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Comparative *in vitro* Evaluation of Three Brands of Hydrochlorothiazide Tablets in Libya

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Hydrochlorothiazide, In Vitro, Quality Control, Dissolution, Pharmacopoeial Specification.

ABSTRACT

Hydrochlorothiazide (HCTZ) is a diuretic of the thiazide class, which is used in the treatment of hypertension, edema, congestive heart failure, and different forms of renal and hepatic dysfunction. The aim and the objective of our present study are to evaluate the quality parameters of some marketed hydrochlorothiazide tablets and to compare the parameters among them. To assess the quality, three different marketed hydrochlorothiazide 25 mg tablets available on private pharmacies of Tripoli, Libya, are selected, and in vitro dissolution test, potency, and disintegration time are carried out. Other general quality parameters of these tablets, like weight variation, hardness, and friability, are also determined according to established protocols. All the brands comply with the requirements of the United States Pharmacopoeia as they show an acceptable weight variation range. Friability of Brand A brands is more than 1% so it does not pass the friability test. The hardness of all brands was below 4 kg/cm$^{2.}$ The limitation of the potency must be within 92.5- 107.5%. All three brands meet this specification. The mean disintegration times of all tested brands were within the pharmacopeia specification (30 minutes). In the case of dissolution profile, all brands show better dissolution time as they release more than 90% of the drug in 30 minutes. The difference factor (f1) and similarity factor (f2) values revealed that all brands maintained the quality and complied with the USP specifications, and are like the comparator product and could be used interchangeably in clinical practice.

Introduction

Hydrochlorothiazide (HCTZ) is the most prescribed thiazide diuretic with or without other antihypertensive medications to control elevated blood pressure (BP). HCTZ is also an adjuvant medication for treating edematous patients secondary to congestive heart failure, hepatic cirrhosis, as well as corticosteroid and estrogen therapies [1]. The drug is presented as a medicine in the form of tablets containing only one active agent or combined in formulations with concentrations of 12.5, 25, and 50 mg. The 25 mg dosage is the most widely used in medical therapy [2]. More than 97% of all HCTZ prescriptions are based on doses of 12.5–25 mg per day. Within this dose range, HCTZ was shown to have a modest effect on 24-hr ambulatory BP by 6.5/4.5 mmHg. This magnitude of reduction in BP was inferior to other antihypertension drug classes. The antihypertensive efficacy of HCTZ was found to be like other antihypertensive drug classes only at the higher daily dose of 50 mg [3,4].

According to the Biopharmaceutics Classification System, HCTZ is classified as Class IV, being of low solubility and low permeability. These characteristics limit their therapeutic action, as these drugs are prone to exhibiting scant oral bioavailability [5,6].

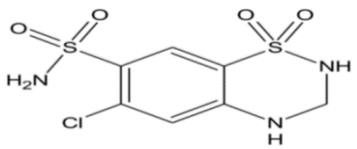

Figure 1. Chemical structure of Hydrochlorothiazide [7].

This drug has the molecular formula $C_7H_8ClN_3O_4S_2$ and its molecular weight is 297.74 g· mol^{-1}. It is presented in the form of a white or almost white crystalline powder, which is odorless with a slightly bitter taste and has a melting point in the range 266 to 270 °C. HCTZ is soluble in acetone and dilute alkaline solutions [7,8]. When it is given orally, the bioavailability of the drug is 70% and peak plasma concentrations are reached 1-2 hours. The drug is widely distributed, reaching concentrations in the CSF that are 50% of those in the plasma and excreted by the kidneys partly by glomerular filtration and partly by tubular secretion [9]. The market availability of different brands of medicines can confuse healthcare professionals and patients regarding the choice of brand and the possibility of interchangeability among the brands. Evaluation of the physicochemical characteristics of different brands of pharmaceutical products is very important to assess their bioavailability and pharmaceutical equivalence. When the

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generic product displays bioequivalence and therapeutic equivalence with the innovator, interchangeability is allowed [10]. The quality of the drugs can be evaluated using in vivo or in vitro tests [11]. To assess the physicochemical properties of pharmaceutical products, various tests are utilized, such as weight variation, friability, hardness, content of the active ingredient, disintegration, and dissolution [12,13]. The present study was conducted to evaluate and assess the quality of three hydrochlorothiazide tablet brands from different manufacturers available in the Libyan market and to ascertain that all the tested brands are pharmaceutically equivalent and could be used interchangeably.

Methods

The study was carried out in May 2025 at the Faculty of Pharmacy, Department of Pharmaceutics, University of Tripoli, Libya. We have subjected all three brands of Hydrochlorothiazide to the compendial specification for visual inspection, uniformity of weight, friability, hardness, disintegration, dissolution test, as well as Infra-red spectroscopy. Samples of three commercial brands of Hydrochlorothiazide 25mg tablets (coded as A, B, and C) were purchased from several private pharmacies in Tripoli (Table 1). All samples were assessed within their valid shelf-life. The reagents, hydrochloric acid and sodium hydroxide, were of analytical grade and used in the study.

Table 1. Brands of Hydrochlorothiazide 25mg tablets

Brand Code	Brand Name	Manufacture Date	Expiry Date	Batch No.	Manufacturer	Country
A	Esidrex	Not present*	4/2026	23FA184	Juvice	France
B	Hydrochlorothiazide	9/2023	9/2028	111583	Remedica Ltd	Cyprus
C	Hidroclorotiazide	Not present*	1/2027	T002	Kern Pharma	Spain

**Brands A and C lack a manufacturing date because the expiration date is the legally required and most critical piece of information for consumers regarding a drug's safety and efficacy.*

Fourier-Transform Infrared Spectroscopy (FTIR)

FTIR spectra were obtained by using an FTIR spectrometer. The samples were mixed thoroughly with Sodium chloride (NaCl) in a sample-to-NaCl ratio of about 1:5, respectively. The NaCl discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Scans were obtained at a resolution of 4 cm^{-1} from 4000 to 300 cm^{-1}.

Drug Content

The drug content in tablets was determined by randomly choosing ten (10) tablets from each brand. The tablets were powdered using a mortar and pestle, and a quantity equivalent to 30 mg of hydrochlorothiazide was weighed and dissolved in 50 ml of 0.1N sodium hydroxide, shaken for 20 minutes, and diluted to 100 ml with 0.1N sodium hydroxide. Mixed, filtered, then 5ml of the filtrate was diluted to 100 ml with water, and the absorbance of the resulting solution was measured at 273nm. The content of $C_7H_8ClN_3O_4S_2$ was calculated taking 520 as the value of A(1%, 1cm) at the maximum at 273nm.. (BP 2020 p.741 vol 3, to % of the stated amount). The BP specifies that the content should not be less than 92.5% and not more than 107.5% [14, 15].

Weight Variation

Twenty (20) tablets from each brand were weighed individually using an analytical weighing balance (Sartorius, Germany). The average weight for each brand was determined, and the standard deviation was calculated. The percentage weight variation for each brand was calculated using the following equation:

$$\% \text{ Weight variation} = \frac{\text{Individual Weight} - \text{Average Weight}}{\text{Average Weight}} \quad \text{.....Eq1}$$

The batch is considered to comply with the USP specifications if the weight of not more than 2 of the tablets differs from the average weight by no more than the percentage permitted, and no tablet differs by more than double that percentage.

Hardness and Tablet Dimensions

Hardness is a force required to break a tablet across its diameter. It is an indication of its strength. The hardness, thickness, and diameter of a sample of ten (10) tablets were determined using a tablet combination tester (PTB311E multicheck tester, Pharma test, Germany). In the hardness test, pressure was applied on the tablet along its diameter, and the force causing the tablet to break up was recorded. In-house acceptable limit for this test is 6 ± 2 $kg/cm^{2,}$ and the optimum hardness regarded for coated tablets

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is 10-20 kg/cm^2. Tablet thickness and diameter should be controlled within ±5% of the mean value.

Friability Test

Ten (10) tablets from each brand were taken randomly and weighed (Initial weight). Tablets were placed in the plastic chamber of the friabilator (PTF 20E Pharma test, Germany) and allowed to rotate and drop 6 inches at each revolution for 100 revolutions (25 rpm/minute). The tablets were removed, de-dusted, reweighed (Final weight), and the percentage friability (% F) was calculated using the following equation:

$$\%F = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100$$

.....Eq2

The tablet complies with the test according to USP-NF if tablets lose less than 1% of their weight.

Disintegration Test

A sample of six (6) tablets was selected from each of the different brands. Tablets were placed in the six tubes of the basket-rack assembly of the disintegration time tester (PTZ Auto 1EZ Pharma test, Germany), and perforated cylindrical plastic discs were put on the top surface of each tablet. The assembly was allowed to move up and down in a beaker containing 900ml of distilled water at 37±2°C.

To comply with the USP-NF standards, the tablets must disintegrate, and all particles must pass through the 10-mesh screen within 30 min. If any residue remains, it must have a soft mass with no palpably firm core.

Dissolution Test

The dissolution test was carried out using the USP apparatus II (paddle method) in 6 replicates for each brand. The dissolution medium was 900 mL 0.1N HCL, which was maintained at 37± 0.5°C. In all the experiments, 5 mL of dissolution sample was withdrawn at 0, 5, 10, 15, 30, 45, and 60 min and replaced with an equal volume of dissolution medium to maintain sink condition. Samples were filtered through a 0.45m cellulose acetate membrane filter and assayed by ultraviolet spectrophotometry (Shimadzu UV-1700; Shimadzu) at 272 nm. The concentration of each sample was calculated, taking 520 as the value of A(1%, 1cm)

Model-independent fit factors

Difference factor (f1) and Similarity factor (f2)

The difference factor is used to determine the percentage difference between two dissolution profiles at each time point, and the relative error between the two profiles is measured.

The similarity factor is used to indicate the average percentage of sameness between two dissolution profiles. According to the guidelines issued by 14 regulatory authorities, f1 values of up to 15 (0–15) and f2 values greater than 50 (50–100) ensure the similarity or bioequivalence of two profiles [16,17].

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

.....Eq3

$$f_2 = 50 \times \log_{10}\left[\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{n} (R_t - T_t)^2}{n}}}\right]$$

.....Eq4

where n is the number of time points, R is the dissolution value of the reference (pre-change) batch at time t, and Tt is the dissolution value of the test (post-change) batch t at time t.

Dissolution efficiency (DE)

is the area under the dissolution curve within a time range, and it was calculated by using the following equation [18]:

$$DE\ (\%) = \frac{\int_0^t y \times dt}{y_{100} \times t} \times 100\%$$

.....Eq5

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Where y is the drug percent dissolved at time t.

Mean dissolution time(MDT)
is determined from the cumulative curves of dissolved DES as a function of time [19].

$$MDT = \frac{\sum[t_i.\Delta Q_i]}{Q_\infty}$$ Eq6

Where ti is an intermediate time of the intervals of sampling time, ΔQi is the amount of HCTZ dissolved in every interval of and Q∞ is the maximum of PRP dissolved

Model-dependent dissolution kinetics
To evaluate the kinetics of drug release from the tablets, the results of the in vitro drug release study of formulations were fitted with various kinetic equations like zero order, first-order, Higuchi, and Korsmeyer–Peppas model [20].
The equations of different release kinetics are given below:
-Zero-order kinetics: $Q_t = Q_0 + K_0t$ Eq7
-First-order kinetics: $\log Q_t = \log Q_0 + K_1t/2.303$ Eq8
-Higuchi kinetics: $Qt = K_ht^{1/2}$ Eq9
-Korsmeyer–Peppas kinetics: $Q_t/Q_0 = Kt^n$ Eq10
where K_0, K_1, and K_h indicate zero-order, first-order, and Higuchi rate constants, respectively, Q_t/Q_0 means fraction of drug released at time t, K means rate constant, and
n means release exponent. The kinetics that gives a high regression coefficient (R^2) value is considered the best fit model.

Statistical analysis
All the results were expressed as mean ± SD. The results of the dissolution test were analyzed by one-way analysis of variance (ANOVA). Microsoft Excel 2010 (Roselle, IL, USA) was used for statistical and graphical evaluations. A probability of $P < 0.05$ was considered significant.

Results and discussion

Description of brands of hydrochlorothiazide tablets
All brands were checked visually to see if there were any manufacturing errors. All tablets were all white in color, with a circular shape, with beveled edges, smooth, scored, and uncoated. They were free from all physical defects like capping, sticking, picking, mottling, and lamination.

Fourier-Transform Infrared Spectroscopy (FTIR)

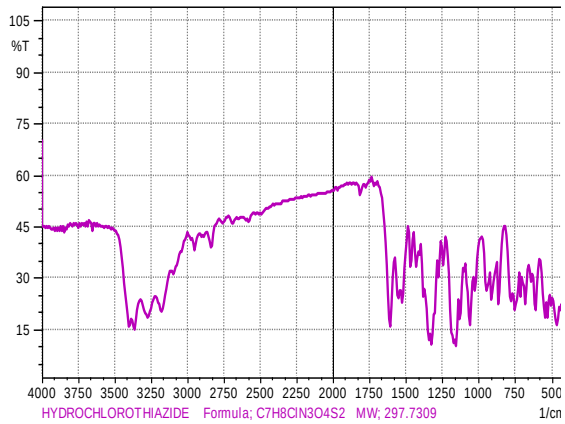

Figure 2: FTIR spectrum of Hydrochlorothiazide

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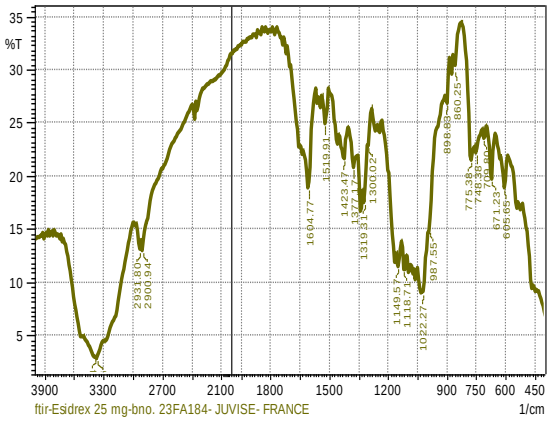

Figure 3: FTIR Spectrum of Brand A

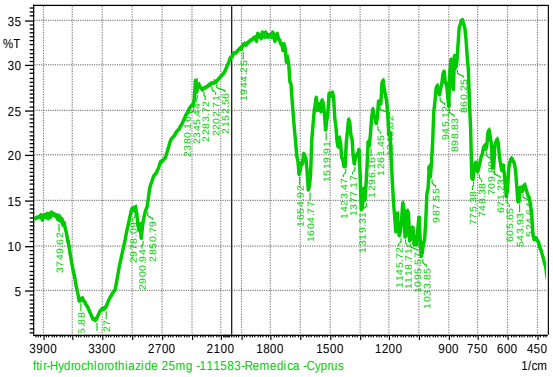

Figure 4: FTIR Spectrum of Brand B

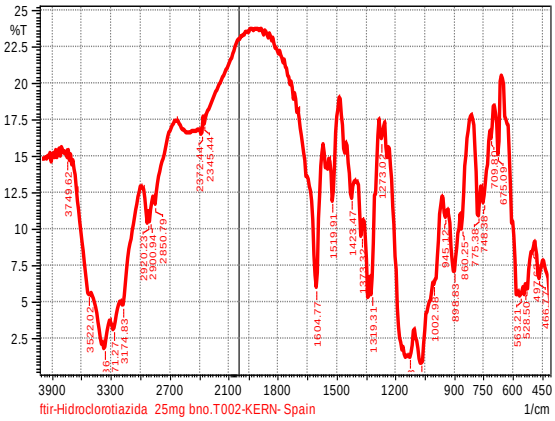

Figure 5: FTIR spectrum of Brand C

The FTIR spectrum of HCTZ (Figure 2): Strong signals were found at the fingerprint region of 650-1,400 cm-1. The absorption peaks at about 670-900 cm-1 are indicative of C-H bending of the aromatic ring. In the double bond region (1,500-2000 cm-1), several peaks were also detected, indicating the carbon-carbon double bond of the aromatic ring and the presence of sulfur-oxy compounds. The peaks detected in about 1,700 cm-1 regions indicated the presence of a carbonyl double bond. Also, in the single bond area (2,500-4,000 cm-1), several peaks were detected; the peaks between 3000 and 3500 cm-1indicated the presence of aromatic bonds (C-H stretching) and primary amine stretching [21]. The IR spectra revealed that there was no difference between brands. It showed Identical peaks compared to the reference. Comparing with brand A, the Matching scores were 97.6 for brand B and 93.5 for brand C.

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Table 3: Thickness (mm) and Diameter(mm) of Hydrochlorothiazide tablet brands

Brand	Thickness (mm) n=20	% Deviation of the individual Tablet thickness	Diameter (mm) n=20	% Deviation of the individual Tablet Diameter
	Mean ± SD	Min and Max values	Mean ± SD	Min. and Max. values
A	2.624±0.056	-0.152 and 5.945*	7.074±0.009	-0.056 and 0.226
B	2.332±0.012	-0.086 and 0.772	7.097±0.026	0.0423 and 0.465
C	2.549±0.007	0.039 and 0.431	6.101±0.007	-0.0164 and 0.147

**For brand A, only one tablet out of pharmacopial specification (% deviation of thickness more than 5%)*

Table 4: Average Weight, Weight variation, Friability, Hardness, and Disintegration time of Hydrochlorothiazide tablets brands.

Brand	Average Weight (g) n=20	%Weight Variation n=20	% Deviation of the individual Tablet Weight	Friability (%) n=10	Hardness (kg/cm²) n=10	Disintegration Time (min) n=6
	Mean ± SD	Mean ± SD	Min. and Max.	Mean ± SD	Mean ± SD	Mean ± SD
A	0.141±0.001	0.858±0.006	-0.0013 and 0.022	1.34±0.003	3.02±0.446	2.02±0.004
B	0.121±0.000	0.234±0.002	-0.0002and -0.008	0.33±0.001	1.61±0.246	1.59±0.004
C	0.104±0.002	0.403±0.003	0.0006 and -0.007	0.53±0.002	3.02±0.446	0.78±0.011

Weight determination is a simple test, but it has significant importance for quality control. Since tablet mass and active ingredient amount are directly proportional, very large variations in weight may lead to incorrect doses. Consequently, it may promote the absence of expected therapeutic action, in case of lower dosage, and side effects and overdose, in case of higher dosage [22]. The weight uniformity for the three brands of Hydrochlorothiazide tablets gave values that comply with the USP specification, with a deviation less than 5 % from the mean value (maximum deviation value 0.002). The friability test is a fundamental test designed to examine whether the tablets have a good withstand strength for transportation, packaging, shipping, and coating. Brands B and C passed the friability test, while Brand A did not pass where it gives friability of 1.34% which is more than the USP limit of 1% suggesting it's prone to chipping/breaking during handling.

Tablet hardness for a drug product is a critical parameter that directly affects the bioavailability of the drug by altering its disintegration time, friability, and dissolution profile [23]. A tablet must have a minimum crushing strength of 4 kg/cm² to withstand mechanical stresses (forces) during the manufacturing, packaging, and shipping processes [23]. The mean hardness values were all below 4 kg/cm², with the minimum value being for brand B. The disintegration is performed to find out the time required for a solid oral dosage form to completely disintegrate in the gastrointestinal tract. The time of disintegration is a measure of the quality of the tablet as it affects the drug release rate. The results show that the disintegration time of all brands is less than 30 minutes, which proves that all these brands pass the quality control limits as per the Pharmacopoeia. The disintegration time results of all brands were below 5 min; such rapid disintegration of the tablet dosage forms implies rapid breakdown of the tablets into smaller particles that will enhance the dissolution rates of the medications into systemic circulation [24].

Table 5: Content uniformity of Hydrochlorothiazide tablet brands

Brand	Absorbance (1)	Absorbance (2)	Absorbance (3)	Average Absorbance	Drug Content (%)
A	0.533	0.528	0.530	0.530	101.27 ± 0.005
B	0.596	0.595	0.594	0.595	97.5 ± 0.002
C	0.349	0.352	0.354	0.352	99.06 ± 0.007

The dosage form having a higher percentage of drugs than it claims may lead to adverse reactions, while lower percentages lead to treatment failure. The loaded dose of Hydrochlorothiazide in the three brands was within the BP standard specifications of 92.5% and 107.5%

Table 6: % Dissolution of Hydrochlorothiazide tablet brands

Time (minutes)	% Released (Mean ± SD)		
	A	B	C
0	00.00±0.00	00.00±0.00	00.00±0.00
5	49.01±0.40	57.46±0.07	64.52±0.19
10	71.72±0.12	92.77±0.64	75.74±0.41

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15	81.28±0.45	93.88±0.36	84.46±0.08
30	90.41±0.57	93.46±0.78	94.29±0.46
45	93.18±0.27	93.46±0.55	95.95±0.45
60	96.51±0.08	93.46±0.72	99.97±0.28

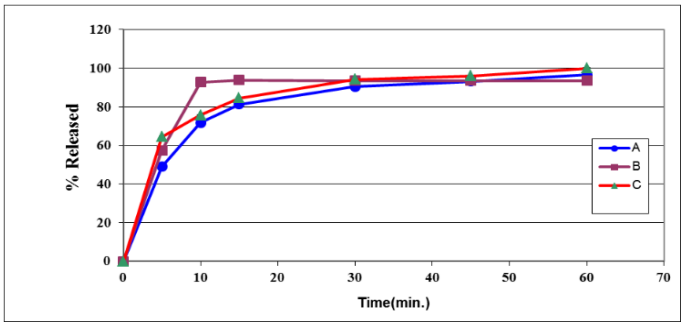

Figure 2: In vitro Drug Release Profiles of hydrochlorothiazide tablet brands

The dissolution of a tablet dosage form is an important quality control parameter that is directly related to the absorption and bioavailability of the drug. The average values of dissolution of the different brands of hydrochlorothiazide tablets tested showed that Brand B exhibits the fastest initial release reaching 92.77 % at 10 minutes, which is close to its maximum release, while Brand A has the slowest initial release. The obtained dissolution content at 30 minutes was found to be 90.41 %, 93.46% and 94.29% for brands A, B, and C, respectively. All the brands released more than the pharmacopoeia (USP 30, NF 25) requirement of 70 % active pharmaceutical ingredient [25].

Table 8: Dissolution-related model-independent fit factors of Hydrochlorothiazide tablets Brands

Brand	Difference Factor (*f*1)	Similarity Factor (*f*2)	Mean Dissolution Time (min)	Dissolution Efficiency (%)	AUC
A	Reference	Reference	9.29	107.8	104.1
B	10.05	53.85	4.42	115.9	108.4
C	6.80	62.67	8.49	108.2	108.1

As shown in (Table 8), the f1 values are 10.05 for brand B and 6.80 for brand C, which are less than 15. The values of f2 were 53.85 and 62.67for brands A and B, respectively, which are more than 50. Both findings of f1 and f2 indicate the similarity of dissolution profiles of both brands (B and C) to that of comparator A. In addition, the release patterns of the tablets are expressed graphically in (Figure 1), and the findings indicate overlapped dissolution profile curves. The f1 (<15) and f2 (>50) values of all test samples were within the accepted ranges [26]. Hence, all test brands were deemed similar or bioequivalent to the comparator drug.

DE and MDT values, on the other hand, are model-independent characteristics that can determine interchangeability between different formulations. The results (Table 1) show that all test samples are equivalent to the reference brand, with a DE difference of less than 10% [27]. The Dissolution Efficiency (DE) and AUC values are all very high and close (ranging from 107.8% to 115.9% for DE and 104.1 to 108.4 for AUC), further suggesting that all three brands release the drug almost completely and efficiently over the measured time. From the results of model-independent fit factors, all Hydrochlorothiazide tablet brands can be considered as interchangeable with each other.

Brand A is best described by the First order model (*highest* R^2 = 0.922), where drug release rate is dependent on the amount of drug remaining in the formulation. Brand B shows the best fit with the Hiquchi model (*highest* R^2= 0.643) where drug release is primarily controlled by diffusion through the matrix (especially for porous matrices). The overall fit is poor compared to A and C, suggesting the formulation is highly variable or complex. Brand C has the strongest overall fit with the Korsmeyer-peppas model (*highest* R^2= 0.962), where drug release is controlled by more than one process, such as a combination of diffusion and polymer relaxation/erosion (non-Fickian release). This is the strongest fit across all brands. The p-value corresponding to the F-statistic of one-way ANOVA is 0.944035 with an f-ratio value is 0.05778. As the p-value is higher than 0.05, it suggests that dissolution data are not significantly different.

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Table 9: kinetic analysis data for hydrochlorothiazide tablets brands

Brand	Zero order model	First order model	Hiquchi Model	Korsmeyer-peppas model
	R^2	R^2	R^2	R^2
A	0.581	**0.922**	0.839	0.874
B	0.364	0.424	**0.643**	0.513
C	0.520	0.861	0.790	**0.962**

Conclusion

The qualities and physicochemical bioequivalence of three different brands of Hydrochlorothiazide 25 mg tablets marketed in Libya were evaluated in this study. The results show that all the evaluated brands of tablets met the quality control parameters as per the pharmacopeia specifications regarding weight variation, disintegration time, and dissolution. All brands fail the hardness test, and one brand (B) fails the friability test. The difference factor (*f*1) and similarity factor (*f*2) values revealed that all brands were like the reference brand. Hence, we showed that these three brands could be used interchangeably in clinical practice.

Conflict of interest. Nil

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