Research Article

Pharmaceutical equivalence study of eight brands of Candesartan cilexetil tablets marketed in the United Arab Emirates

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Abstract

Objectives: This work aimed to develop a simple HPLC method and apply in the pharmaceutical equivalence study of seven imported and one local product of candesartan cilexetil tablets (4, 8 and 16 mg). **Methods:** A simple RP-HPLC method was developed and validated in-terms of linearity, precision and accuracy, and applied in assay and dissolution study. The physical parameters and infrared scanning of the tablets were determined. The dissolution study was carried out at eight sampling data points to generate dissolution profiles for each brand and similarity factors of dissolution profiles were calculated. **Results:** The developed HPLC method was accurate and precise with ≤2% relative standard deviation observed in intra- and inter-day precision. In assay, the product contained 100.74 to 102.52% candesartan cilexetil and the acceptance value for dosage content uniformity were less than 15. The dissolution test at 45 minutes the tablet released >80% drug. The infrared spectrum of eight products showed the similarity in the presence of functional groups. The dissolution profiles generated with eight sampling data points were compared with a reference product. Two products in 8 mg strength and one in 16 mg strength had similarity factors ≥50% similar in dissolution pattern as the reference products and were deemed as pharmaceutical equivalent. **Conclusion**: The studied products met the quality standards based on the physical parameters, assay contents, dosage content uniformity and dissolution test results compared to the United States Pharmacopeia44-National Formulary39 specification. The local product was more affordable and had the same pharmaceutical quality as the reference product.

Keywords: Candesartan cilexetil tablets, pharmaceutical equivalence, RP-HPLC, dosage content uniformity, dissolution profiles, similarity factors

Introduction

Candesartan cilexitil [(2-ethoxy-1-({4-[2-(2*H*-1,2,3,4-tetrazol-5-yl) phenyl]phenyl}methyl)-1*H*-1,3-benzodiazole-7-carboxylic acid)] is classified as an angiotensin II receptor type 1 antagonist. It has antihypertensive effects, and can help with heart failure, myocardial infarction and diabetic nephropathy (Roche et al., 2019). Eight brands of candesartan cilexitil are available in United Arab Emirates (UAE) pharmaceutical markets, and seven come from three different countries. There are 23 Drug Manufacturing Units in UAE that create about 2500 medication at present, as opposed to 2010 when the country only had four manufacturing units (Nagraj, 2022). Foreign medicine that conforms to the UAE standards for safe consumption can be imported by UAE to maintain a steady supply of all types of medication within the country (Pateriya et al., 2011; Hassan et al., 2017). Generic medication in UAE has 60% lower prices than their branded counterparts (Nagraj, 2022). Also, the locally manufactured product is cheaper than the imported products and all are deemed as quality products as every pharmaceutical manufacturing company abides by strict guidelines for the production, packaging, storage and transportation of pharmaceutical products. However, the quality of the marketed medicinal agents may be affected or altered during transportation and poor storage condition. Therefore, it is also important to perform quality control test on market products periodically to verify whether they have similar quality in strength, drug contents and dissolution rate. Dissolution testing is a key tool for assessing the quality and performance of solid oral dosage forms, such as tablets and capsules (Anand et al., 2011; Chen et al., 2017; Gray and Rosanske, 2020; Figueroa-Campos et al., 2020). One of the applications of dissolution

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testing is to evaluate the similarity of dissolution profiles between different batches or formulations of the same drug product, or between a test product and a reference product (Moore and Flanner, 1996; Sathe et al., 1996). Dissolution similarity can support the demonstration of pharmaceutical equivalence and/or bioequivalence, which are required for the approval of generic medicinal products (Xie et al., 2015). The comparison of dissolution profiles based on more than one sampling data point provide us % in similarity and differences between the two products. If similarity of dissolution rate is ≥50%, two products are considered as identical (Moore and Flanner, 1996; Sathe et al., 1996). Quantification of candesartan cilexitil from tablets and dissolution media requires a very sensitive analytical method. The development of HPLC methods for quantification of candesartan cilexitil has been shown in several researches. Most of the reported methods used buffer with organic solvents as a mobile phase for quantification of candesartan cilexitil, such as acetonitrile: 0.05 M KH2PO4 buffer (65:35) by Akula et al. (2010), ortho phosphoric acid-adjusted phosphate buffer- acetonitrile (55:45) at pH 4.6 by Veeranjaneyulu et al. (2013), methanol/sodium phosphate monobasic buffer (0.01 M, pH 6.5) by Marghany et al. (2020), and phosphoric acid-adjusted 0.02 M mono basic potassium phosphate buffer: acetonitrile: triethyl amine (40:60:0.2) at pH 6.0 by Revathi et al., (2013). Mhaske et al. (2012) also reported a RP-HPLC method that used a mobile phase comprised of 0.05 M sodium dihydrogen phosphate buffer and acetonitrile. Furthermore, Hamid et al. (2018) published a HPLC method for estimation of candesartan celexitil from human plasma where the mobile phase was the blend of acetone, diethylamine and distilled water acidified with phosphoric acid to pH 2.5. In this paper, we aimed to create a buffer-free HPLC method that can measure candesartan cilexitil in tablets and dissolution media with high accuracy and precision. We chose various physical and chemical parameters, including hardness, dissolution rate, disintegration, friability, assay, dosage content uniformity and infrared fingerprinting, to assess the quality of candesartan cilexitil tablets sold in UAE. Furthermore, we used the similarity and difference factors of the dissolution profiles to evaluate the pharmaceutical equivalent of the products we studied.

Materials and methods

Chemicals and reagents

Candesartan cilexitil standard (Sigma-Aldrich, USA), potassium dihydrogen phosphate (Serva, Feinbiochemica Heidelberg/New York), polysorbate 20 (Alpha Chemika, India), HPLC grade acetonitrile (Honeywell, France), phosphoric Acid (80%) (Alpha Chemika, India) and sodium hydroxide (Alpha Chemika, India), Milli-Q Ultrapure (Type 1) water (Millipore, Bedford, MA, USA), 0.45 µm membrane syringe filters (Fisher Scientific, UK) and pyrex grade glassware were used in this study.

Sample description

Eight brands of candesartan cilexitil tablet dosage form such as CAND 1 (4 mg, Sweden), CAND 2 (8 mg, Sweden), CAND 3 (16 mg, Sweden), CAND 4 (8 mg, Oman), CAND 5 (16 mg, Oman), CAND 6 (8 mg, Jordan), CAND 7 (16 mg, Jordan), and CAND 8 (8 mg, UAE) were purchased from the Pharmacies of United Arab Emirates (UAE) and studied for their quality evaluation. The prices for 28 tablets in blister package form were AED (United Arab Emirates Dirham) 63.50 (CAND 1), 76.00 (CAND 2), 92.50 (CAND 3), 30.00 (CAND 4), 37.00 (CAND 5), 70.50 (CAND 6), 86.00 (CAND 7) and 40.50 (CAND 8) respectively.

The physical parameters determination

The physical parameters such as individual weight, average weight, diameter, hardness, friability, and disintegration times of the studied products were recorded (USP-NF, 2021). The equipment, operating conditions for this measurement and their results expression units are provided in Table 1.

Table 1. The list of equipment and their operation conditions was used in the determination of physical parameters of eight brands of candesartan cilexetil tablets.

Physical Parameters	Number of Tablets	Name of Machine/Equipment	Equipment Operating conditions	Results Expression Unit
Weight variation Test	20	Analytical balance (KERN & Sohn GmbH).	At ambient temperature 25°C	mg ± standard deviation (SD*) % Weight variation = |Individual weight - Average weight|/Average weight *100
Tablet length	20	Micrometer	-	mm (± SD*)
Friability test	20	Friability test apparatus (Grover Enterprises, India)	At 25 rpm for 4 min	% loss of tablets (± SD*) % Friability = |Initial weight - Final weight|/Initial weight *100
Disintegration Time	9	Disintegration Tester (India)	The temperature of the water bath was maintained at $37^0C \pm 2^0C$	min (± SD*)
Hardness/ Tablet breaking force	10	Erweka hardness tester (Germany)	At ambient temperature 25°C	**kg-f (± SD*).

*Standard deviation (SD); **kg-f (kilogram force)

HPLC instrument operating parameters

A RP-HPLC (Reversed Phase-High Performance liquid chromatography) method was developed and validated according to ICH guidelines (ICH, 2005) and applied for the identification and quantification of candesartan cilexitil from tablet dosage forms. Waters HPLC System equipped with Binary gradient pump, Water-UV-VIS Detector, Autosampler and Breeze-2 Software was used in HPLC analysis. Pinnacle DB C18 column (150 mm x 4.6 mm, 5 µm particles, Restek, USA) was used as a stationary phase and the mobile was comprised of acetonitrile and acidified Mili-Q Ultra water (1% phosphoric acid) (80:20 v/v). The mobile phase was degassed and filtered through 0.45 µm membrane filter at prior of analysis. The wavelength for detection of candesartan cilexitil was 282 nm and it was determined by scanning standard solution using Shimadzu UV-VIS spectrophotometry-1900 (Japan). The injection volume for sample and standards was 10 µL with a flow rate of 1 mL/min and the sample run time was 6 min. The mixture of acetonitrile: water (80:20) was used as diluent and the analysis was carried out at room temperature (25°C).

Standard preparation and calibration curves

Standard candesartan cilexitil solution ranges from 0.001 to 1000 µg/mL were prepared in acetonitrile: MilliQ water (80:20) and utilized for RP-HPLC method development, method validation and in qualitative and quantitative analysis of candesartan cilexitil present within the tablets. An eight-point calibration curve at 282 nm was prepared by using the standard concentrations from 1 to 500 µg/mL to check the linearity of the detector. Six-point calibration curves were prepared by utilizing concentration ranges from 10 to 500 µg/mL used for assay and content uniformity of dosage form determination, and a five-point calibration curves (1 to 500 µg/mL) was used for dissolution study. The limit of detection (LOD) and limit of quantification (LOQ) were determined by HPLC analysis of lowest concentration ranges from 0.001 to 1.0 µg/mL standard solution and 3:1 for signal to noise ratio was considered as LOD and 10:1 for signal to noise ratio was considered the LOQ limit (ICH, 2005). The HPLC analysis was repeated three times for each standard concentration level.

Sample preparation

Samples were prepared for identification and quantitative analysis (USP-NF, 2021). For assay, the mean weight of 10 tablets for each brand was recorded and ground into fine powder using a mortar and pestle. Three replicates of 100 µg/mL equivalent of powdered tablet samples were transferred into 100 mL volumetric flask and added 50 mL acetonitrile: Mili Q water (80:20 v/v) to the flask. The mixtures were sonicated for 20 to 25 min to facilitate the solubility of the drug into the solution and final volume were made up to 100 mL with diluent. The sample solutions were then filtered through a Whatman No.42 filter paper and 0.45 µm membrane filter respectively for qualitative and quantitative analysis. For content uniformity of dosage form determination, 10 units of each studied product were recorded individually and prepared the sample solution separately according to the assay sample preparation. Individual sample solution was analyzed and acceptance value was calculated according to the USP-NF (2021).

Validation of RP-HPLC method

The RP-HPLC method used in this study was validated as per guideline of ICH (2005). The suitability of the developed HPLC method used in quantitative analysis was checked by injecting 10 µL of 1, 10, 100 and 500 µg/mL standard solution of candesartan cilexitil into the HPLC system and the samples were run for six min at 282 nm. Each concentration was repeated six times and the results were expressed as mean area with standard deviation (SD) and % relative standard division (%RSD). The precision of the HPLC method was analyzed by repetitive analysis of 5, 25 and 250 µg/mL standard solution of candesartan cilexitil five times within a day at one hr interval between the analysis and for the intermediate precision, the analysis was repeated for the same concentration for the 5 consecutive days to check the variability and stability of the standard solution from day to day. The intra and inter-day analysis results were expressed as peak area with their SD and %RSD. The accuracy of the analytical method was studied by analyzing the recovery of spiked three different standard concentrations (10, 50 and 250 µg) from the samples (CAND 2). In this aspect, three replicates of CAND 2 powdered sample with added standard and without added standard were prepared according to the method described in assay and analyzed using the RP-HPLC system. The results were expressed as % recovery and calculated using the following formula (1):

$$\text{Recovery (\%)} = [(C_{Total} - C_{Unspiked})/ C_{spiked}]*100 \quad \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

where C_{Total} = calculated concentration of the spiked standard with CAND 2, $C_{Unspiked}$ = calculated concentration of the sample CAND 2, and C_{spiked} = calculated concentration of the spiked standard.

Dissolution study and comparison of dissolution profiles

The dissolution study was carried out as per guideline described in USP-NF (2021), however, quantitative analysis was carried by utilizing the newly developed and validated HPLC method. USP dissolution apparatus

(Paddle type, speed of rotation - 50 rpm and vessel volume 900 mL) was used in this study. The 0.35% polysorbate 20 in 0.05 M phosphate buffer solution (pH 6.5) was prepared and used as a dissolution media (USP-NF, 2021). Six tablets for each products were used for dissolution study and the samples (5 mL) were collected at 5, 10, 15, 20, 25, 30, 45, and 60 min intervals and replaced the withdrawn sample volume with 5 ml buffer for maintaining the volume of vessel. The collected samples were then filtered using 0.45 µm membrane filter and run through the HPLC system using the same experimental conditions used in assay. The injection of dissolute sample solution was repeated three times at each time interval. The results were expressed % cumulative drug release (% dissolution) at each sampling time-point and plotted against the time interval. The similarity of dissolution profiles between two products were calculated by considering a product as a reference product and the remaining were considered as test products. In this instance, a product of Sweden (CAND 2) was used as a reference product for 8 mg strength products, whereas CAND 3 (Sweden) was used for comparison of 16 mg strength products. The difference factor (f1) and similarity factor (f2) was calculated using the formulas (2 and 3) as described by Moore and Flanner, (1996) as follows:

$$f1 = \{[\ Rt - Tt\ ]/[\ Rt\ ]\} \times 100 \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (2)$$

$$f2 = 50 \times \log \{[1+(1/n)\ (Rt - Tt)^2\ ]^{-0.5}\} \times 100 \ldots\ldots\ldots\ldots\ldots\ldots\ldots (3)$$

where, Rt and Tt are the cumulative release of drug from reference and test products respectively, and n represent the number for sampling time-points. The reference values for f1 are 0% to 15% and f2 are 50% to 100% respectively. f1 (%) represent the differences and relative errors in between two dissolution curves and f2 represents the measurement of similarity in cumulative release of drug in between two curves at each sampling time-point.

Statistical analysis

The results of this study were expressed as mean with their standard deviation (SD) and % relative standard deviation (%RSD). The mean results of assay and dissolution test at 45 minutes interval were compared for similar strength products using ANOVA (One-way Analysis of Variance) and Tukey B ($P < 0.05$) was also conducted for multiple comparison using IBM SPSS Statistics (Version 23).

Results

Physical parameters

This study was conducted on three different strengths of candesartan cilexitil tablets such as 4 mg (CAND 1), 8 mg (CAND 2, CAND 4, CAND 6 and CAND 8) and 16 mg (CAND 3, CAND 5, and CAND 7) respectively. The average tablet weight of the product from Oman (CAND 4 and CAND 5) were 259.87 to 262.5 mg much higher than the products of Jordan, Sweden, and UAE and their average weight were in between 128 mg to 131 mg respectively. The individual tablet weight variation of the studied products fell in between ±0.25% to ±1.21% and complied with the limits of USP-NF (2021). The tablets were circular in shape and seven brands showed the length around 7 mm except the product of Oman had 9.55 to 9.62 mm in length. The tablet breaking force were similar 6 kg-f (kilogram force) for the three different strength products of Sweden (CAND 1, CAND 2, and CAND 3). The breaking force for the products of Oman, Jordan and UAE exhibited 4 kg-f. The products were disintegrated within 2 to 3 min and the friability were less than 1% (0.1%) and complied with the limits of USP-NF (2021). The recorded physical parameters of the studied products are shown in Table 2.

Validation of RP-HPLC method

Table 2. The recorded physical parameters of eight different brands of tablets that contained candesartan cilexetil

Tablet Brands Name	Tablet weight mg±SD*	% Weight variation of tablet	Diameter (Length) mm±SD*	Tablet Breaking Force **kg-f±SD	Friability %loss	Disintegration Time min± SD*
CAND 1	128.75±1.98	±1.21	7.09±0.014	6.45±0.27	0.104	3.21±0.22
CAND 2	131.12±0.83	±0.50	7.08±0.019	6.43±0.59	0.102	3.05±0.26
CAND 3	129.37±1.76	±1.06	7.04±0.004	6.44±0.34	0.105	3.52±0.34
CAND 4	259.87±0.83	±0.25	9.55±0.014	4.9±0.32	0.111	3.2±1.07
CAND 5	262.5±4.7	±1.61	9.62±0.013	3.97±0.04	0.115	2.14±0.23
CAND 6	128.12±1.45	±0.87	7.11±0.015	3.77±1.19	0.116	2.90±0.25
CAND 7	128.13±1.81	±1.07	7.09±0.010	4.85±0.71	0.108	2.65±0.43
CAND 8	130.5±0.92	±0.57	7.07±0.013	4.4±0.07	0.112	2.99±0.67

*Standard deviation (SD); **kg-f (kilogram force)

Candesartan cilexitil standard exhibited UV absorption maxima at 282 nm, hence, in HPLC analysis it is used for identification and quantification of candesartan cilexitil present within the tablets. The detector showed wide linear responses and the regression coefficient was 0.9996 (y = 10542x + 31519) from eight point calibration curve constructed using concentration ranges of standard solution from 1 to 500 µg/ml under the same experimental conditions. The limit of detection (LOD) and limit of quantification (LOQ) was 0.05 µg/mL and 0.5 µg/mL respectively. The suitability of the developed HPLC system for quantitative analysis was checked by injecting 6 replicates of 1, 10, 100 and 500 µg/mL standard solution and the reported retention time ± SD and peak area ± SD are presented in Table 3. The %RSD for retention time and peak area were <2%. The peak asymmetry of candesartan cilexitil was 1.05 (<1.5) and Theoretical Plane Number (N) was 5323 with plate height (H) 0.02 (ICH, 2005; USP-NF, 2021). The RSD for intra-day and inter precision was < 2%. The developed HPLC method was accurate and the recovery of drug from the sample was 99 to 100% with RSD <2% as shown in Table 4. A RP-HPLC overlay chromatogram of candesartan cilexitil standard concentration ranges from 1 to 500 µg/mL is shown in Figure 1.

Identification, assay and dosage content uniformity of candesartan cilexitil tablets

The mean retention time of 10 replicates of 100 µg/mL candesartan cilexitil standard solution was 3.0906 ± 0.0086 min (RSD: 0.28%) under the same HPLC experimental conditions. The studied products exhibited the similar retention time (3.084 to 3.098 min) and confirmed the studied

Table 3. HPLC System suitability study results from 1, 10, 100 and 500 µg/mL standard solution of candesartan cilexitil (n = 6)

Replicates	Candesartan cilexitil standard concentration							
	1 µg/mL		10 µg/mL		100 µg/mL		500 µg/mL	
	*t_R	Area	*t_R	Area	*t_R	Area	*t_R	Area
Injection # 1	3.088	11735	3.097	92364	3.095	997173	3.098	4995623
Injection # 2	3.088	11185	3.088	92865	3.097	1002599	3.093	5035136
Injection # 3	3.089	11980	3.092	92872	3.089	1000223	3.079	5036900
Injection # 4	3.089	11588	3.079	92178	3.075	994999	3.089	5028225
Injection # 5	3.087	11694	3.093	92466	3.092	993278	3.095	5040544
Injection # 6	3.091	11692	3.091	92028	3.093	990729	3.091	5044442
Average	3.088	11646	3.09	92462	3.09	996500	3.091	5030145
**SD	0.0013	260.68	0.0061	349.03	0.0079	4414.75	0.0065	17768.16
#%RSD	0.04	2.23	0.19	0.37	0.25	0.44	0.21	0.35

*t_R = Retention times (min); **SD = Standard deviation; #RSD = Relative standard deviation

Table 4. Precision and recovery study of candesartan cilexitil standards analyzed by using developed RP-HPLC machine parameters. Results are expressed as mean ±SD (n = 3)

Standard conc. (µg/mL)	Within Day precision		Day to day precision		Recovery			
	*t_R (min) ±SD	Area ±SD	*t_R (min)±SD	Area±SD	Added standard conc. (µg)	Calculated standard conc. (µg)	% Recovery	Average recovery ±SD
5	3.091±0.002 (RSD: 0.085%)	54134.66±974.11 (RSD: 1.79%)	3.089±0.003 (RSD: 0.09%)	50131±180.17 (RSD: 0.35%)	10	9.78 9.89 10.14	97.8 98.9 101.4	99.36 ±1.84 (RSD:1.85%)
25	3.09±0.003 (RSD: 0.09%)	303005±2240.30 (RSD: 0.73%)	3.091±0.004 (RSD: 0.14%)	292200±8289.79 (RSD:2.83%)	50	50.88 49.19 50.95	101.76 98.38 101.90	100.68 ±1.99 (RSD:1.97%)
250	3.091±0.003 (RSD: 0.11%)	2557219±6750.12 (RSD: 0.26%)	3.089±0.002 (RSD: 0.15%)	2429487±61049.77 (RSD: 2.51%)	250	251.34 250.89 248.87	100.53 100.36 99.54	100.14 ±0.53 (RSD:0.52%)

* t_R = Retention time in minute, SD = Standard deviation, RSD = Relative standard deviation

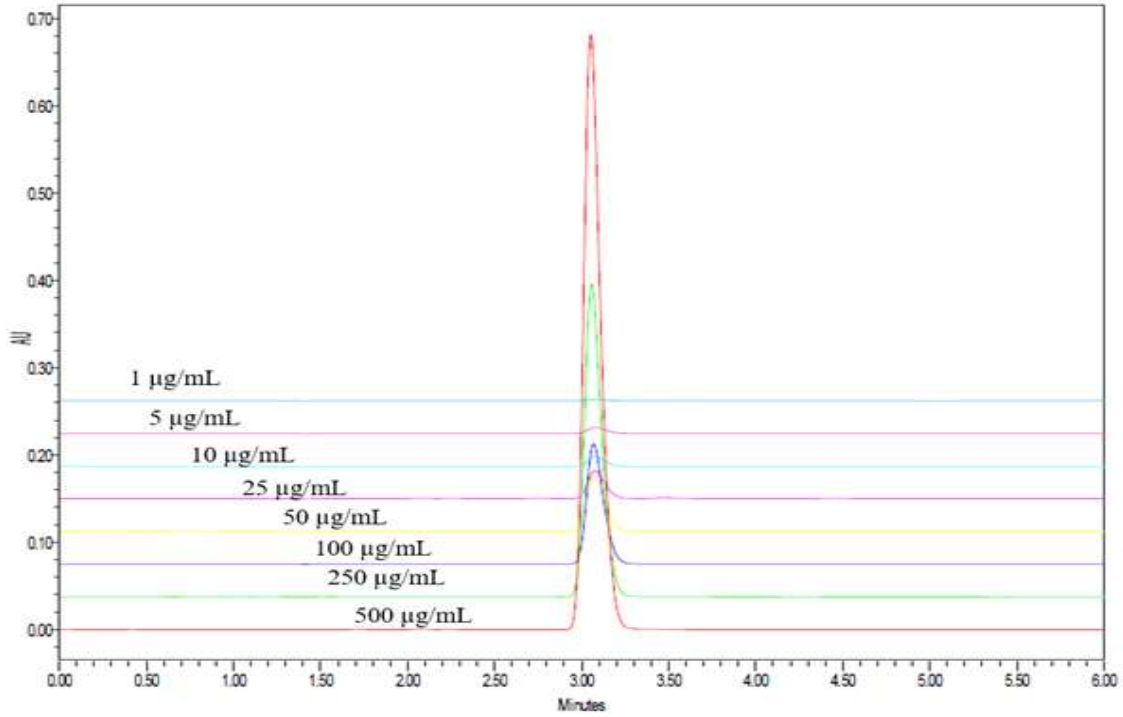

Figure 1. RP-HPLC overlay chromatogram of candesartan cilexitil standard concentration ranges from 1 to 500 µg/mL

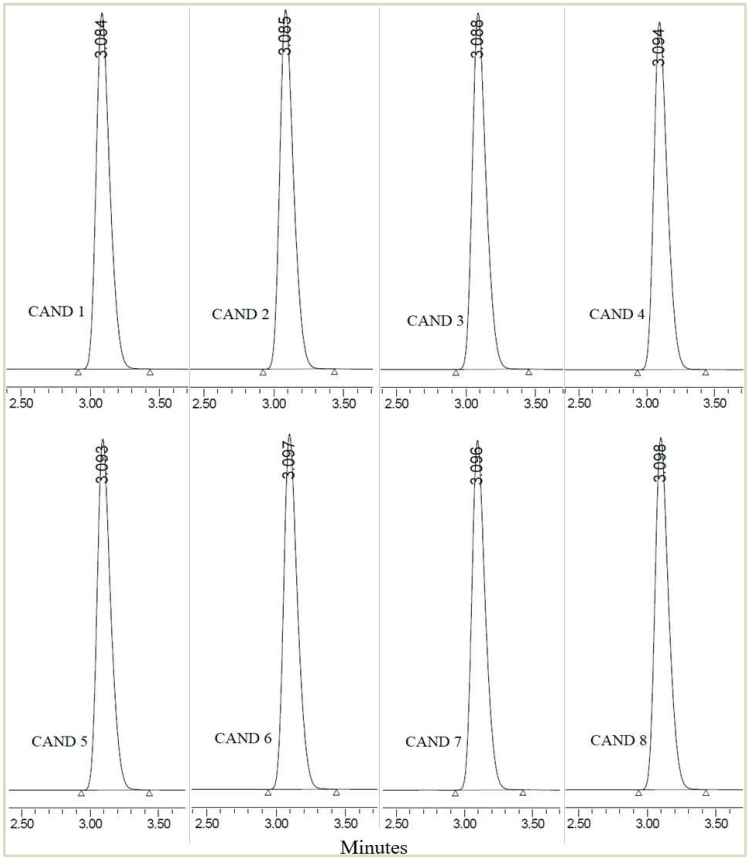

Figure 2. The RP-HPLC chromatogram of eight different brands of tablets that contained candesartan cilexetil

products contained candesartan cilexitil as the active chemical ingredient (Figure 2). The studied products were also scanned using a FT-IR Spectrometry (Fourier Transform Infrared, IRAffinity-1S, SIMADZU, Japan) equipped with single reflection ATR to obtain the chemical fingerprint for candesartan cilexitil tablets and all the products showed similarity in their IR spectrum (Figure 3). The most important characteristics stretching vibration peaks were observed at 3562 cm^{-1} (free O-H), 3327 cm^{-1} (O-H, broad, hydrogen bonded), 3263 cm^{-1} (N-H, broad, hydrogen bonded), 2927

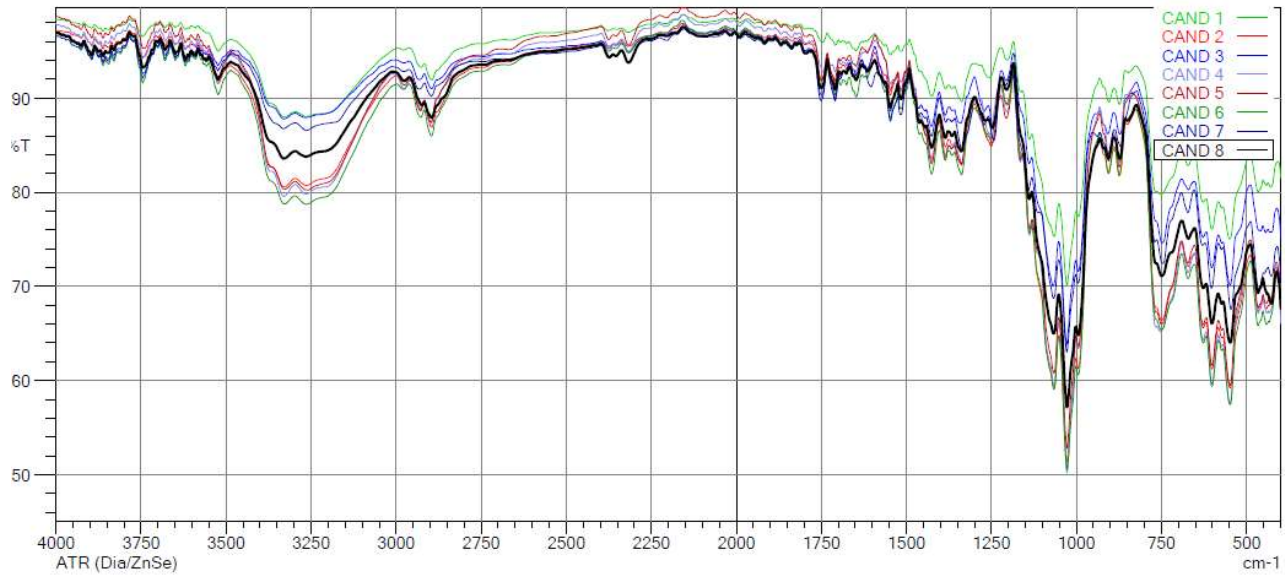

Figure 3. FT-IR spectrum (overlay) of studied eight brands of candesartan cilexitil tablet dosage form

Table 5. The dosage content uniformity study results of eight brands of three different chemical strength 4, 8 and 16 mg candesartan cilexitil tablets dosage form

	Individual tablet assay (%)							
Tablet No.	**CAND 1**	**CAND 2**	**CAND 3**	**CAND 4**	**CAND 5**	**CAND 6**	**CAND 7**	**CAND 8**
1	101.32	100.89	102.89	103.11	104.12	101.11	100.79	102.34
2	101.19	99.44	103.44	105.44	103.89	100.89	99.89	100.89
3	99.56	103.56	104.56	101.56	104.56	103.56	101.57	103.56
4	99.06	99.65	100.89	100.56	103.11	98.99	103.45	105.44
5	104.52	98.99	99.44	99.65	105.44	99.78	99.88	101.56
6	100.13	99.78	102.66	103.99	101.56	100.08	100.09	100.58
7	99.66	105.08	98.65	99.78	100.56	104.89	103.56	98.81
8	100.45	104.89	103.99	103.08	104.89	100.98	98.99	99.67
9	99.88	100.98	99.78	101.66	100.98	98.97	99.79	105.45
10	103.09	98.97	102.08	102.67	98.97	102.34	100.08	101.33
Average	100.88	101.22	101.83	102.15	102.81	101.16	100.81	101.96
SD	1.72	2.39	2.04	1.86	2.16	1.93	1.57	2.25
%RSD	1.71	2.36	2.00	1.82	2.10	1.91	1.55	2.21
*AV	4.53	5.75	4.89	5.12	6.49	4.64	3.77	5.87

*AV = Acceptance Value <15 (USP-NF 2021; SD = Standard deviation, RSD = Relative standard deviation

cm-1 (aromatic C-H), 2897 cm^{-1} (aliphatic C-H), 1750 cm^{-1} (ester C=O), 1710 cm^{-1} (acid C=O), 1610 cm-1 (C=N), 1570 cm^{-1} and 1540 cm^{-1} (aromatic C=C) respectively (Anwar et al., 2020).

Six-point calibration curve was constructed using 5 to 500 µg/mL standard solution and used for quantification of drug present within the tablets. The linear regression coefficient of the curve was $R^2 = 1$ (y = 10076x - 6963.1). The assay results of three replicates of powdered sample analysis for each product showed in Figure 4 and the studied products contained 100.74% to 102.37% active component and the overall results were as follows: CAND 4 (102.37%) CAND 5 (102.29%) ≥ CAND 8 (101.44%) CAND 2 (101.29%) CAND 1(101.25%) CAND 6 (101.18%) CAND 3 (101.15%) ≥ CAND 7 (100.74%). The RSD from assay results were 0.33% to 1.87% and complied with limits of the USP-NF (2021) that stated the product should be contained 90 to 110% active ingredient. There were no statistically significant differences in candesartan cilexitil contents amongst the studied products irrespective of their different chemical strengths.

Dosage content uniformity

The strength of studied product was <25 mg, hence the uniformity of dosage unit was determined as per guidelines of USP-NF (2021). In this instance, 10 dosage units of each product were analyzed individually and their active contents were determined utilizing the calibration curves constructed using similar concentration ranges used in the assay. The individual tablet assay and the average results from 10 dosage units are shown in Table 5. The acceptance value

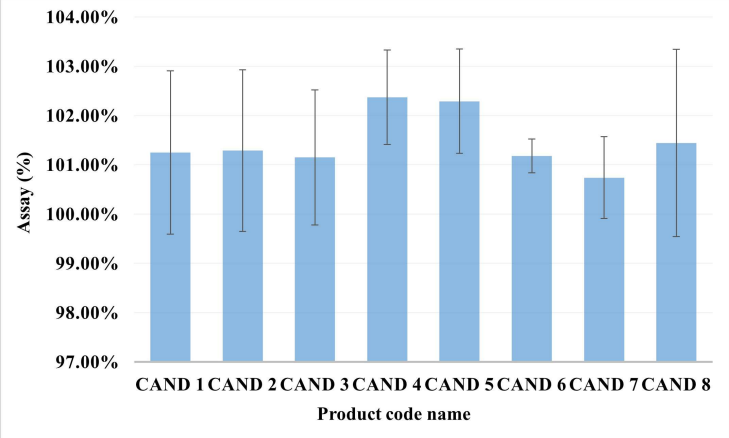

Figure 4. Assay of eight brands of candesartan cilexetil tablets (n =3 ± SD)

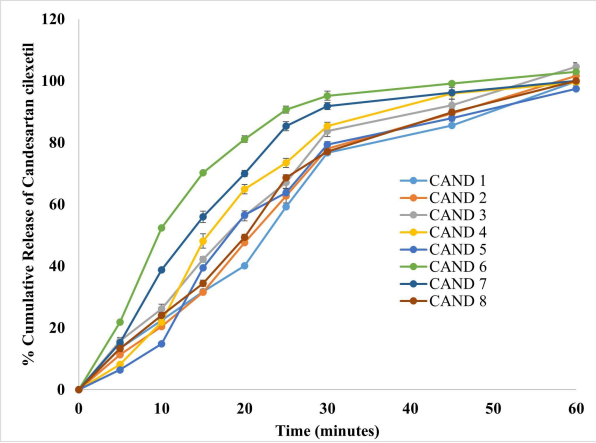

Figure 5. Generation of dissolution profiles of cumulative release of candesartan cilexetil from tablets (%) versus sampling intervals

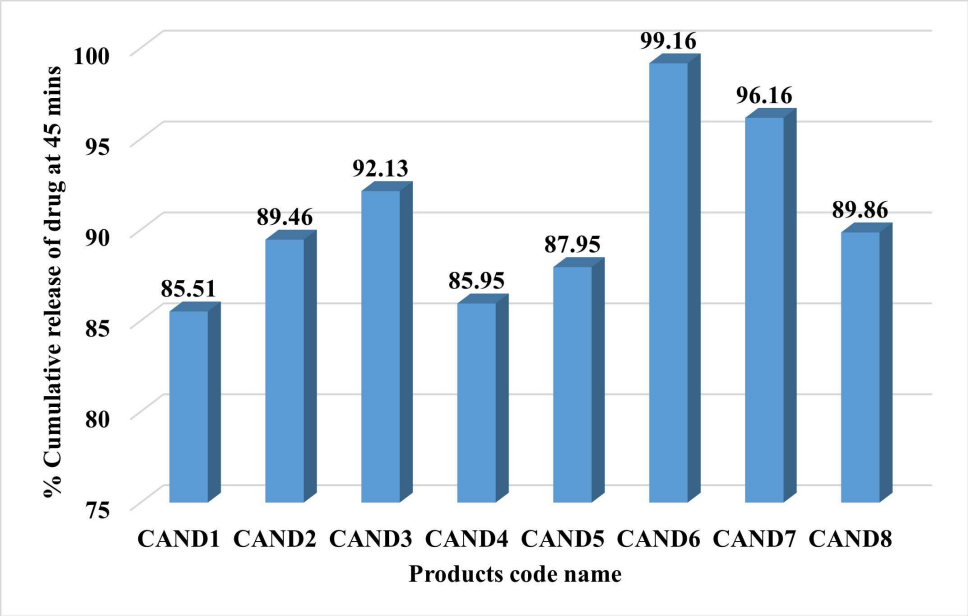

Figure 6. Percent cumulative release of drug at 45 minutes from eight brands of tablets contained candesartan cilexetil

(AV) for individual tablet content variation was less than 15 and it met the limits set by USP-NF (2021).

Dissolution study

For dissolution test study, calibration curves were constructed using 1 to 500 µg/mL standard solution and the regression coefficients (R^2) of the curve was 0.9999 (y = 10293x – 17965). In this study, samples were collected and analyzed at eight sampling data points by using validated HPLC method. The dissolution test results showed product released variable amounts of drugs at different data sampling intervals as shown in Figure 5. Amongst the three products of Sweden, at 15 min interval CAND 3 released about 42% drug and the other two products released 31% drug. The product of Oman CAND 4 and CAND 5 released 48% and 39% drug respectively. CAND 6 and CAND 7, the product of Jordan released 70% and 56% of drug. CAND 8, a product of UAE released 34% of drug at 15 min intervals. At 30 min intervals, CAND 3, CAND 4, CAND 6, and CAND 7 released ≥ 83% of drug. However, USP-NF (2021) stated that the cumulative release of drug from the products should not be less than 80% at 45 minutes. The cumulative release of drug at 45 minutes from eight different brands are shown in Figure 6 and it can be seen that release of drug was higher from CAND 6 (99.16%) and CAND 7 (96.16%) respectively than other studied products and both products were imported from Jordan. The product of UAE (CAND 8) and Sweden (CAND 2) were similar in chemical strength (8 mg) released about 89% of drug at 45 minutes. The product of Oman released about 95.95% (CAND 4) and 87.95% (CAND 5) drug at 45 minutes interval and the other two remaining products of Sweden released 85.51% (CAND 1) and 92.13% (CAND 3)

Table 6. Calculated similarity factor (f2) and difference factor (f1) for studied different brands of tablets containing candesartan cilexetil

Test Products	Reference Product	*f1	*f2
	*CAND 2 (8 mg)		
CAND 1 (4 mg)		5.03	71.98
CAND 4 (8 mg)		14.70	49.88
CAND 6 (8 mg)		38.60	30.25
CAND 8 (8 mg)		4.28	75.86
	**CAND 3 (16 mg)		
CAND 5 (16 mg)		8.73	59.61
CAND 7 (16 mg)		15.51	47.77

*For 4 and 8 mg strength products, CAND 2 was used as a reference product for f1 and f2 calculation

**For 16 mg strength products, CAND 3 was used as a reference product for f1 and f2 calculation.

respectively. In conclusion, the studied eight products complied with the limits set by USP-NF (2021).

Dissolution profiles comparison

The dissolution profiles were constructed using %cumulative release of drugs against sampling interval as shown in Figure 5. Comparison of dissolution profiles between two products provided us more insight regarding the similarity and differences in dissolution to be expected in vivo. This study covered 8 mg strength of four products such as CAND 2, CAND 4, CAND 6 and CAND 8, three were in 16 mg strength such as CAND 3, CAND 5 and CAND 7, and one was in 4 mg strength. For dissolution profile comparisons CAND 2 (8 mg, Sweden) was used as a reference product and other remaining seven products were counted as test products. In case of 16 mg strength product CAND 3 was used as a reference product. The calculated similarity factor (f2) and difference factor (f1) for the test products are presented in Table 6. Overall, four products such as CAND 1 (4 mg, Sweden), CAND 4 (16 mg, Sweden), CAND 5 (16 mg, Oman) and CAND-8 (8 mg, UAE) exhibited ≥ 50% in similarity in dissolution profiles with the reference products. The product of Jordan (CAND 6 and CAND 7) were 30 to 48% similarity with the reference products. In aspect of difference factor f1, the calculated values for all the studied products were ≤ 15% except CAND 6 and CAND 7, both of the products were from Jordan.

Discussion

Candesartan cilexitil tablets come in four different doses worldwide: 4, 8, 16 and 32 mg. However, only the 4, 8 and 16 mg doses are sold in UAE pharmaceutical markets. Therefore, we focused on these three doses of candesartan cilexitil tablets in this work. The quality of the marketed medicinal agents can deteriorate with high temperature and high humidity exposure, so periodically checking the quality of marketed products provides us an insight of the storage condition maintained from transportation to the pharmacy shelves. In UAE, only 8 mg strength (CAND 8) was produced locally, the other products were imported from Oman, Jordan and Sweden. The 8 mg tablets had the highest price for the product from Sweden (CAND 2, AED 76.00) and the lowest price for the product from Oman (CAND 5, AED 37). The product from UAE (CAND 8, AED 40) was also cheaper than the products from Jordan (CAND 6, AED 70.50) and Sweden. All the physical parameters of the studied products passed the specification set by USP-NF (2021). For dosage content uniformity, the acceptance value (AV) was 5, much lower than the USP-NF (2021) specifications (<15).

For the comparison of dissolution profiles, the f1 and f2 factors were calculated based on eight sampling data points. The f1 factor is also used with the f2 factor in the assessment of pharmaceutical equivalence for generic drugs (Anand et al., 2011; Diaz et al., 2016). Regulatory agencies use these factors to determine whether the dissolution profiles of generic drug products are similar to those of the corresponding reference products (Diaz et al., 2016). The f1 factor provides additional information by considering the absolute differences between dissolution profiles, complementing the overall similarity assessment provided by the f2 factor (Moore and Flanner, 1996; Diaz et al., 2016). Based on dissolution test comparisons of 8 mg strength, the product of UAE (CAND 8) and Sweden (CAND 2) released about 89.46% and 89.86% drug at 45 min intervals, whereas, Oman (CAND 4) and Jordan (CAND 6) product in similar strength released about

95.95% and 99.16% drug respectively. The comparison of the similarity (f2) in dissolution profiles of reference product (Sweden, CAND 2), the product of UAE showed 76% in similarity based on eight data sampling time. The Oman product (CAND 4) was within the acceptance criteria 50%. Based on the f2 values, 8 mg in strength product of Sweden, Oman and UAE can be considered are pharmaceutical equivalent. Based on calculated f1 factors, CAND 2, CAND 4 and CAND 8 also exhibited similarity in dissolution profiles (f1≤ 15%). Pharmaceutical equivalent of medicinal agents are drugs that have the same active ingredients, dosage form, strength, and route of administration as the original or reference product. They may differ in characteristics such as shape, color, flavor, or inactive ingredients (*Roy, 2011;* FDA*, 2022*). The comparison of the similarity factor f2 for the 16 mg strength products, the product of Oman (CAND 5) was 60% similar in dissolution profiles with the reference product (Sweden, CAND 3), whereas CAND 7 a Jordan product showed 48% similarity with the reference product. In case of difference factor, CAND 5 showed acceptable differences (<15%) in comparison with the reference. In this aspect CAND 5 and CAND 3 can be considered are pharmaceutically equivalent. In this study, only one imported product was in 4 mg in chemical strength (CAND 1, Sweden), and it had a 72% similarity in dissolution profiles with the reference product and both were imported from Sweden. A high f2 value (typically ≥50) indicates a high degree of similarity, suggesting comparable drug release characteristics and, by extension, similar in vivo performance. A study on 16 mg candesartan product from Indonesia demonstrated that the test and reference product were bioequivalence (Tjandrawinata et al., 2013). However, in our study, 16 mg product of Jordan (CAND 7) was not pharmaceutical equivalent with the reference product based on the f1 and f2 values. In summary, f1 and f2 values provided valuable information regarding the similarity in rate of dissolution at several sampling data points.

Conclusion

The pharmaceutical equivalence study of seven imported and one local products were conducted. The physical parameters, FT-IR data, assay contents, dosage content uniformity and dissolution test results showed that all the products met the quality standards following the USP-NF specifications. Based on similarity factors (f2), two 8 mg strength products (UAE and Oman) and one 16 mg strength product (Oman) were >50% similar with the reference (Sweden) product. Hence, these products can be deemed as pharmaceutical equivalents. However, this does not mean that they are therapeutically equivalent, which means that they have the same clinical effect and safety profile in patients. Pharmaceutical equivalence is an important concept for drug development and substitution. The products from Sweden have higher prices in UAE compared to the local and other imported products. A patient who requires this medication for a prolonged period may prefer the local product to reduce the cost of expenses without compromising the quality of the product, as the products from UAE and Oman have lower prices in UAE than the products from Sweden and Jordan.

Conflict of interests

We declare no conflicts of interest.

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