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# Quality Control Measurement and *in vitro* Bioequivalence of Candesartan Cilexetil Tablets Marketed in Saudi Arabia

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***Authors' contributions***

*This work was carried out in collaboration among all authors. Authors MAB, HAA and HAM designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors AN, RMRA, MSA and MIA managed the analyses of the study. Authors HMAM and NA managed the literature searches. All authors read and approved the final manuscript.*

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## ABSTRACT

**Aim:** Some generics were reported to be counterfeit and inferior quality than the innovators. This study was aimed to make sure about the compliance with standard specifications and evaluation of the quality of different selected brands (generic and innovator), after performing different pharmacopeial quality control tests, of Candesartan cilexetil tablets (16 mg) commercially available in Saudi Arabia for hypertensive patients.

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**Study Design:** *In vitro* study of tablets.
**Place and Duration of Study:** College of Pharmacy, Jazan University, Jazan, KSA, between September 2018 and May 2019.
**Methodology:** The different generic brands of Candesartan cilexetil (CC) and innovator brand (16 mg) were subjected to weight variation, hardness, friability, assay, and disintegration tests following the established protocols. The purity of active ingredient was authenticated by comparative analysis of FT-IR spectra with pure drug. In vitro bioequivalence was studied after analyzing the results of dissolution summaries in phosphate buffer (pH 6.5) mixed with polysorbate 20 (0.35% v/v).
**Results:** The results of the tests conducted for evaluation of the tablets were found to be in acceptable limits for all the selected brands. After comparative analysis of FT-IR spectra with pure drug, it was inferred that correct active ingredient was used for the preparation of tablets. The drug release profile exhibited 96.89 – 101.97% of release of CC from all generic brands, in comparison to 99.4% for innovator brand after 60 min of study. The assessment of difference factor (f1<15) and similarity factor (f2>50) revealed the resemblance of generic brands with that of innovator brand. Furthermore, the dissolution efficiency (DE = ±10% of the innovator value) of all generic brands (73.12 – 73.25%) exhibited equivalency with that of innovator brand (70.45%).
**Conclusion:** The selected generics were considered to be biopharmaceutically equivalent to the innovator and maintained their efficacy. As a consequence, these brands can be used interchangeably by the hypertensive patients in Saudi Arabia.

*Keywords: In vitro bioequivalence; candesartan cilexetil; hypertension; FT-IR; dissolution.*

## 1. INTRODUCTION

Candesartan, a well-known antihypertensive agent belongs to the class of selective Angiotensin-II receptor antagonist [1]. Candesartan cilexetil is a prodrug of the active Candesartan metabolite. It converts to active metabolite inside the body on hydrolysis by endogenous esterase enzymes [2]. Chemical structure of Candesartan cilexetil is shown in Fig. 1.

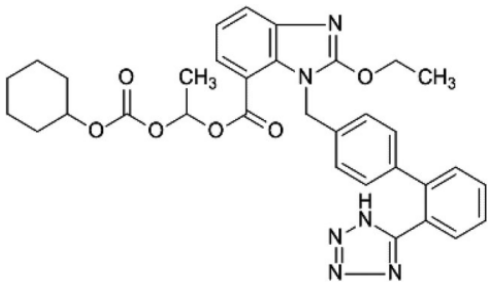

**Fig. 1. Chemical structure of Candesartan cilexetil**

Candesartan cilexetil (CC) is beneficial over the other marketed antihypertensive agents as there is no any severe first dose hypotension effect been reported. Also, on termination of treatment, this drug does not show any rebound effect. In the market, different doses of CC tablets are available but the best suggested starting dose found to be 16 mg once daily. It is reported well that candesartan reduces the mortality rate in heart failure patients and is the most suitable drug for the treatment of ventricular systolic dysfunction. It has low solubility profile with biological half-life and bioavailability of 9 h and 15% respectively [2].

In the last few decades, cost of the medications is accelerating very fast and it became very difficult to afford lifelong medications for hypertension treatment. Different strategies have been planned by the healthcare systems to reduce the medication costs. The most significant approach to reducing the medication cost in the healthcare has been the introduction of the generic equivalent of innovator brand in the market after performing bioequivalence studies. A big number of newer generics are introducing in the market every year. So, proper awareness of the safety-efficacy parameters of these generics is the main challenge to our health system [3]. Generic brands are expected to be low cost, easily accessible and of equivalent in pharmacodynamics and pharmacokinetic profile compared to the available innovator brand in the market. Therapeutically equivalence of any drug can be confirmed by comparing their quality control parameters [3].

Results of quality control testings' such as friability, weight variation, hardness, percentage purity, and disintegration suggest that up to

which level the GMP guidelines had been followed during the manufacturing of these generic products. When the generic and the innovator brand would have comparable dissolution profile then the in vivo bioequivalence test of the generics can be waived [4]. It was reported that fewer generics in the market were found to be counterfeit and inferior quality than the innovators. So, identifying these fake and suspicious generics is the prime challenge to our health department and quality control units. This research will assist to highlight such pharmaceutical products which are found to be spurious, inferior in quality and dangerous to the users.

The objective of the present research was to perform the quality control measurements and evaluate dissolution test through different statistical methods including dissimilarity factor (f1), similarity factor (f2) and dissolution efficiency (% DE) of different brands of CC tablets available in Saudi Arabia.

## 2. MATERIALS AND METHODS

Pure Candesartan cilexetil powder was purchased from MedChemExpress LLC, NJ, USA. Three marketed generic brands of CC tablets as well as the innovator (16 mg each) with expiry date of more than 1 year were purchased from the different pharmacies. Furthermore, the reagents including $KH_2PO_4$, $K_2HPO_4$, methanol, absolute ethanol, glacial acetic acid, 0.1 M HCl were purchased from Sigma Aldrich (USA). Powder KBr–spectroscopic grade was purchased from Thermo Scientific (USA). All other selected reagents were of analytical grade.

The innovator brand was selected and labeled as CC-1 (ATACAND, AstraZeneca, Sweden). Moreover, the different generic brands were selected and labeled as CC-2 (BLOPRESS, Arab Pharmaceutical Manufacturing Company, Jordan), CC-3 (CANDEPRESS, Riyadh Pharma, Saudi Arabia), CC-4 (CANDAN, Middle East Pharmaceutical Industries Co. Ltd., Saudi Arabia).

### 2.1 Extraction, Identification and Compatibility Study of Active Ingredient

Tablets of different brands (16 mg) were crushed and powdered in a mortar with pestle. It was dissolved in 50 mL of methanol and followed by sonication for 15 min. Solution was then filtered with Whatman Filter paper (MN615, Macherey-Nagel, Duren, Germany). The filtrate was dried on a water bath to obtain a powder residue.

Compatibility study of CC with the used excipients in different generic and innovator tablets was studied by FT-IR (Thermo Scientific, Nicolet iS10, Fourier Transform spectrophotometer). The FT-IR spectrum of pure CC drug was compared with the spectra of extracted powdered residue of different tablets. The wave numbers of the functional groups of CC of the tablet extract and pure drug were recorded and analyzed. The extracted powder residue (2 mg) of each brand and pure CC drug were triturated with 200 mg of the finely powdered analytical grade KBr using mortar and pestle. A pellet of the mixture was prepared with suitable disc using 10 tons pressure. FT-IR spectra of the prepared pellet of pure drug and generic products were obtained against the reference pellet of KBr alone in the range of 600-4000 $cm^{-1}$.

### 2.2 Weight Variation Test

The weight variation test was performed on 20 tablets selected from each brand. All twenty tablets were weighed together on a digital balance (PW124, Adam, UK). A mean weight of twenty (20) tablets of each brand was determined. Tablets were individually weighed and the percentage deviation of each tablet from the mean was determined [5].

### 2.3 Friability Test

Ten tablets of each brand were arbitrarily selected, dusted and weighed before placing inside the Roche Friability tester (Copley scientific, Nottingham, UK). It was rotated for 4 minutes at a speed of 25 rpm (i.e., total hundred rotations). These tablets were weighed again after completion of rotation and weight loss (%) was determined. The percentage friability was calculated using the following formula:

$$\text{Friability (\%)} = \frac{\text{Initial weight of 10 tablets} - \text{Final weight of 10 tablets}}{\text{Initial weight of 10 tablets}} \times 100$$

### 2.4 Hardness Test

The hardness test was accomplished on ten tablets of each brand. The hardness was

determined using Monsanto hardness tester (Copley scientific limited, Nottingham, UK). The force of compression used for breaking of each tablet was recorded. A mean hardness (±S.D) was determined for all brands.

## 2.5 Disintegration Test

Disintegration test was studied using disintegration apparatus (Copley scientific, Nottingham, UK). The apparatus consists of basket rack assembly with six open-ended glass tubes. Each tube of the assembly was fixed with 10 mesh size sieve at the bottom. Six tablets from each brand were taken and transferred to each tube (i.e., one tablet in each tube). The assembly was suspended in disintegration medium in a beaker of 1000 mL. The disintegration medium selected for the study was 900 mL of 0.1 N HCl solutions. The temperature of beaker was maintained in a water bath at 37 ± 2ºC. The assembly of tubes was attached to a mechanical device for lowering and raising at a constant frequency of 28 to 32 cycles per minute. The disintegration time was estimated for each tablet when no broken piece remained on 10 mesh sieves to pass into disintegration medium [5].

## 2.6 Calibration Curve

The standard solution of CC was prepared in Phosphate buffer (pH 6.5) mixed with polysorbate 20 (0.35 % w/v). Accurately weighed amount of CC (25 mg) was taken in 100 mL of volumetric flask and 10 mL of methanol was added. The resulting solution was sonicated for 10 minutes and brought to the volume of 100 mL with Phosphate buffer (pH 6.5) mixed with polysorbate 20. The stock solution was further sonicated for 5 minutes and filtered using 0.45 µm filter (Nylon 0.45 µm, Millipore, Millex-HN). Different dilutions of CC were prepared from stock solution with concentrations of 5, 10, 15, 20 and 25 µg/mL and absorbance was taken at $\lambda_{max}$ of 255 nm by UV spectrophotometer (Labomed, 8 Auto cell, USA) [6].

## 2.7 Drug Content

Three tablets (16 mg dose each) were taken and average weight was determined. All these tablets were crushed and powdered. An equivalent weight to dose (16 mg) of powder was taken into 100 mL of volumetric flask and mixed with 10 mL of methanol. The mixture was sonicated for 10 minutes. The volume was occupied with pH 6.5 phosphate buffer mixed with polysorbate 20 (0.35 % w/v) and sonicated further for 5 minutes. The resulting solution was filtered using 0.45 µm filter (Nylon 0.45 µm, Millipore, Millex-HN) and diluted (10 times) with buffer. These solutions were analyzed by UV spectrophotometer at $\lambda_{max}$ of 255 nm. The amount of drug present in final solution and the percentage purity was determined [7].

## 2.8 Dissolution Study

In vitro dissolution study of different brands of CC tablets in 900 mL of dissolution medium was performed using USP type II dissolution apparatus (DIS 6000, Copley scientific, Nottingham, UK) [5]. As per recommendation of FDA, 0.35% of polysorbate 20 mixed with pH 6.5 phosphate buffer at 37 ± 1°C was used as dissolution medium for the release study of CC from different tablets. One tablet was placed in each vessel and the paddle speed was maintained at 50 ± 2 rpm. At the fixed time intervals of 10, 20, 30, 45 and 60 minutes, 5 mL of the samples were withdrawn and replaced with 5 mL of fresh dissolution medium. The collected samples were analyzed by UV spectrophotometer at $\lambda_{max}$ of 255 nm. Drug release from each tablet at particular time interval was calculated from the mean values of absorbance of all the six tablets [8].

As per recommendation from US FDA, the dissolution profile was analyzed by plotting released (%) amount of drug versus time. Furthermore, the release profiles were compared in terms of difference factor (f1) and similarity factor ($f_2$). The difference factor ($f_1$) signifies the relative error between two curves which is calculated as the difference (%) between two curves at each point. Similarity factor ($f_2$) measures the similarity between two curves obtained in release study which is estimated as logarithmic reciprocal square root transformation of the sum of squared errors. Thus, the release data of all the generic brands were assessed with reference to the innovator brand.

$$f_1 = \left\{\frac{\sum_{t=1}^{n}|R_t - T_t|}{\sum_{t=1}^{n} R_t}\right\} \times 100$$

$$f_2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

$R_t$ and $T_t$ are the dissolution value at each time point for the innovator and generic brand

respectively. If $f_1$ is found in between 0-15 and $f_2$ in between 50-100, the dissolution profile of test generic brand is considered as bioequivalent with the innovator brand [9,10].

Additionally, the release behavior of CC was described by the estimation of dissolution efficiency (DE). It is a non-comparative parameter of dissolution kinetics. The DE for CC was determined as the ratio of $AUC_{0\rightarrow t}$ (where, t = 60 min) and the total area of the rectangle ($TR_{100}$). It is represented by the following equation [11,12]:

$$\text{Dissolution efficiency (D.E.)} = \frac{\int_0^t y\,.dt}{y_{100}\,.\,t} \times 100\%$$

## 2.9 Data Analyses

Sigma plot 14.0 software, Microsoft Office 2010, and Add-In to Excel 2010 were used to determine area under drug release curve (AUC), mean dissolution time (MDT), dissolution efficiency (% DE), difference factor (f1) and similarity factor (f2). ANOVA was applied to the results. Data were statistically analyzed using the Student's t-test with the significance level of $p \leq .05$.

# 3. RESULTS AND DISCUSSION

## 3.1 Extraction, Identification and Compatibility Study of Active Ingredient

Characteristic IR peaks of the prominent functional groups present in pure CC drug are presented in Table 1. The FT-IR spectrum of pure Candesartan cilexetil, innovator brand (CC-1) and three generic brands (CC-2, CC-3 & CC-4) have been compared in Fig. 2.

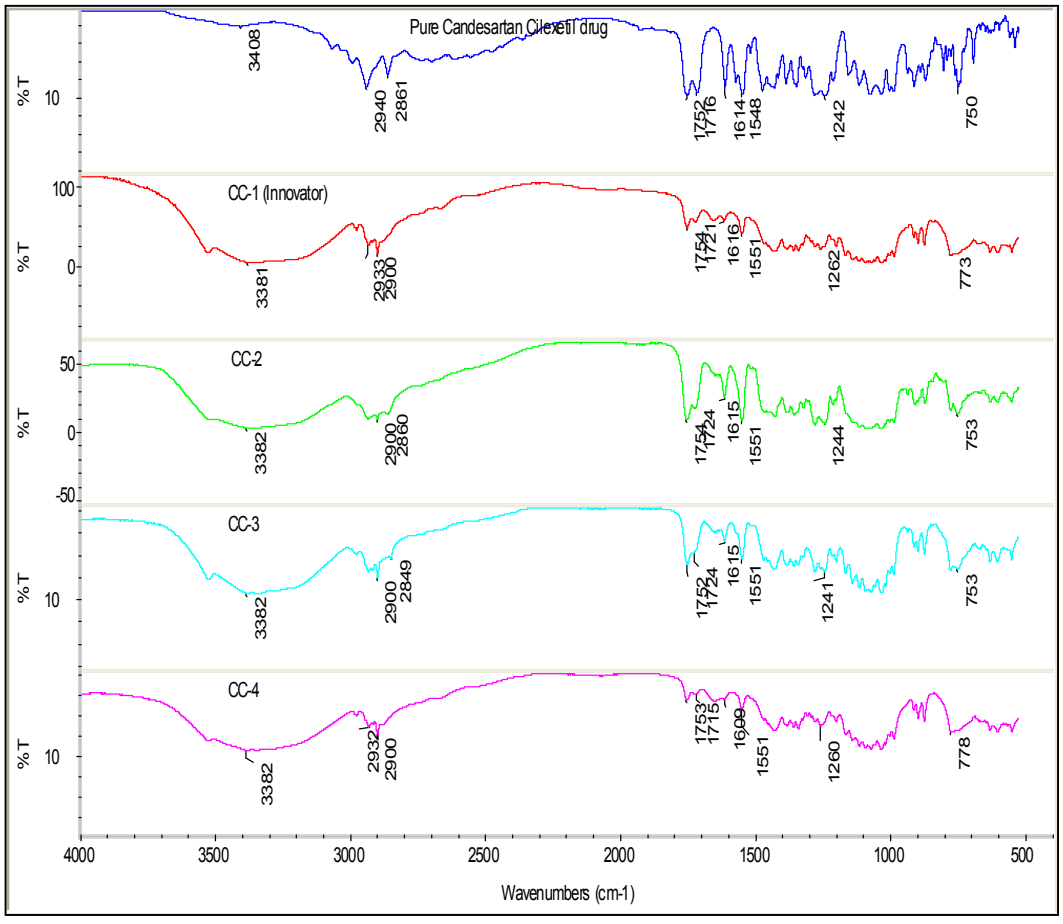


**Fig. 2. FT-IR spectra of pure Candesartan cilexetil (a), CC-1 (Innovator brand) (b), CC-2 (c), CC-3 (d) and CC-4 (e)**

The prominent functional group of FT-IR spectra of pure CC drug was found to be nearly superimposed on the spectra of all the CC generic products. It showed negligible variations of wave numbers. It indicates the absence of any chemical interactions between the active ingredient and excipients. These findings suggested that the excipients present in all the selected brands were compatible with the drug. Thus, it advocates the extent of similarity of the generic products with the innovator.

**Table 1. Characteristic IR peaks ($\tilde{v}$, $cm^{-1}$) of the functional groups present in pure CC**

| Functional group | Wave number ($\tilde{v}$,$cm^{-1}$) |
|---|---|
| NH Stretching | 3408 |
| Aromatic CH Stretching | 2940 |
| Aliphatic CH Stretching | 2861 |
| Ester C=O Stretching | 1752 |
| Acid C=O Stretching | 1716 |
| C=N Stretching | 1614 |
| C=C Stretching | 1548 |
| C=O Ester | 1242 |
| Aromatic CH bending | 750 |

## 3.2 Weight Variation, Friability, Hardness, Disintegration and Drug Content Analysis

All the selected tablet brands of CC (16 mg) were studied for weight variation test. The data of weight variation are shown in Table 2. All the tablets of selected four brands were found to be within the weight variation limits when compared with the USP guidelines. Uniformity in weight of tablets ensures consistency of dosage units. Variation in weight of tablets must be reduced to minimum for uniform dose to be given to the patients. Many factors are involved that affect the weight of tablets during manufacturing including machine speed, head pressure, tooling of the compression machine and flow properties of powders.

All the brands have been studied for friability testing using Roche friabilator to check the resistance of abrasion during transportation and handling. Percentage friability was calculated as per USP. The result was varied from 0.537-0.862% for all brands (Table 2). Thus, the friability test was passed (< 1%) by all brands. Friability is defined by the loss of weight in percentage of tablets due to mechanical action during the test. This test was performed to express the ability of compressed tablet to avoid breaking and fracture during transport. Tablets were subjected to mechanical stress, shock and aberration during manufacturing, packaging and transportation process. This may lead to capping, aberration, or even breakage of tablets. Therefore, tablets were formulated in such a way so that these can withstand the mechanical stress. Thus, the friability test was performed to monitor the stress resistance ability of tablets.

Tablet hardness test results have been presented in Table 2. The mean value of hardness (±S.D) was found to be in the range of 4 - 4.75 Kgf. So, all the brands passed the hardness test. The force required to break tablet is measured and expressed in terms of hardness. Consequently, the hardness measures the crushing strength of tablets. A crushing strength of 4 Kg is considered to be the minimum value for satisfactory tablets. It is associated with the tablet property including density and porosity. A too hard tablet may not disintegrate within the required period of time. Such tablet will fail the dissolution test. A too soft tablet may break easily or may not be able to withstand handling during subsequent processing including coating, packaging or transportation. There are different factors on which hardness of tablet depends which include shape, chemical properties, binding agent, pressure applied during compression and storage conditions.

Data of disintegration studies are shown in Table 2. The mean disintegration time of the all tablets was found to be less than 5 minutes and thus undoubtedly passed the disintegration test. The innovator product took a maximum of 290 sec for complete disintegration; however, CC-2 took a minimum of 120 sec. The process of loosing of strength among the component particles of tablet is called disintegration. It is an earlier step of evaluation for a drug to be available in solution form. A drug to be available to the body it must be in solution form. Moreover, disintegration offers a greater surface area to the dissolution media that must be related to the increased availability of the drug in the body. Disintegration offers no assurance about the drug present in solution at appropriate rate. This is assured by performing dissolution study. The disintegration time of tablets is influenced by the quality and quantity of disintegrant and lubricant. The lubricant decreases the wettability of tablets thereby increasing the disintegration time. Other factors include amount of binder, force of compression during tablet manufacturing and design of granulation procedure.

**Table 2. Physicochemical properties of different brands of CC tablets**

| Brand code | Average weight mg (S.D) n = 20 | Hardness Kgf (S.D) n = 10 | Friability (%) (S.D) n = 10 | Disintegration time (Sec) n = 6 | Drug content (%) n = 3 |
|---|---|---|---|---|---|
| CC-1 (Innovator) | 130.40±1.36 | 4.75±0.26 | 0.537±0.004 | 290.17±1.47 | 99.62±6.24 |
| CC-2 | 128.55±2.24 | 4.15±0.41 | 0.862±0.007 | 120.83±1.6 | 97.22±7.7 |
| CC-3 | 203.51±3.24 | 4.05±0.44 | 0.842±0.012 | 155±1.41 | 96.44±9.72 |
| CC-4 | 129.24±2.10 | 4.00±0.47 | 0.541±0.004 | 150.166±2.56 | 97.7±5.22 |

**Table 3. Difference factor ($f_1$), similarity factor ($f_2$), AUC and MDT of different tablets**

| S. No. | Brand | Difference factor (f1) | Similarity factor (f2) | AUC (% min) | MDT (min) |
|---|---|---|---|---|---|
| 1. | CC-1 | - | - | 4201.88 | 8.404 |
| 2. | CC-2 | 3.13 | 75.86 | 4250.44 | 8.501 |
| 3. | CC-3 | 6.39 | 61.91 | 4481.78 | 8.964 |
| 4. | CC-4 | 5.27 | 65.51 | 4433.21 | 8.866 |

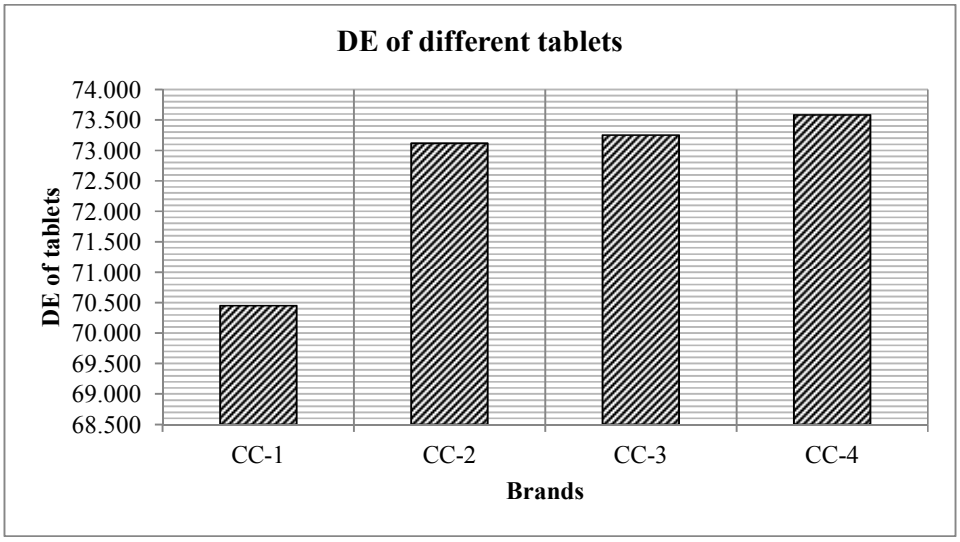


**Fig. 3. DE value of innovator (CC-1) and generic brands (CC-2, CC-3, CC-4) of tablets**

The result of percentage purity of all the brands is shown in Table 2. The drug content was determined to be highest for CC-1 followed by CC-4, CC-2 and CC-3. The drug content was assessed once compared with the calibration curve. The correlation coefficient ($r^2$) was found to be 0.9998 and the regression equation was obtained as, y = 0.0306x + 0.1926.

## 3.3 Dissolution Studies

Dissolution study is an important parameter used to predict the bioavailability and in vivo drug release performance [13]. Dissolution study play pivotal role in determining the release of drug from different dosage forms including tablets. The active absorption of oral dosage forms depend on adequate release of drug.

Comparative dissolution profiles of innovator product (CC-1) and generic product (CC-2, CC-3 and CC-4) are shown in Fig. 4. Drug release profile of product CC-2 was found to be slightly lower while product CC-3 and CC-4 showed better release profile than the innovator product. The dissolution profile of all the selected brands was estimated to be within the standard limits and was acceptable.

Results of difference factor ($f_1$) & similarity factor ($f_2$) of generic CC tablets are shown in Table 3. The difference factor ($f_1$) of all the tested generic products were found to be in between 0-15 and similarity factor ($f_2$) were also found to be in between 50-100. So, their dissolution profile was similar to the innovator brand and it confirmed that the generic products were

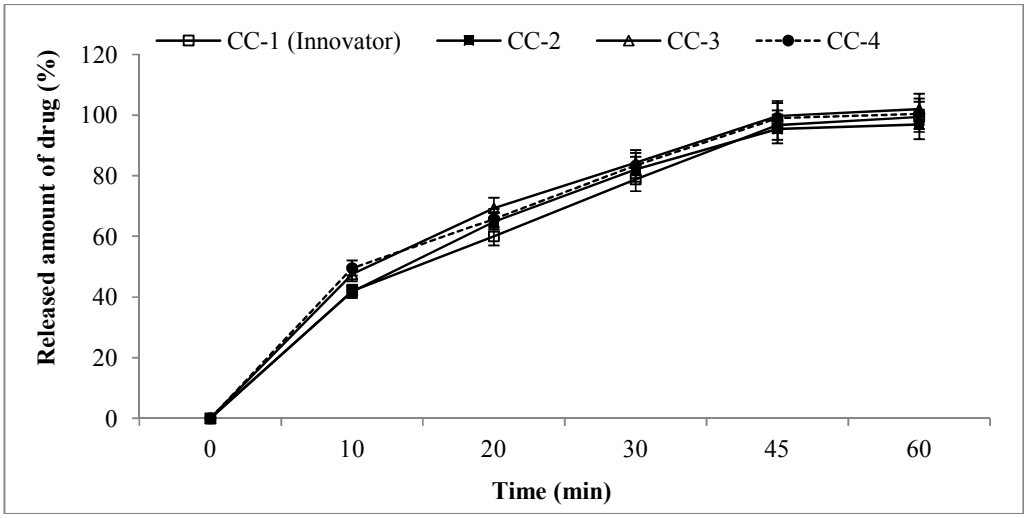


**Fig. 4. Comparative dissolution profiles of Innovator brand (CC-1) and generic brands (CC-2, CC-3 & CC-4) in phosphate buffer (pH 6.5)**

equivalent with the innovator product. Based on the value of f1 and f2 the generic products CC-2 and CC-4 were considered to be closest to the innovator. These were found to give lowest f1 value (3.13 and 5.23 respectively) and highest f2 values (75.86 and 65.51 respectively). Moreover, the generic product CC-3 was found to be least equivalent, as it exhibited highest f1 value (6.39) and lowest f2 value (61.92).

Dissolution efficiency (% DE) of all brands was determined (Fig. 3) that provides better prediction of in vivo drug release [7]. The generic products were considered to be equivalent when their DE values were closer to innovator product (% DE within ±10% is often acceptable). The highest DE was determined for CC-4 (73.58%) followed by CC-3 (73.25), CC-2 (73.12%), and CC-1 (70.45%). Thus DE of all generics was found to be under the range of acceptance. Furthermore, mean dissolution time (MDT) of all brands was estimated for better understanding the release profile. The MDT of all generics was found to be very similar to that of innovator. The brand CC-3 (8.96 min) exhibited highest MDT followed by CC-4 (8.87 min), CC-2 (8.5 min) and CC-1 (8.4 min).

The statistical analysis including student t-test was performed for dissolution profile for all brands to make a reliable and confident decision for the results achieved. Student's t-test method gave a *P* value less than .05 for formulations CC-3 (*P* = .012) and CC-4 (*P* = .016). However, the *P* value was determined to be more than .05 for the formulation CC-2.

## 4. CONCLUSION

Unavailability and price of innovator brand urges patients to go for alternate options including generic brands. The different quality control tests are performed to make sure about the resemblance of efficacy of generic with that of innovator. Thus, the selected generic brands were evaluated and compared with that of reference or innovator brand to assure the potential for the cure of the disease. In accordance, the quality control tests of all the selected brands of CC (16 mg) were performed and exhibited outcomes that compliance with the standard limit of USP-NF specifications. The compatibility of the excipients with the active ingredient was assured by FT-IR study. Moreover, the outcomes of dissolution studies and DE values of all the brands were found to be within the standard limits of acceptance. This suggested that the proper GMP guidelines were followed during the manufacturing of these brands to be proved to be of good quality. Hence, these generics may be considered to be a substitute for innovator brand in case of unavailability. Thus, as a matter of fact, all the brands selected for the study complied with the standard specifications and the definite observations on similarity efficacy of these generics may be obtained after performing the in vivo studies.

## DISCLAIMER

The products used for this research are commonly and predominantly use products in our

area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

## CONSENT AND ETHICAL APPROVAL

It is not applicable.

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

## REFERENCES

1. Gleiter CH, Mörike KE. Clinical pharmacokinetics of candesartan. Clin Pharmacokinet. 2002;41(1):7–17.
PMID: 11825094
DOI: 10.2165/00003088-200241010-00002
2. Husain A, Azim MS, Mitra M, Bhasin PS. A review on candesartan: pharmacological and pharmaceutical profile. J Appl Pharm Sci. 2011;1(10):12–17.
3. Danchev N, Nikolova I. Generics—Present and future. Biotechnol Biotechnological Equip. 2007;21(1):94-99.
DOI: 10.1080/13102818.2007.10817423
4. Kaur P, Jiang X, Duan J, Stier E. Applications of In Vitro–In Vivo Correlations in Generic Drug Development: Case Studies. AAPS J. 2015;17(4):1035-1039.
PMID: 25896303
DOI: 10.1208/s12248-015-9765-1
5. USP-NF. United States Pharmacopoeial Convention Inc. 2007;1:1480.
6. Charoo NA, Bashir M, Abdalla E, Ali KIH. Determination of Candesartan Cilexetil in Tablet Dosage Forms and Dissolution Testing Samples by First Derivative UV Spectrophotometric Method. Anal Lett. 2009;42(13):2232–2243.
DOI: 10.1080/00032710903137434
7. AlBratty M, Alhazmi HA, Alam MS, Alam MI, Javed SA, Alam N. Assessment of Physicochemical Properties and Comparison of Dissolution Profiles of Metformin Hydrochloride Tablets in Saudi Arabia. Dissolution Technologies. 2020; 27(1):36-44.
DOI: 10.14227/DT270120P36
8. Spireas S, Bolton M. Liquisolid systems and methods of preparing same. US Patent. 1999;5:538-550.
9. Moore JW. Flanner HH. Mathematical comparison of dissolution profiles. Pharm Technol. 1996;20:64-74.
10. Popy FA, Dewan I, Parvin MN, Islam SMA. Evaluation of in vitro equivalence for tablets containing the poorly water-soluble compound atorvastatin. Dissol Technol. 2012;19(4):30-33.
DOI: 10.14227/DT190412P30
11. Costa P, Lobo JMS. Modeling and comparison of dissolution profiles. Eur J Pharm Sci. 2001;13:123 –133.
DOI: 10.1016/S0928-0987(01)00095-1
12. Khan KA. The concept of dissolution efficiency. J Pharm Pharmacol. 1975;27, 48–49.
DOI: 10.1111/j.2042-7158.1975.tb09378.x
13. Balan G, Timmins P, Greene DS, Marathe PH. In vitro-in vivo correlation (IVIVC) models for metformin after administration of modified-release (MR) oral dosage forms to healthy human volunteers. J Pharm Sci. 2001;90:1176-1185.
PMID: 11536222
DOI: 10.1002/jps.1071



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