas the Solution B.

Preparation of diluent

Prepare diluents by mixing acetonitrile and distilled water in the ratio of 300:700.

Gradient program was as follows:

Time	Solution A	Solution B
0	5	95
15	5	95
22	25	75
35	25	75
40	5	95
50	5	95

Preparation of reference solution

- Prepare a standard stock solution of CTZ by transferring 100 mg of CTZ into 20 mL of volumetric flask, add 10 mL of diluents and sonicated to dissolve, cool at room temperature and volume make up with diluents to 20 mL
- Transfer 5 mL of stock solution into 50 mL volumetric flask and make up the volume with diluents

- Transfer 5 mL of 2nd solution into 25 mL volumetric flask; add diluents up to the mark. The final concentration of working standard solution was 100 µg/mL.

Preparation of test solution

Weigh accurately the amount of syrup that is equivalent to 10 mg of CTZ and transfers to 100 mL of volumetric flask. Add 80 mL of diluents; sonicated to dissolve followed by stir through magnetic stirrer. Cool the solution and make up the volume with diluents, filter the solution through 0.45 micron filter, and use filtrate as test solution (100 µg/mL).

Stability studies

The stability studies were conducted on both the formulations, namely tablets and syrup of CTZ under similar conditions that are accelerated and long-term studies at 40 ± 2°C and 65% RH ± 5 and 30 ± 2°C and 65% RH± 5, respectively, as per the ICH guideline.

RESULTS

Tablets are the most popular oral dosage forms with respect to patient's compliance whereas the syrup dosage form has an important place in the medication management of geriatrics and children. The prescribing pattern of drug dosage form is based on the age and condition of patients. The quality of the dosage forms is assessed by conducting quality control parameters on a regular basis to check the quality of the products. In the present study, the stability of CTZ dihydrochloride in formulated tablets and syrup were performed by a HPLC method that is present in USP.[12] It was first validated and used to study the degradation of CTZ dihydrochloride in acidic, alkaline, reductive, and oxidative conditions. The separation was carried out on a Symmetry C18 column, and a mixture of 50 mM KH_2PO_4 and acetonitrile (60:40 v/v, pH = 3.5) was used as the mobile phase.

The linear relationship between the concentration and the instrument response was confirmed by plotting the graph between the varying concentrations of the analyte and its area [Figure 1a and b].

Repeatability (precision) of the method was estimated by six replicate assays of the sample containing analyte at 100%, of label claim [Table 2].

Intermediate precision was carried out by preparing five test samples equivalent to 100% of label claim and assayed individually by two analysts to compensate [Table 3a and b].

The selectivity of the method was established by injecting the diluent (used for preparing test and reference solutions), mobile phase and the placebo of the syrup and tablets. It was also confirmed by "forced degradation" of reference solution by exposing the solution to force stress conditions [Table 4].

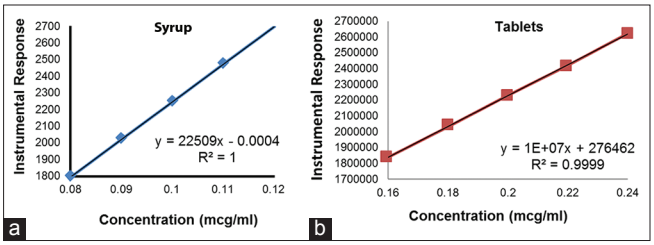


Figure 1: (a and b) Calibration curve for cetirizine syrup and tablets

Physicochemical characterization of CTZ tablet and syrup formulations

Before keeping the sample of formulated tablets and syrup for stability studies, the quality attributes of both formulations including weight variation, hardness, friability, disintegration, and dissolution test for tablets and pH identification and assay for syrup were performed [Table 5].

Stability study of CTZ tablets and syrup

Solutions of CTZ tablets and syrup were prepared with diluents having 200 µg/mL and 100 µg/mL, respectively. These solutions were stored at 40 ± 2°C and 65% RH ± 5 for accelerated stability studies and 30 ± 2°C and 65% RH ± 5 for long-term studies, respectively, as per the ICH guideline. The stability of these prepared solutions was checked after 1st, 3rd, and 6th months for accelerated condition and after 1st, 3rd, 6th, 9th, 12th, 18th, 24th, and 36th months for long-term studies and all analysis of each interval was compared against freshly prepared solutions. The initial peak area was considered 100% and the recoveries of the samples were evaluated [Figures 2 and 3].

DISCUSSION

In the present study, two different dosage forms such as tablets and syrup of cetirizine were designed to evaluate the stability of the drug in the presence of different excipients. The tablets were made with polyvinylpyrrolidone (PVP) starch and lactose. PVP and corn starch were the excipients having largest porosity and to reduce this porosity magnesium stearate was added as a lubricant into the formulation. On the other hand, the combination of lactose monohydrate, PVP and starch showed good flowability with magnesium stearate that is one of the important parameters to get a uniform weight of tablets, that indirectly indicates the content uniformity of drug in dosage forms also.[13]

The second formulation was designed for syrup that consists of sorbitol with two derivatives of paraben, namely propylparaben and methylparaben along with citric acid

Table 2: Analytical performance of the method regarding repeatability

	Repeatability *n*=6	Weight of sample (g)	Mean	Standard deviation	% RSD
Formulated syrup	Assay (mg/5 mL)	10.16	5.025	0.0628	1.251
	Percentage of label claim		100.50	1.279	1.3
Formulated tablets	Assay (mg/tablet)	244.87	9.82	0.0089	0.0911
	Percentage of label claim		98.20	0.114	0.116

Table 3a: Interday variation analysis in formulated syrup of cetirizine HCl

S. No	Wt of sample-1 (g)	Wt of sample-2 (g)	Analyst-1 Assay (mg/5 mL)		Analyst-2 assay (mg/5 mL)		Percentage of LC-1	Percentage of LC-2
1	10.36	10.08	5.14	5.01	5.04	5.01	101.5	100.5
2	10.12	10.02	5.01	5.02	4.98	5.02	100.3	100
3	10.03	10.12	5.02	5.06	5.08	5.00	100.8	100.8
4	10.21	10.03	5.08	5.10	5.03	5.06	101.8	100.9
5	10.09	9.98	5.04	5.08	4.90	5.03	101.2	99.3
Mean			5.06		5.015		101.12	100.3
Standard deviation			0.044		0.049		0.59	0.66
% RSD			0.87		0.98		0.58	0.66

Table 3b: Interday variation analysis in formulated tablets of cetirizine HCl

S. no	Wt of sample-1 (mg)	Wt of sample-2 (mg)	Analyst-1 assay (mg/tablet)		Analyst-2 assay (mg/tablet)		Percentage of LC-1	Percentage of LC-2
1	245	246.0	9.91	10.23	9.90	9.88	100.7	98.9
2	245.8	245.8	9.89	9.98	9.89	9.98	99.35	99.35
3	245.9	245.0	9.83	10.01	9.84	9.99	99.2	99.15
4	246	246.1	9.85	9.87	9.91	10	98.6	99.55
5	245.9	246.0	9.90	9.99	9.88	10.2	99.45	100.4
Mean			9.946		9.947		99.46	99.47
Standard deviation			0.117		0.104		0.768	0.573
% RSD			0.3480		0.2735		0.772	0.576

monohydrate. Liquid dosage forms have a high risk of microbial contamination. It must be protected from microbiological spoilage or from microorganisms that are introduced during or subsequent to the manufacturing process. The selection of accurate preservatives is the challenging task for formulation pharmacist. In the present study, parabens were selected for CTZ dihydrochloride stability study. It comes under the group of alkyl esters of p-hydroxybenzoic acid which acts effectively at the pH range of 4.0–8.0. Propylparaben with log $P = 3.04$ and methylparaben with log $P = 1.95$ showed increase antimicrobial activity. In formulated syrup, combinations of these two parabens were used to estimate the effectiveness of a compound for CTZ stability. Several attempts have been made to identify the stability study of CTZ liquid formulations with preservatives.[14,15] The previous observation of the study revealed that transesterification reaction occurred between sorbitol and methylparaben forming one of the six sorbitol monoesters of p-hydroxybenzoic acid with 1% degradation of drug product on storage at 30°C for 1 year.[6] This transesterification reaction determined by previously published studies indicated that the hydroxyl groups in a sugar alcohol molecule (3,4,5 carbon sugar alcohols) can react with methylparaben and cause possible incompatibility due to the formation of 6 isomer products.[16-18]

Table 4: Condition used for "forced degradation" studies

Formulation	Degradation type	Experimental conditions	Storage conditions	Sampling time hours
Tablets and syrup	Acidic degradation	1N HCl	Ambient temperature	1, 2, 4
	Alkaline degradation	1N NaOH	Ambient temperature	1, 2, 4
	Reductive degradation	10% Na_2SO_3	Ambient temperature	1, 2, 4
	Oxidative degradation	10 mL of H_2O_2	Ambient temperature	1, 2, 4
	Ultraviolet degradation	Diluents (acetonitrile: Distilled water, 300:700)	Short wavelength UV light	1, 2, 4

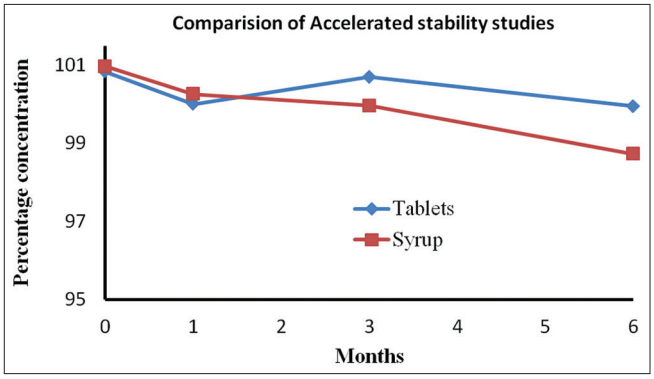


Figure 2: Comparison of degradation in cetirizine tablets and syrup at accelerated condition

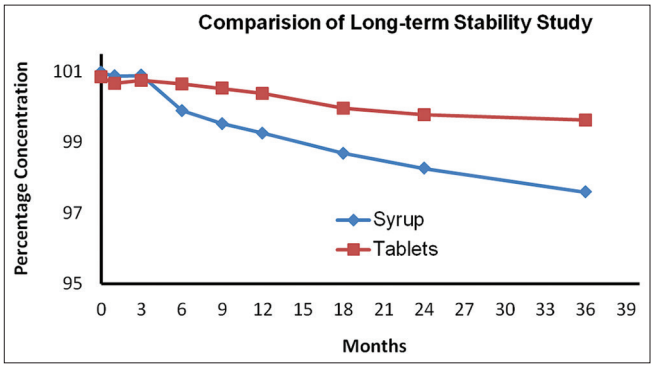


Figure 3: Comparison of degradation in cetirizine tablets and syrup at the long-term condition

To get a proper knowledge about the stability of drugs in its dosage form, a thorough study is required about the drug and excipients that are present in the formulation. However, for this purpose, an appropriate and validated analytical method is required that must be capable to analyze the cetirizine in pharmaceutical preparations. The analytical method used in this study was taken from USP.[12] Before using the method for the stability studies, it was validated and verified by different parameters such as linearity, precision, and selectivity.

The method was linear over the range of 1–20 µg/mL of CTZ dihydrochloride ($r^2 > 0.999$) [Figure 1a and 1b] and the intraday values were <1.5%. The interday variations for tablets and syrup were performed by a different analyst to verify the accuracy of the analytical method [Table 3a and b]. Whereas regarding the selectivity of the analytical method, no changes were observed in the peak area of the analyte. It was also observed that the chromatograms of the diluent showed no peak, but the excipient has peaked but does not interfere with the peak of analyte (CTZ HCl) obtained with the reference solution. Thus, the procedure identified is selective for detection and quantitation of the analyte. Moreover, no peak of degradation product was detected in the chromatograms, suggesting the analyte is stable under stress conditions. Except for oxidative reduction (1N HCl and 10% H_2O_2), the peak of the analyte is completely degraded [Table 4]. This result is supported by the review of literatures that reveal the kinetics of the acidic degradation showed a pseudo-first-order reaction at the temperature range of 70–90°C and the kinetics of hydrogen peroxide-mediated degradation was pseudo-first-order at the temperature range of 50–80°C.[19]

Both the products (tablets and syrup of CTZ) were prepared the same day. After complete physiochemical evaluation of CTZ tablet and syrup, samples were kept for stability studies for long-term at 30 ± 2°C and 65% RH ± 5 and short-term study at accelerated condition, i.e., 40 ± 2°C and 65% RH ± 5 in stability chamber as per the ICH guideline. Samples were analyzed periodically for long-term conditions, after completion of 3rd, 6th, 9th, 12th, 18th, 24th, and 36th months[20] and for short-term at 0, 1, 3rd, and 6th months separately for syrup and tablets [Table 6 and Figures 2 and 3].

In the case of CTZ syrup, 3.38% degradation was observed in real-time stability studies (100.97–97.59%) after 36th months; this is not a significant deviation in potency. While at 40°C ± 65% RH, the change in potency of CTZ occurred from 100.97% to 98.73% after 6th month of storage [Table 6]. This reduction may be due to the formation of monoesters between CTZ and sorbitol solution. Previously reported study indicated the degradation of CTZ >1% at a lower temperature as 40°C, on transformation of CTZ content into a monoester within 1 week in marketed preparations containing sorbitol and glycerol.[21]

The analysis of the five replicates of reference solution shows RS deviation <2%. During the analysis the numbers of theoretical plates were >1500, and the tailing factor was <2. It indicated the validity and fulfillment of system suitability and accuracy of analytical method used to estimate the stability of the drug.

At the same time, the stability of CTZ tablets was also evaluated under the same specification as those maintained

Table 5: Quality attributes of Tablet and Syrup formulations

Formulation	Weight variation mg (±SD)	Hardness kg (±SD)	Friability %	Disintegration time (min)	Dissolution (NLT 85% in 30 min) *n*=6	Assay %
Tablets	121.63±1.521	4 kg±0.2	<1%	5 min	95.26	101.06
	Weight/mL (±SD)		pH		Assay	
Syrup	NLT 1.25 g		4.0–5.1		100.87	

SD: Standard deviation

Table 6: Stability studies of CTZ syrup and tablets by the content assay method

Content assay of CTZ	Long-term 30±2°C and 65% RH ± 5 (%)		Accelerated 40±2°C and 65% RH±5 (%)	
	Syrup (mean of *n*=5)	Tablets (mean of *n*=5)	Syrup (mean of *n*=5)	Tablets (mean of *n*=5)
0-month	100.97	100.85	100.97	100.84
1-month	100.87	100.66	100.26	100.01
3-month	100.89	100.75	99.97	100.70
6-month	99.89	100.64	98.73	99.95
9-month	99.52	100.52	-	-
12-month	99.26	100.38	-	-
18-month	98.69	99.96	-	-
24-month	98.25	99.77	-	-
36-month	97.59	99.63	-	-

for syrup. It was observed that 1.21% change occurred on real-time stability, while on accelerated condition only 0.89% degradation of CTZ occurred in a tablet. However, the results explain that CTZ in both dosage forms is stable for the shelf life of 3 years, but as compare to syrup, it is more stable in tablets. In case of tablets, the presence of polyvinylpyrrolidone as a binder forms a compressed mass,[22] resulting in increased CTZ stability due to compact binding of ingredients that decrease the exposure surface for temperature and humidity which is not possible in case of syrup, therefore, results in more degradation as compare to tablet that is 3.38% after long-term stability studies.

CONCLUSION

The effect of excipients on ceterizine in tablets and syrup dosage form was evaluated by a validated HPLC analytical method. It was concluded that the selection of accurate adjutant's for different dosage form is a challenging task, especially when the ingredients activities are affected with a change of pH. The accelerated stability and long-term studies were carried out to estimate the consequences of excipient on potency, efficacy, and integrity of cetirizine in tablets and syrup. The formulations were also subjected to "forced degradation" under different storage conditions. The data obtained from the stability studies indicated that the CTZ in both dosage forms is stable for the shelf life of 3 years, but as compare to syrup, it is more stable in tablets.

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