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PHYSICOCHEMICAL QUALITY ASSESSMENT OF VARIOUS BRANDS OF LEVOCETIRIZINE DIHYDROCHLORIDE FILM-COATED TABLETS, COMMERCIALLY AVAILABLE IN SALALAH, SULTANATE OF OMAN.

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ABSTRACT
Generic drugs are generally less expensive than innovator drugs, which can make them more accessible to a broader population. How ever, generic drugs, must meet the same quality and safety standards in comparison with innovator drugs. Quality control and regulatory oversight become crucial to ensure that these generics meet the required standards. Three brands of Levocetirizine dihydrochloride were purchased from different local retail stores. We assessed the quality and equivalency of 3 different Generic brands of Levocetirizine dihydrochloride film-coated tablets against Innovator brand "**Xyzal"** serving as the reference. All the experiments are carried out by using validated HPLC methods in Oman Pharmaceutical products Co. L.L.C., Sultanate of Oman. The tablets were evaluated for weight variation, hardness, water content by KF, disintegration time, drug content, and pharmaceutical equivalence was determined from the dissolution profile which gives acceptable difference (f_1) and similarity (f_2) factor values for all the brands compared with the Innovator brand "**Xyzal".** The physicochemical parameter results for all three brands met the acceptable limits. All the 3 brands also met the USP criteria for assay of not less than 90.0% and not more than 110.0% of the labeled amount of levocetirizine dihydrochloride. All the 3 brands showed evidence of dissolving within 15 minutes. The values observed are within the recommended range of 80 (Q) within 30 minutes for oral solid dosage forms intended for immediate release. According to the f1 and f2 results, all 3 brands were comparable to Innovator "**Xyzal"**, and demonstrated similar dissolution profiles and could potentially be used interchangeably with "**Xyzal"**.

KEYWORDS: Three brands of Levocetirizine dihydrochloride were purchased from different local retail stores.

1. INTRODUCTION
The quality of medicine is very important for effective healthcare and patient well-being. High-quality medicines ensure that patients receive the intended therapeutic benefits. This is crucial for managing illnesses effectively and promoting positive health outcomes. Inaccurate dosages, impurities, or the absence of active ingredients can lead to adverse reactions, treatment failure, or even harm to the patient's health. The spread of generic drug products in low-income countries requires a comprehensive approach. This includes strengthening regulatory capabilities, fostering international collaboration, and ensuring that affordable medicines meet rigorous quality standards. Generic drugs are considered pharmaceutically equivalent to the reference (innovator) product when they have the same active ingredient(s), dosage form, strength, and route of administration. This is a common practice to ensure that generic drugs are interchangeable with the original branded products.

Levocetirizine is the R-enantiomer of cetirizine. It is considered a third-generation non-sedative antihistamine. It acts by blocking histamine receptors, specifically the H1 receptors, which helps alleviate symptoms associated with allergic reactions. Unlike some antihistamines, levocetirizine primarily inhibits the binding of histamine to its receptors, rather than preventing the release of histamine from mast cells.

The medication is commonly used to treat upper respiratory tract allergies, such as hay fever or pollinosis. It is also effective in managing symptoms of urticaria (hives), atopic dermatitis, and can be used as an adjuvant in seasonal asthma.

Levocetirizine dihydrochloride is a white to off-white crystalline powder. It is highly soluble in water and soluble in methanol, and it is classified as BCS-III (high solubility and low permeability) under the biopharmaceutical classification system.

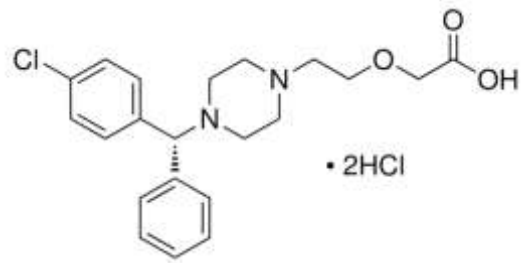

Fig. 1: The chemical structure of Levocetirizine dihydrochloride.

2. OBJECTIVE

To Evaluate the quality and equivalence of three brands of Levocetirizine Dihydrochloride 5 mg film-coated tablets by assessing their quality by measuring the control parameters, including description, average weight, hardness, water content, disintegration time and Drug content. In-vitro dissolution studies were also conducted for the three brands, and similarity was determined using the difference factor (f1) and similarity factor (f2).

3. METHODS

3.1. Study setting, design, and period.

This was an experimental study that involved laboratory analysis of different brands of Levocetirizine Dihydrochloride 5 mg film-coated tablets. The study was conducted from Dec. 2023 to Jan. 2024 at the Oman Pharmaceutical Products Co. L.L.C. Quality control laboratory, Salalah, Sultanate of Oman.

3.2. Sample collection.

A random selection of four distinct brands of Levocetirizine Dihydrochloride 5 mg film-coated tablets was procured from various pharmacies within Salalah. This random acquisition took place in Dec. 2023.

Levocetirizine dihydrochloride working standard prepared at Oman Pharmaceutical products Co. L.L.C was used as pure standard during analysis.

4. PHYSICOCHEMICAL EVALUATION

The samples were analyzed using Physicochemical parameters, which included tests like weight variation, hardness, water content by KF, disintegration time, drug content & invitro Bioequivalence studies.

4.1 Visual Examination

This involved inspecting the parameters such as product description, packaging type and integrity, physical damage, and other observations of each sample.

Table 1: Visual Inspection Results.

Sl. No.	Brand Name	Product Description	Manufacturer Name	Batch No.	Manufacturing & Expiry date	storage conditions
1	Xyzal	Uniform white-colored, oval-shaped film coated tablets. No cracks and the tablets did not break prior to removal from the blister.	UCB Farchim SA Switzerland	359405	Mfg. Date: 10/2022 Exp. Date: 09/2027	Store below 30°C
2	Levar 5	Uniform white-colored, round-shaped film coated tablets. No cracks and the tablets did not break prior to removal from the blister.	Al-Taqaddom Pharmaceutical Industries Aman-Jordan	23139	Mfg. Date: 07/2023 Exp. Date: 07/2027	Store below 30°C
3	Glencet	Uniform white-colored, oval-shaped film coated tablets. No cracks and the tablets did not break prior to removal from the blister.	Glenmark Pharmaceutical Ltd. Baddi, India	05222463	Mfg. Date: 11/2022 Exp. Date: 10/2024	Store below 30°C
4	L-Cet	Uniform white-colored, round-shaped film coated tablets. No cracks and the tablets did not break prior to removal from the blister.	Oman Pharmaceutical products Co. L.L.C., Salalah, Sultanate of Oman	3XC024B	Mfg. Date: 10/2023 Exp. Date: 10/2026	Store below 30°C

Mfg date: Manufacturing date, Exp date: Expiring date.

4.2: Weight variation and Average weight

The analytical balance (Make: Mettler Toledo, Model: XPE205) was calibrated before use and twenty tablets of each brand were weighed individually on the balance and recorded in Milligrams (mg). Then the average and standard deviation were calculated.

Average weight = weight of 20 tablets / 20

%Weight Variation = Average weight - weight of each tablet × 100 / Average weight

Acceptance criteria: According to USP, the products passed the weight variation test if no more than two tablets/capsules out of 20 deviated by ± 7.5% of the average weight.

4.3 Hardness test

The crushing strength was determined with an automatic Tablet Hardness Tester (Make: Pharmatron, Model: Multi test 50). The Tablet Hardness Tester was calibrated before use and ten tablets were randomly selected and placed in between two anvils of the hardness tester. The pressure was applied to the anvils until the tablet was broken. The crushing strength needed to break the tablet was measured in "N" (Newton).

4.4: Disintegration time

The disintegration test was performed by using the USP disintegration apparatus (Make: Electrolab, Model: ED 2L). The Tablet disintegration apparatus was calibrated before use. Six tablets of each brand were placed individually in each of the six baskets with distilled water at 37 ± 0.5 °C filled into each beaker. The test started immediately after the basket was attached. The disintegration time (DT) was recorded when no particles remained in the basket.

Acceptance criteria: The acceptable disintegration time for film coated tablet is not more than 30 minutes.

4.5: Water Content

The water content test was carried out by using KF titrator (Make: Mettler Toledo, Model: V305 with Labx software). A suitable quantity of dried methanol, transferred into the titration flask and titrated by using KF titrator until the end point to make the inside flask water free. About 0.2 g of the tablet powder, transferred quickly to the titration flask, dissolved by stirring and titrate using KF titrator to the end point. The water content calculated by using following formula.

$$\%\ \text{Water Content} = \frac{\text{V x KF Factor x 100}}{\text{Weight of sample in mg}}$$

Where, V = Volume in ml of KF solution consumed for sample titration.

Acceptance criteria: Not more than 7.0 % W/W

4.6: Identification test

The identification tests were conducted by using the HPLC instrument (Make: Thermo scientific, Model: Ultimate 3000, with chromeleon software) to establish the presence of Levocetirizine Dihydrochloride active ingredients in the samples. A validated HPLC method (validation carried out in Oman pharmaceutical products LLC) was used to establish the presence of active ingredient.

Acceptance criteria: The retention time of the major peak in the chromatogram of the sample preparation should correspond to that in the chromatogram of the standard preparation obtained in the assay.

4.7: Drug content: (By HPLC)

The drug content studies were performed by using the HPLC techniques and HPLC instrument (Make: Thermo scientific, Model: Ultimate 3000, with chromeleon software) to determine the amount of Levocetirizine Dihydrochloride that is present in four selected brands of Levocetirizine Dihydrochloride film-coated tablets.

A validated HPLC method (validation carried out in Oman pharmaceutical products LLC) was used to estimate the content of active ingredient. Details of the HPLC method used mentioned as follows.

Chromatographic Condition

Column	Xterra RP-18, 4.6 x 150 mm, 5 µm
Flow rate	1.0 ml/minute
Detection	230 nm
Injection Volume	20 µl
Column Temperature	Ambient
Run Time	10 minutes

Preparation of Dilute Orthophosphoric Acid

10ml of orthophosphoric acid diluted to 100 ml with water and mixed.

Preparation of Buffer

Weighed and transferred about 2.77g of sodium dihydrogen phosphate dihydrate into a beaker containing 1000 ml of water, sonicated to dissolve. The pH of the solution is adjusted to 3.97 with dilute orthophosphoric acid. Finally, the buffer solution is filter through 0.45µ membrane filter.

Preparation of Mobile Phase

Prepared and degassed mixture of buffer and Acetonitrile in the ratio of 65:35 % v/v.

Preparation of Diluent

Water and methanol in the ratio of 60:40 % v/v mixed properly; the pH of the solution adjusted to 3.03 with dilute ortho phosphoric acid.

Preparation of Standard Solution

Accurately weighed and transferred 50.79 mg of Levocetirizine Dihydrochloride working standard into a 100 ml volumetric flask, 60m1 of diluent added into the flask and sonicated to dissolve. Finally, the volume is adjusted up to the mark with diluent and mixed. Further 5.0 ml of above solution transferred in to 25.0 ml volumetric flask, the volume is adjusted up to the mark with diluent and mixed.

Preparation of Sample Solution

Transferred 20 tablets of each brand into four different 200 ml volumetric flasks with 120 ml diluent and sonicated for 30 min with intermediate shaking. Finally, the volume is adjusted up to the mark with diluent and mixed. A portion of the solution filtered through 0.45µm membrane filter.

Further 5.0 ml of above solution transferred in to 25.0 ml

volumetric flask, the volume is adjusted up to the mark with diluent and mixed.

Procedure
The column is equilibrated with mobile phase for 60 minutes at a flow rate of 1.0 ml/min.
Separately injected 20 µl of diluent, standard solution (five replicate injections) and Sample solution into the chromatographic system.
Peak responses observed measured and recorded.

System Suitability Parameters
The column efficiency for the Levocetirizine Dihydrochloride peak from standard solution should not be less than 2000 theoretical plates.
The tailing factor for the same peak should not be more than 2.0.
The %RSD of areas obtained from five replicate injections of standard solution should not be more than 2.0 %.

Calculation
Levocetirizine Dihydrochbride (% Labeled amount)

$$= \frac{A_T}{A_S} X \frac{W_S}{100} X \frac{5}{25} X \frac{200}{N} X \frac{25}{5} X \frac{1}{L} X \frac{P}{100} X 100$$

Where,
AT = Area of Levocetirizine Dihydrochloride peak in sample solution
AS = Average area of Levocetirizine Peak obtained from replicate injections of standard solutions
WS = Weight of Levocetirizine Dihydrochloride working standard taken in mg
N = No. of tablets taken for preparation of sample solution
P = Purity of Levocetirizine Dihydrochloride working standard used (On as is basis)
L = Labeled claim of Levocetirizine Dihydrochloride per tablet in mg

Acceptance Criteria: The amount of levocetirizine dihydrochloride shall be between 95 %–105 % w/w of the labeled amount of Levocetirizine Dihydrochloride as stated by BP Vol. 3 (2017).

4.8: Dissolution test: (By HPLC)
The oral bioavailability of a drug depends entirely on the rate of drug dissolution. Therefore, it is very important to evaluate the dissolution data and comparison of dissolution profiles for different brands available in the market. The dissolution test was performed using Dissolution Apparatus (Make: Electrolab., Model: EDT 14 LX) and HPLC instrument (Make: Thermo scientific, Model: Ultimate 3000, with chromeleon software). A validated HPLC method (validation carried out in Oman pharmaceutical products LLC) was used to estimate the % of active ingredient dissolved at different time intervals. Details of the HPLC and Dissolution method used mentioned as follows.

Chromatographic conditions

Column	Xterra RP 18,150x4.6mm, 5µm
Flow rate	1.0 ml/minute
Detection	230 nm
Injection Volume	20 µl
Run time	10 mins

Preparation of Dilute Orthophosphoric Acid
10ml of orthophosphoric acid diluted to 100 ml with water and mixed.

Preparation of Buffer
Weighed and transferred about 2.77g of sodium dihydrogen phosphate dihydrate into a beaker containing 1000 ml of water, sonicated to dissolve. The pH of the solution is adjusted to 3.97 with dilute orthophosphoric acid. Finally, the buffer solution is filter through 0.45µ membrane filter.

Preparation of Mobile Phase
Prepared and degassed mixture of buffer and Acetonitrile in the ratio of 65:35 % v/v.

Preparation of Standard solution
Accurately weighed and transferred about 55 mg of Levocetirizine Dihydrochloride working standard into a 200 ml volumetric flask, 120 m1 of dissolution medium added into the flask and sonicated to dissolve. Finally, the volume was adjusted up to the mark with dissolution medium and mixed. Further 2.0 ml of above solution transferred in to 100 ml volumetric flask, the volume is adjusted up to the mark with dissolution medium and mixed.

Sample preparation
Dissolution Parameters

Medium	Purified water
Volume	900 ml
Apparatus	USP type II (Paddle)
Speed	50 rpm
Temperature	37.0°C ± 0.5°C
Sampling time	15, 30, 45 and 60 minutes

The dissolution medium was 900 ml of Purified water, the temperature was set to 37 ±0.5 °C, and the paddle speed was set to 50 rpm as mentioned above. Samples of 10 ml of the solution were withdrawn at each time interval (15, 30, 45 and 60 minutes) and were replaced with equal volumes of fresh dissolution medium at the same temperature. The samples were filtered through 0.45µm membrane filter.

Procedure
The column is equilibrated with mobile phase for 60 minutes at a flow rate of 1.0 ml/min.
Separately injected 20 µl of diluent, standard solution (five replicate injections) and Sample solution into the chromatographic system.
Peak responses observed measured and recorded.

System Suitability Parameters

The column efficiency for the Levocetirizine Dihydrochloride peak from standard solution should not be less than 2000 theoretical plates.

The tailing factor for the same peak should not be more than 2.0.

The %RSD of areas obtained from five replicate injections of standard solution should not be more than 2.0 %.

Calculation: % labeled amount of Levocetirizine Dihydrochloride dissolved

$$= \frac{AT}{AS} X \frac{WS}{200} X \frac{2}{100} X \frac{900}{L} X \frac{P}{100} X 100$$

Where,

AT = Area of Levocetirizine Dihydrochloride in sample solution

AS = Averag area of Levocetirizine Dihydrochloride obtained from five

replicate injection of standard solution

WS = Weight of Levocetirizine Dihydrochloride working standard taken in mg

P = Purity of Levocetirizine Dihydrochloride working standard

L = Labeled claim of Levocetirizine Dihydrochloride per tablet in mg

The dissolution curves were constructed by plotting the mean percentages of Levocetirizine Dihydrochloride released against time.

Acceptance Criteria: Not less than 80 % (Q) of the labeled amount of Levocetirizine Dihydro- chloride is dissolved in 30 minutes. The similarity factor (f2) should be between 50 and 100 to define the pharmaceutical equivalence of the generic brand against Innovator.

5.0 RESULTS AND DISCUSSION

5.1 Visual inspection.

Table 1 provides detailed information about the visual inspection test results for the different brands of Levocetirizine Dihydrochloride tablets. All brands had full details of names and batch numbers, with manufacturing and expiry dates and storage condition. They were all in their original packages as distributed to the various pharmaceutical outlets.

5.2 Weight variation and Average weight

Weight variation statistical quality control test is used to confirm uniformity of the dosage unit and therefore also to support product safety, identity, and quality. From the results obtained it is observed that each brand had uniform weights that were within the permitted range as defined by USP requirements, with no tablets deviating from 7.5 %. The results of the weight variation test are shown in Table 2.

Table 2.

Sl. No.	Brand	Average weight in mg	Minimum Weight in mg	Maximum weight in mg	% weight variation
1	Xyzal	103.65	101.52	105.83	+2.10 -2.07
2	Levar 5	103.11	101.12	106.25	+1.92 -3.04
3	Glencet	103.72	101.09	106.23	+2.53 -2.51
4	L-Cet	102.83	100.92	106.01	+1.85 -3.09

5.3 Hardness test

Tablet hardness testing is useful to determine the breaking point and structural integrity of a tablet and find out how it changes "under conditions of storage, transportation, packaging and handling before usage". From the results obtained it is observed that the lowest mean hardness (56.1 N) was recorded for product L-Cet, whereas Glencet was able to withstand the highest mechanical force (60.7 N). All products had uniform average hardness ranging from (56.2-60.7 N), and all tablet brands passed the test. The results of the hardness test are shown in Table 3.

5.4 Disintegration time

The disintegration test is used to determine the time required for the tablet to break down into smaller particles, allowing for a greater surface area and availability of the drug when taken by a patient. From the results obtained it is observed that all the selected tablet brands passed the disintegration test. Among the tested brands, the fastest average disintegration was for product Xyzal (3.45 min), and the slowest was the innovator, Levar 5 (4.41 min). The results of the disintegration test are shown in Table 3.

5.5 Water content

The water / moisture content is a critical quality attribute of tablet dosage form. Low moisture content directly affects flowability and particle agglomeration of raw materials whereas high moisture content in raw materials promotes microbial growth and sometimes increase the % of Impurities. From the results obtained it is observed that the percentage of moisture present in all brands varies approximately between 5.07 % w/w to 5.87 % w/w. The results of the water content test are shown in Table 3.

5.6 Identification test (by HPLC)

The identification test confirmed the presence of Levocetirizine Dihydrochloride in each sample. In identification test it is observed that, the retention time of the Levocetirizine Dihydrochloride peak in the chromatogram of the sample preparations of each brand of tablet, correspond to that in the chromatogram of the Levocetirizine Dihydrochloride standard preparation. This evidence underscores that all Levocetirizine Dihydrochloride brands evaluated in this study contained the requisite Levocetirizine Dihydrochloride content as their active ingredient. Sample chromatograms of the Identification test are mentioned below.

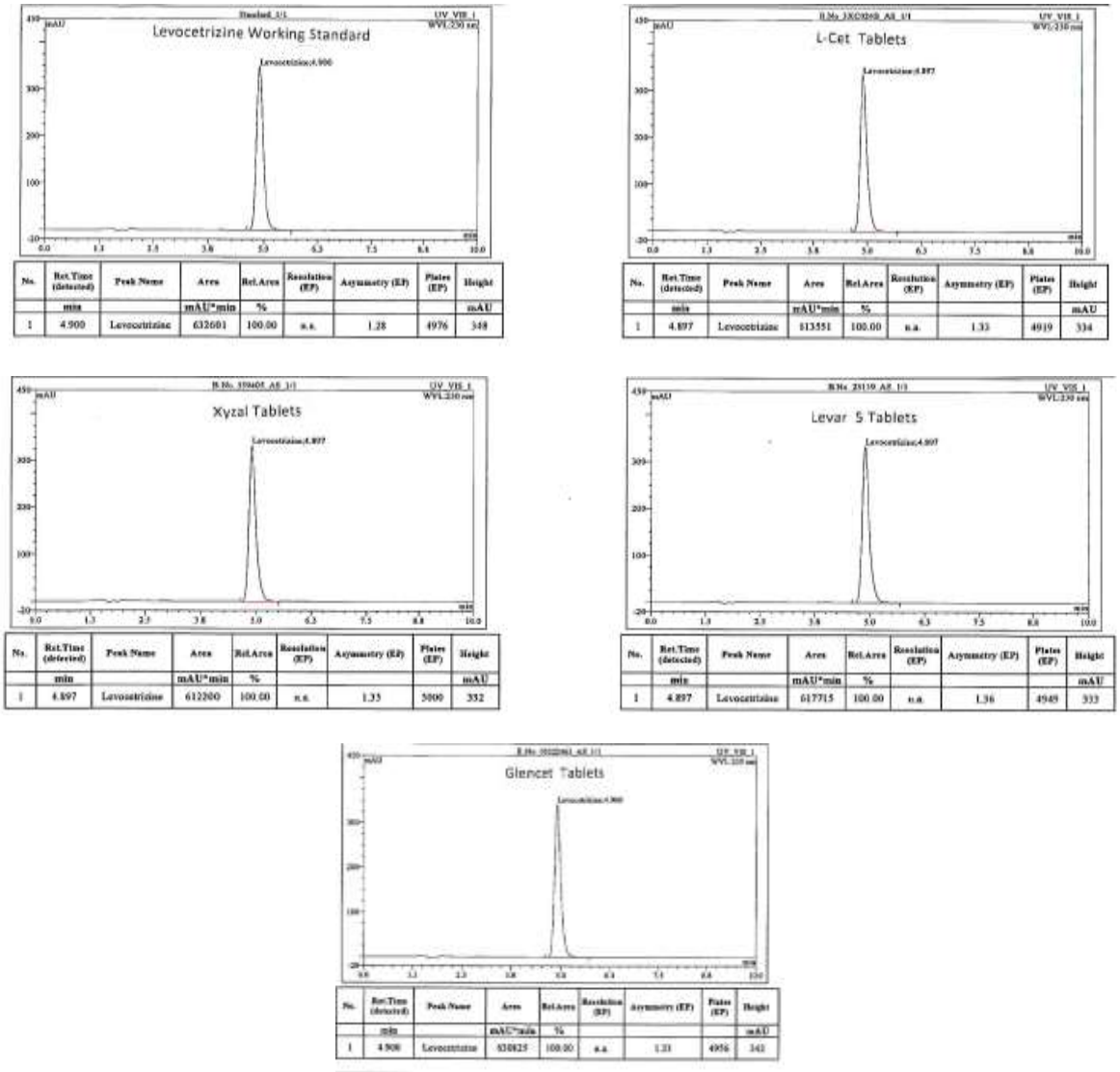

Fig. 1: Sample chromatograms.

5.7 Drug content: (By HPLC)

The Drug content (assay) of Levocetirizine Dihydrochloride tablets was performed to determine the percentage content of Levocetirizine Dihydrochloride active ingredient in each sample. The result of the assay tests is comprehensively outlined in Table 3. The percentage assay across the different brands ranged from 97.0 % (Xyzal)) to 100.0 % (Glencet), aligning with the accepted range of 95 %–105 % w/w as stated by BP Vol. 3 (2017).

Table -3.

Sl. No.	Brand	Average Hardness in "N" (Newton)	Disintegration time in minutes.	Moisture content in % w/w	% of drug content
1	Xyzal	60.3	3.45	5.21	97.0
2	Levar 5	60.3	4.41	5.07	97.9
3	Glencet	60.7	3.58	5.31	100.0
4	L-Cet	56.1	4.10	5.87	97.3

5.8 Dissolution test: (By HPLC)

This test is based on the principle that tablets must dissolve in the gastrointestinal tract to produce their effect. The dissolution rate depends on several factors, such as the formulation, manufacturing process, storage conditions, and physicochemical properties of the drug substance and the excipients.[8] The poor dissolution performance of some brands may be due to factors such as low solubility, high crystallinity, poor wettability, or inappropriate compression force.[8,9] In addition, dissolution is important for monitoring approved and post-marketing drug products to assess their quality, therapeutic effectiveness, and safety for the public. The percentage drug release in 30 minutes across the different brands ranged from 92.9 % (Levar 5)) to 96.0 % (Glencet), aligning with the accepted range of "Not less than 80 % (Q) of the labeled amount of Levocetirizine Dihydrochloride dissolved in 30 minutes".

Dissolution profile analysis is an important tool for establishing the similarity between generic brands and their reference products. Here the similarity factor (f2) which is the most appropriate method to compare release profiles used to compare the three different brands with innovator sample "Xyzal". f_2 values between 50 and 100 were used to define the pharmaceutical equivalence of two dissolution profiles. It evaluates the degree of similarity between the two profiles and is sensitive to significant variations at any time point. The results of f2 of all three brands are similar to brand Xyzal (innovator) because the obtained values of f2 are greater than 50. According to the obtained results, all three brands "Levar**, L-CET and Glencet** "can be used as generic substitutes for brand **Xyzal**. The results of the water content test are shown in Table 4.

Table 4: (In-Vitro Dissolution Test Results).

Time		Xyzal	L-Cet	Levar 5	Gencet
15	Minimum	87.0	79.6	87.3	80.0
	Maximum	94.7	96.9	94.3	96.9
	Average	92.4	90.7	92.1	92.8
30	Minimum	89.1	94.3	89.6	91.3
	Maximum	96.0	97.5	94.1	98.0
	Average	93.6	95.6	92.9	96.0
45	Minimum	90.6	94.4	90.0	91.7
	Maximum	96.6	97.6	93.8	99.2
	Average	93.8	95.9	92.6	96.0
60	Minimum	91.2	94.4	89.9	91.7
	Maximum	96.9	97.3	93.6	99.4
	Average	93.9	95.9	92.6	96.2
f2 Value		-	69.7	83.2	69.2
	Acceptance criteria for f2 values shall be Between 50 and 100				

CONCLUSION

According to the study of physicochemical parameters, the results is revealed that Levocetirizine Dihydrochloride tablets available in Sultanate of Oman market are of satisfactory quality & meet the pharmaceutical standard and are safe for use by consumers. Furthermore, all tested brands exhibited dissolution of more than 80 % of the labeled amount of Levocetirizine Dihydrochloride within 15 minutes. The comparison of the dissolution profile by calculating the similar factor (f2) indicated that four brands are interchangeable.

DATA AVAILABILITY STATEMENT

Most of the data is included in the manuscript. Additional data can be found from the corresponding author based on reasonable request.

CONFLICT OF INTEREST

The authors disclosed no conflicts of interest related to this article.

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