RESEARCH ARTICLE

Pharmaceutical and Clinical Assessment of Multi-source Tegretol® Sold in Egypt

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ABSTRACT

Background: Numerous studies have shown significant variability in quality and efficacy commonly exists upon switching across generic Narrow therapeutic index (NTI) medications compared to brands. However, little attention has been given to possible inequality within the same brand due to transportation and storage conditions, production site, manufacturing condition, and product specification requested by different countries. Market surveys has shown that Egypt is one of the countries suffering from this problem, which consequently augments the need for comparing and evaluating brand products marketed under the same brand name, manufactured in different countries under its own licensing trademark™ and sold in Egypt. This work studies the drug carbamazepine (CBZ) available in Egypt as Tegretol® tablets used as an oral first-line anti-epileptic drug (AED).

Objectives: The present work investigate and evaluate the pharmaceutical quality and clinical efficacy of Tegretol®, obtained from Egypt and Saudi Arabia and being marketed and sold in Egypt from 2020 to 21.

Methods: *In-vitro* quality testing included potency and uniformity of content tests performed according to USP 2019 monograph. Dissolution rates were also carried by adopting USP dissolution test for the drug. Studies of stability were adjusted at 25°C/65% RH, 45°C/75% RH and 10°C/15% RH. The clinical efficacy was studied by evaluating the pharmacokinetics parameters and blood sodium level during six months of therapy.

Results: Variability between multisource Tegretol® brand products were ensured. Potency results and uniformity of content revealed statistically significant difference between Tegretol® sources. Also, variations in dissolution rates were recognized in both Tegretol® sources when dissolved in HCL/KCL, Acetate and Phosphate Buffer dissolution media. Dissimilarities were obtained for hardness and friability testing. Furthermore, a pharmacokinetically and pharmacodynamically inequivalence was ensured. Hence, hyponatremia was more prominent in patients receiving Saudi Arabian Tegretol® compared to patients taking Egyptian Tegretol®.

Conclusion: Interchangeability between multi-source Tegretol brand products should be limited.

Keywords: Multi-source brand products, Narrow therapeutic index drugs, Interchangeability.

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INTRODUCTION

Carbamazepine (CBZ) products present a history of non-uniform drug performance and clinical failures. For several decades a prime focus in pharmaceutical research was given to equivalence and acceptance of CBZ generics compared to their corresponding brand Tegretol®. In contrast, little attention has been given to possible variation in quality and efficacy within the same brand Tegretol® though some reports showed high dissolution variability among CBZ tablets of the same brand marketed world-wide.[1] Possible factors contributing to this variability may include geographical location of the production site, quality of raw material and excipients used, manufacturing conditions, storage conditions and transportation. Other aspects are the manufacturing standards and methods that may differ among production sites in different countries, which, consequently, can lead to differences in the quality and performance of the brand versions under license.[2] Kobayashi et al. reported that CBZ form I transforms faster to its dihydrate

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than form III *in-vitro* and consequently results in lower bioavailability *in-vivo*. However, some studies reported different transformation points within commercial CBZ samples, though the use of same polymorphic form. This is explained using different solvents and additives for the crystallization of CBZ raw materials. These dissimilar processes lead to different crystal habits resulting in changed solubility and dissolution behavior of CBZ crystals.[3] Furthermore, physical processes during manufacturing, such as milling or grinding, can cause crystal defects, mechanical activation, and formation small amount of amorphous CBZ, which then also lead to faster and inhomogeneous dissolution behavior of CBZ samples.[1] In addition, Carbamazepine shows significant elastic deformation during compaction process resulting in high tendency to capping even at low doses. Moreover, CBZ possesses low solubility but high permeability, assuming that dissolution can play a significant role in the oral absorption of marketed CBZ brands.[4,5] Furthermore, variations among the acceptable impurities content between pharmacopeias are present. Hence, the European Pharmacopoeia sets the maximum concentration of an individual impurity at 0.1%, while the United States Pharmacopeia (USP) indicates 0.2% as the maximum limit for any individual impurity and 0.5% as the maximum total limit for all present impurities.[6,7]

Occurrences and Cases of Tegretol® Withdrawal Overtime

A present investigation done in India demonstrates that carbamazepine tablets of the same brand manufactured by different Indian manufacturers show different but acceptable results for all physicochemical tests.[8] In contrast, another study done in Germany, linked the differences in raw material sources to irregular dissolution behavior and consequently clinical failures of CBZ therapy.[1] This agrees with a study done in 1992, that stated the cause for the withdrawal of several CBZ lots due to remarkable differences in dissolution rate among them that generated several clinical failures among patients.[9] In that manner; a multinational survey in 1995, showed high variability after 15 minutes dissolution rate's testing among commercial CBZ tablets of the same brand.[10] Also, in 1997 a significant difference in pharmacokinetic parameters was evident which lead to its recall.[11] Yet, the fact of unequal bio-availability and bioinequivalence problems was not solved instead it is still arising. In February 2015; Tegretol® 200 mg was recalled from the Philippine Market by the Health Government due to inequivalent drug distribution and the presence of a lot to lot variation. The recall was classified under Class II with the Identification number: 0215–38931.[12] Another recall was in the 5th of July 2017, the Precision Dose Inc. Company voluntarily recalled Carbamazepine 200 mg tablets assuming inequivalence of drug content and a lot to lot variation, Identification number: NDC 68094–301-59. The FDA designated the recall Class II.[13] Recently, in the 21st of August 2019; the American Health Packaging announced a recall for a lot of Carbamazepine 200 mg tablets under Class II with the Identification number: 181677 that failed to meet dissolution specifications.[14] Moreover, in the 29th of January 2020, the Canadian health authority avowed a type II recall of several Tegretol® batches of the 200 mg strength produced by Taro Pharmaceuticals Inc. Company because the dissolution was out of the specification in the affected lots. (Identification number: RA-72279).[15] Thus; the use of reliable and discriminatory pharmaceutical evaluation tests are of major importance for Carbamazepine drug assessment.[16]

Carbamazepine as an Effective Antiepileptic Drug (AED)

The International league against epilepsy (ILAE) define epilepsy as a cerebral disease that is characterized by the presence of at least two seizures occurring more than 24 hours apart.[17] Another detailed definition was given by the Epilepsy Foundation of America specifying a condition, where two or more consecutive seizures happen with loss of consciousness between them, or a persistent seizure that lasts for more than 30 minutes, as status epilepticus (SE).[18] The WHO states that epilepsy causes a major public health concern because it is an important cause for mortality and morbidity around the world. Also, population-based studies show that SE is considered the second most frequent neurologic emergency associated with high annual occurrence that increases almost logarithmically with age.[18,19] Prevalence studies of neurological disorders showed high rates of epilepsy in Arab countries including Egypt, Saudi Arabia and Lebanon, yet very few published studies evaluate the situation in these countries. The AED can control epilepsy by reducing seizure frequency in almost 67% of patients.[17] The CBZ is still one of the most widely used antiepileptic drug since 1974. The CBZ blocks voltage-gated sodium channels preventing repetitive and sustained triggering of an action potential.[20] This widely prescribed tricyclic anticonvulsant is available in several commercial forms like tablets, capsules and suspensions and in different strengths ranging from 200 to 1600 mg. However, Carbamazepine tablets of strengths ranging from 200–400 mg are the only commercially available form that is sold in Arab countries.[21,22] Concomitant administration of CBZ is associated with increased risk of hyperammonemia in patients thus careful monitoring of plasma sodium level should be done.[23] Hyponatremia is present when sodium plasma level is less than 136 mmol/L. In particular, very low levels of serum sodium less than 120 mEq/ dL can cause seizures and coma, which has been directly linked to increased mortality and morbidity.[24-26] A rising incidence of Carbamazepineinduced hyponatremia from 1.8–40% is declared in several studies. CBZ, also affects sensitivity of renal tubules to antidiuretic (ADH) activity. Since, many patients don't share their experience while using CBZ therapy some cases of hyponatremia may be missed.[24,25,27]

Consequences of Switching between CBZ Products

The CBZ is sold in the market under the brand name Tegretol®. The originator patent terminated quite a while in 1986 and since, some generics are available. Generally, substitution to generics or within same brand for the treatment of epilepsy is controversial because CBZ has a narrow therapeutic index

drug meaning that the relationship between dose and plasma concentrations must be equal in all offered generics and within same brand.[28] Nevertheless, switching failure can cause serious lifestyle changes including serious injury, or death.[29] In that manner, a change in government program policies caused a 15-year-old boy to receive CBZ of different source, that lowered his serum CBZ level from 12.4 to 6.7 Jlg/mL and consequently loss of seizure control. Another case of a 21-year-old woman who substituted brand CBZ experienced seizures due to decreased CBZ plasma levels from 11.8 to 8.5 Jlg/mL. Therefore, the American Academy of Neurology (AAN), other medical associations, and patient organizations prohibited substitution without approval of the prescribing physician and substantial necessity, owing to the inadequate policies of bioequivalence studies[30,31] Hence, Oles and colleagues found pharmacokinetic differences between branded CBZ products.[32,33] Also, Yacobi et al. stated significant differences when compared to generics.[34] Conclusively, substitution may cause serious failure of seizure control.[35]

Aim of the Work

The present paper focuses on the pharmaceutical quality of multisource Tegretol® tablets marketed in Egypt and purchased from local pharmacies in Alexandria. In this case, all quality control (*In-vitro* assessment) and *In-vivo* aspects of CBZ are being studied.

MATERIALS AND METHODS

Five batches of Tegretol® 200 mg tablets from each of the two sources (manufactured by Novartis Pharma SAE Cairo-CCR-11108, Egypt under license from Novartis Pharma AG Basle, Switzerland) and (manufactured by Novartis Farma S.P.A. Torre Annuziata, Italy Fore Novartis Pharma AG, Basle, Switzerland exported to Saudi Arabia), marketed in Egypt were selected. Products were purchased from local pharmacies in Alexandria. Their relevant data are shown in Table 1. All batches were manufactured during the period of 04/2018 to 07/2023.

HPLC Assay

HPLC method was used for the assay, determination of Uniformity of Content, Impurities and for monitoring dissolution rate. The HPLC system used is in accordance with USP 2019 in CBZ tablets monograph. It consisted of Spheri-Cyano column (250 x 4.6 mm), particle size 5 µm and a mobile phase composed of methanol, tetrahydrofuran and water (12:3:85), and 0.22 mL of formic acid to be added and then followed by addition of 0.5 mL triethylamine to each liter. A Standard preparation consisted of 10 mg of standard Carbamazepine in 50 mL volumetric flask and 20 mL methanol to be sonicated for 10 minutes then complete to the mark with methanol. A Diluent prepared of (Methanol:Water) = (50 :50%) was also used. UV detection wavelength was 230 nm. The flow rate was adjusted at 1.5mL/min. The injection volume was 10 µL.[36]

Uniformity of Content and Assay (Potency)

A total of 10 CBZ tablets were weighed at random from each batch, grinded in mortar and transferred in 100 mL volumetric flask then sonicated with 30 mL methanol for 10 min, then completed to the mark with methanol. A 5 mL of this solution is then taken in another 50 mL volumetric flask to be diluted where the diluents is added until it reached the mark.[36]

Dissolution Rate Testing

The dissolution rate was determined using dissolution test system, SR8-plus, HANSON Research Corporation, USA. It was performed in triplicate, for three tablets from each batch in three different media according to USP-2019 and FDA regulations concerning dissolution apparatus (Apparatus II, rotating paddle at 75 rpm and 37°C). Dissolution media (900 ml) used consisted of 1% SLS, Buffer (pH 1.2), Buffer (pH 4.5) and Buffer (pH 6.8). Sampling points were withdrawn according to the following intervals 5, 10, 15, 30, 45, 60 and 90 minutes.[36]

Impurities Assessment Assay

The Mobile phase, Diluent, and System suitability solution are proceed as directed in the Assay. Standard stock solution of 0.02 mg/mL for each of Impurity, 10,11 dihydrocrabamazepine (USP Carbamazepine related compound A) and Iminostilbene (USP Carbamazepine related Compound B) RS were added in methanol and sonicated till dissolution. Standard solution of 0.001 mg/mL of each Impurity from standard stock solution

Table 1: Carbamazepine 200 mg tablet brands, under study

Brand	*Manufacturer and Marketing Authorization holder*	*Manufactured for*	*Batch code*	*Batch numbers*	*Manufacture date*	*Expiry date*	*Patient group*
Tegretol® (Egyptian)	Novartis Pharma S.A.E.Cairo, Egypt	Egypt	T_1	Y0635	08/2019	07/2023	Group A
	Novartis Pharma S.A.E.Cairo, Egypt	Egypt	T_2	Y0606	10/2018	09/2022	Group B
	Novartis Pharma S.A.E.Cairo, Egypt	Egypt	T_3	Y0665	02/2019	01/2021	Group C
	Novartis Pharma S.A.E.Cairo, Egypt	Egypt	T_4	Y0245	07/2018	06/2021	Group D
	Novartis Pharma S.A.E.Cairo, Egypt	Egypt	T_5	Y0236	10/2019	09/2021	Group E
Tegretol® (Saudi Arabian)	Novartis Farma S.P.A. Torre Annuziata, Italy	Saudi Arabia	T_1	TR073	04/2018	04/2021	Group F
	Novartis Farma S.P.A. Torre Annuziata, Italy	Saudi Arabia	T_2	TX872	03/2019	03/2021	Group G
	Novartis Farma S.P.A. Torre Annuziata, Italy	Saudi Arabia	T_3	TV645	10/2018	10/2021	Group H
	Novartis Farma S.P.A. Torre Annuziata, Italy	Saudi Arabia	T_4	TS531	06/2019	06/2021	Group I
	Novartis Farma S.P.A. Torre Annuziata, Italy	Saudi Arabia	T_5	TR918	08/2018	08/2021	Group J

were put in Diluent. Sample solution of 20 Carbamazepine tablets were powdered and transfered to a 100 mL volumetric flask. A 50 mL of the Diluent were added in the volumetric flask and sonicated for 15 minute. The solution was left to cool at room temperature and then dilute with Diluent to volume. Finally, the solution was filtered and the first few milliliters of filtrate were discarded.[36]

Infra-red Spectrum

Infra-red spectrum of standard CBZ powder was determined using FTIR, Perkin Elmer infra-red spectrophotometer. A quantity of 250 mg of carbamazepine from powdered tablets is solubilized in 15 mL of acetone. The Sample solution is then boiled for 5 minutes in a suitable beaker and filtered while hot, using two 5-mL portions of hot acetone to affect transfer. Subsequently, the filtrate is evaporated with the aid of nitrogen to 5 mL, and cooled in an ice bath until crystals are formed. Finally, the crystals were filtered and washed with 3 mL of cold acetone and dried under vacuum at 70° for 30 minutes.[36]

Hardness

Based on the USP, the test was carried out on 10 tablets from each batch of the two Tegretol® sources using DR.SCHLEUNIGER® Pharmatron AG Switzerland, Model SY Tablet Hardness Tester, version 4.22, USA. An average value was recorded.[37]

Friability

Friability tester (COPLEY Friability Tester FRV 2000, USA) was used at 100 drops in 4 minutes. The USP recommends 6.5 g of tablets weight (equal ≈ 30 Carbamazepine tablets 200 mg / batch of the two sources). Tablets were accurately weighed (Winitial) and placed in the friability tester drum. The drum was rotated at 25 rpm for 4 minutes. The tablets were then removed, de-dusted and reweighed (Wfinal). The weight loss was determined, and the percent friability (F) was calculated: F = Winitial– Wfinal/ Winitial×100.[36]

Thickness

The test was carried out on 10 tablets. An average value was recorded. Ten tablets were randomly selected from each batch. Thickness was determined using a Vernier caliper and the reading was recorded in millimeters.[37]

Stability Determination Tests

The tablet potency and dissolution data for multisource Tegretol® tablet batches were examined after storage in the following conditions.

Intermediate Stability Conditions (25°C/65% RH)

These conditions are assumed to prevail during shelf life in local pharmacies in Alexandria. The tablet batches were stored in their blisters in a stability cabinet adjusted at 25°C/65% RH for a period of 6 months.

Accelerated Stability Conditions (45°C/ 75%RH)

These conditions simulate climatic zone (IVa) as recommended by the ICH and WHO guidelines for stability zones.[38,39] The tablets were stored in their blisters in a stability cabinet adjusted at 45°C/75% RH for a period of 6 months.

Low Temperature Stability Conditions (10°C/15%RH)

These conditions simulate the fridge as many patients store their drugs in the fridge without consultancy.[40] Also, the manufacturer provided no information regarding storage at low temperature. The tablet batches were kept in their blisters to be stored at 10°C/15% RH in the stability cabinet for 6 months.

Clinical Study Location

The study took place in epilepsy clinic of the Neurology department located in (El Hadara) Alexandria University Hospital and affiliated to the faculty of Medicine, Alexandria University. Approval of the clinical study protocol was given by the Research Ethics Committee of the Faculty of Medicine, Alexandria University, prior to patient enrolment. Informed consent forms written in Arabic with simplified explanation of the study objectives, duration and risks were signed by all patients enrolled in this study, prior to the screening procedure.

Study Population and Sample Size

The study was carried out on adult patients aged from 18–60 years, attending Neurology Outpatient Clinics in El Hadara, Alexandria University Hospital. The patients were newly diagnosed for epilepsy and first time on treatment. In total, 30 patients participated in the study. An open-label, randomized, multiple dose (one dose/day), parallel-design study was carried out on epilepsy patients. The enrolled patients were classified into two groups; randomly chosen 15 patients received Egyptian Tegretol® 200 mg tablets daily as monotherapy with follow-up periods at 1 and 6 months while the other remaining 15 patients received Saudi Arabian Tegretol® 200 mg tablets following same therapy routine. The study was conducted during the period from 08/2019 to 08/2020. Tablets were administered before breakfast at least 1 hour before the meal.[41,42] Demographic data of patients are shown in Tables 2 and 3. Pregnant or breast-feeding women, immunocompromised, liver failure and kidney failure patients were excluded from the study.

Monitoring and Laboratory tests (Diagnosis criteria)

CBZ plasma level was used to diagnose efficacy of Tegretol® and sodium plasma level was also measured during the study. Five milliliters of blood samples per patient were drawn on each visit at the beginning and after 1 and 6 months from the initiation of the treatment. Samples were stored as plasma at -20ºC until analysis. The primary monitoring parameter was the CBZ plasma level, where blood samples were drawn at the following intervals after 1, 2, 3, 4, 6, 8, 12 and 24 hours. The secondary monitoring parameter was the sodium plasma level, where blood samples were taken from patients before the treatment initiation as a reference baseline and at the end of the first and sixth month after beginning of the treatment.[42]

Analysis of Blood Samples

The CBZ plasma test was done using CBZ ELISA Plate kit, Eurofins Abraxis, Warminster, USA in the laboratory of the Medical Research Institute, Alexandria University.[43] The sodium plasma level test was done in the laboratory of the Main Alexandria University Hospital, Alexandria University.

Table 2: Demographics of patients taking egyptian tegretol®

Patients (n=15)	*Group A (n=3)*	*Group B (n=3)*	*Group C (n=3)*	*Group D (n=3)*	*Group E (n=3)*	*Statistical significance (p-value)*
Gender:						
Female	2	1	0	3	1	0.05>
Male	1	2	3	0	2	
Age:						
Min-max	33–59	18–35	18–27	35–46	20–57	0.05>
Median	41	29	21	43	47	

Table 3: Demographics of patients taking Saudi Arabian Tegretol®

Patients (n=15)	*Group F (n=3)*	*Group G (n=3)*	*Group H (n=3)*	*Group I (n=3)*	*Group J (n=3)*	*Statistical significance (p-value)*
Gender:						
Female	2	2	1	1	0	0.05>
Male	1	1	2	2	3	
Age:						
Min-max	18–44	24–45	20–55	28–33	25–58	0.05>
Median	20	35	27	30	48	

Statistical Analysis

Two-way analysis of variance (ANOVA) was used to evaluate variations in CBZ plasma level and sodium plasma level between multi-source Tegretol® tablets.

In-vitro In-vivo Correlation Analysis

IVIVC was evaluated by plotting the mean CBZ plasma values after 1 month and 6 months treatment versus the dissolution and potency parameters identified above under In-vitro data. The IVIV correlation analysis included; dissolution efficiency (%D.E.), over 90 minutes, % dissolved at 45 minutes and % potency of the different batches of multisource Tegretol® tablets. Linear regression analysis was applied and (r2) was calculated to evaluate the strength of the correlation.

RESULTS AND DISCUSSIONS

Infra-red Identification of Multisource CBZ Brands

IR spectra are considered fingerprints to check for product quality. Collective IR spectra of all batches tested are illustrated in Appendix I (Figures 1 and 2). Figure 1 indicates the percentage of identical tablets (96% correlation) across different batches of multisource Tegretol®, indicating a high degree of homogeneity within each of the ten batches studied; ensuring the absence of intra-batch variability. In addition, Figure 1 also confirms the presence of inter-brand variability by comparing Egyptian Tegretol® batches to Saudi Arabian ones owing to restrict inter-brand interchangeability because they cannot be considered identical.

Tablets Assay (Potency)

Assay (potency) of different batches of multisource Tegretol® tablets is shown in Figure 2. The results of the selected batches of the two sources were falling within the acceptance limit of the USP 2019 (92–108%). In addition, batches of the two sources showed comparable potency with a mean of 100.49 ± 1.85 ($p > 0.05$) for the Egyptian Tegretol® and a mean of 102.94 ± 1.57 ($p > 0.05$) for the Saudi Arabian Tegretol®. Therefore, no statistical significant difference was identified regarding the mean values of the potency of the two sources ($p > 0.05$).

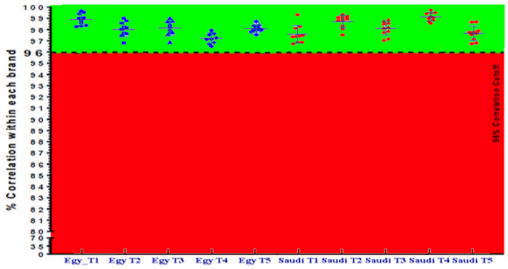

Figure 1: Percentage Correlation within each brand of multisource Tegretol® tablets computed by qualitative IR analysis. Green area represents correlation within each brand more than 96%. Red shaded area represents correlation less than 96%

Uniformity of Content

Values obtained for uniformity of content (expressed as %of label claim) of different batches of multisource Tegretol® tablets were within the USP limit (92–108%) as shown in Figure 3. Ten tablets were assayed individually per batch. Generally, the Saudi Arabian Tegretol® showed higher values for %content uniformity ranging from (98.76–105.40%) than values obtained for Egyptian Tegretol® that ranged from (96.98–103%). Despite this variation, no statistical significant difference was observed.

Inter-source Variability in Dissolution Profiles in Different Dissolution Media

Some significant differences were detected regarding the dissolution behavior of multi-source Tegretol®, where Saudi Arabian Tegretol® batches always showed higher dissolution rates at each sampling point in the four dissolution media comparable to Egyptian Tegretol® batches (Figure 4). In addition, a dissimilar dissolution behavior between both Tegretol® sources was ensured owing to the similarity factor f2 (47.28) attained in the Acetate Buffer (pH 4.5) and Phosphate Buffer (pH 6.8) media. A borderline similarity factor f2 of 52.76 was noted in HCl/KCl Buffer (pH 1.2) dissolution medium. However, the highest f2 value of 65.44 was obtained in 1% SLS

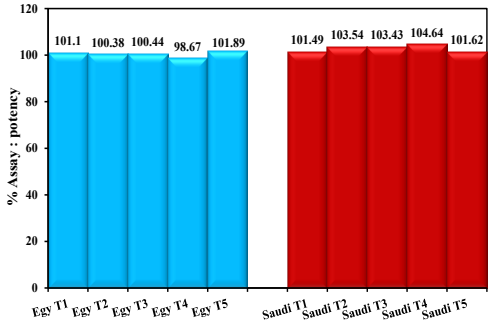

Figure 2: Variability in assay (potency) as average of ten individual tablets across and within batches of multisource Tegretol® determined according to the USP 2019

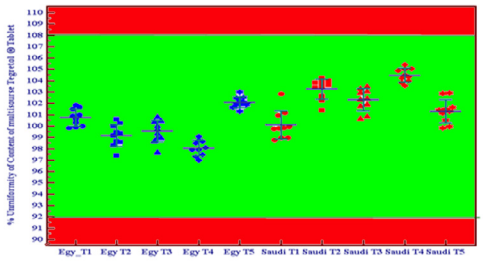

Figure 3: Intra-batch variability in uniformity of content of different batches of multisource Tegretol® tablets determined according to the USP 2019. Acceptance range from 92–108% (Green area)

dissolution medium, reflecting similar dissolution behavior of both Tegretol® sources.

Stability of Carbamazepine Tablets

Content uniformity results after six months storage in three different conditions

Values obtained for Egyptian Tegretol® and Saudi Arabian Tegretol® stored under normal conditions (25°C and 65% RH) were within the USP limit (92–108%). The situation was different for multisource Tegretol® stored under accelerated conditions defined as 45°C and 75% RH, where all Egyptian batches showed borderline value per tablet ranging from (91.05 -91.91%), while all Saudi Arabian batches were out of the USP limit, the observed values ranged from (89.01–90.64%). Also, storing of multisource Tegretol® under cold conditions (10°C and 15% RH) caused decrease in the observed values per tablet compared to those values obtained at zero time. Hence, some Egyptian and Saudi Arabian Tegretol® tablets exhibited out of limit and borderline values per tablet ranging from (89.91 -92.65%) (Figure 5).

Inter-source variability of potency in response to change in temperature and relative humidity

Inter-source variability in potency was assessed in Figure 6. Results indicated significant difference in potency values between the two sources of Tegretol® after storage in three different conditions compared to values observed at zero time for both sources. Saudi Arabian Tegretol® was more affected by change in temperature and relative humidity than Egyptian Tegretol®, as the percent reduction in potency values

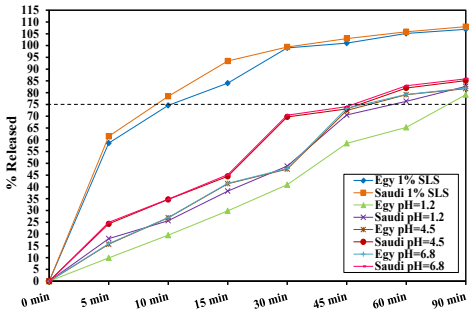

Figure 4: Inter-source Variability of dissolution profiles of Tegretol® tablet brands under study assessed in different dissolution media at 25°C and 65%RH (USP 2019)

was greater among Saudi Arabian source than Egyptian one. In normal storage conditions, the Saudi Arabian Tegretol® presented a percent reduction of 5.61% with a potency value of (97.33%), while the Egyptian Tegretol® manifested 3.45% reduction and 97.04% potency. However, in accelerated storage conditions, the Saudi Arabian Tegretol® revealed a significant increased percent reduction of (13.17%) with a potency value of 89.77% compared to a 9.10% reduction with a 91.39% potency of Egyptian Tegretol®. Similarly, storage in cold conditions produced a percent reduction of 13.28% with a potency value of 89.66% in Saudi Arabian Tegretol® and a 9.13% reduction with a 91.36% potency in Egyptian Tegretol®. Collectively, the percent reduction in potency values of multisource Tegretol® was at the greatest for those stored under cold and accelerated conditions, while accepted percent reduction in potency values was observed among multisource Tegretol® stored under normal conditions.

Inter-source variability in dissolution after storage

In the three different storage conditions; Saudi Arabian Tegretol® batches always showed significant increased dissolution rates at each sampling point in the four dissolution media comparable to Egyptian Tegretol® batches. In 1% SLS dissolution medium, for the three conditions of storage, a similar dissolution behavior of Egyptian and Saudi Arabian Tegretol® was observed ($p > 0.05$). Though, a borderline similarity factor f2 of 57.23 was noted among batches stored under accelerated conditions. In HCl/KCl Buffer (pH 1.2)

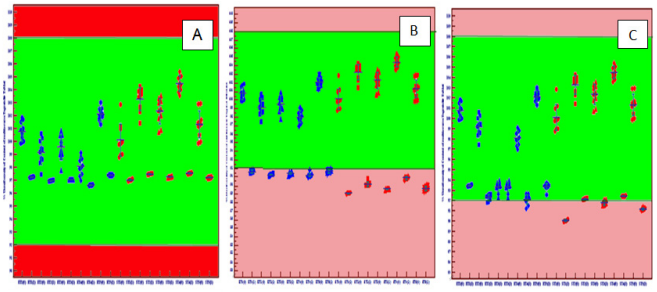

Figure 5: Effect of Temperature and Humidity on intra-batch variability of uniformity of content of multi-source Tegretol® after six month storage: A: Normal Shelf life condition (25°C/65%RH), B: Accelerated Condition (45°C/75%RH), C: Cold Condition (10°C/15%RH)

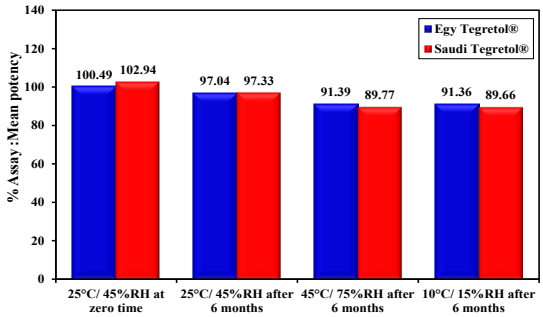

Figure 6: Inter-source variability in potency of multisource Tegretol® Tablets after six months storage at different conditions

dissolution medium, the relatively lowest similarity factor f2 of 66.09 was seen among multisource Tegretol® batches stored under cold conditions. However, results obtained indicate a similar dissolution behavior of Egyptian and Saudi Arabian Tegretol® in the three conditions of storage ($p > 0.05$). In, Acetate Buffer (pH 4.5) dissolution medium, similarity factors (f2) obtained for dissolution behavior of Egyptian Tegretol® compared to that of Saudi Arabian Tegretol® in normal, accelerated, and cold conditions were 73.01, 74.75 and 67.42, respectively. Results also indicated a similar dissolution behavior of both sources in all studied storage conditions ($p > 0.05$). In Phosphate Buffer (pH 6.8) dissolution medium, a borderline similarity factor (f2) of 52.01 was prevailed by comparing dissolution behavior of Egyptian Tegretol® batches stored under cold conditions to those of Saudi Arabian Tegretol® batches under same conditions, ensuring a very low similar dissolution behavior yet a statistical significance was absent ($p > 0.05$) (Table 4).

Total impurity content of multisource Tegretol® tablets before and after storage

A linear trend between total impurities content of multisource Tegretol® and change in temperature and humidity was observed. As batches of both sources that were stored under accelerated conditions showed a significant high percent for total impurities content in comparison to batches assessed at Zero time and after storage in normal and cold conditions. This ensures that CBZ exerts high degradation rate in high temperature degrees and increased relative humidity, reflecting the need for good storage conditions to limit Tegretol® degradation. For multisource Tegretol® batches stored under cold conditions a relatively slow degradation rate was noted in comparison to batches stored under normal conditions. However, all batches tested before and after storage were accepted according to the acceptance limit specified by USP 2019. Other aspects that may influence degradation of Tegretol® tablets are the manufacturing sites, climate conditions and transportation. Hence, all Saudi Arabian Tegretol® batches demonstrated higher total impurities content in all assessment conditions compared to Egyptian Tegretol® batches. On that account, the discovered changes upon storage were statistically significant ($p < 0.05$) and more prominent among Saudi Arabian Tegretol® batches (Table 5).

Table 4: Dissolution profiles similarity factor (f2) of Carbamazepine tablets

Dissolution medium	*Storage condition*	*Factor (f2) of Egyptian Tegretol® and Saudi Arabian Tegretol®*	*p-value*
1% SLS	25°C/65%RH	88.39	> 0.05
	45°C/75%RH	57.23	> 0.05
	10°C/15%RH	60.86	> 0.05
pH=1.2	25°C/65%RH	78.61	> 0.05
	45°C/75%RH	74.07	> 0.05
	10°C/15%RH	66.09	> 0.05
pH=4.5	25°C/65%RH	73.01	> 0.05
	45°C/75%RH	74.75	> 0.05
	10°C/15%RH	67.42	> 0.05
pH=6.8	25°C/65%RH	76.49	> 0.05
	45°C/75%RH	90.64	> 0.05
	10°C/15%RH	52.01	> 0.05

Tablet Hardness and Stability

Figure 7 displays hardness values of multisource Tegretol® batches before and after storage. For hardness test measurements ten tablets were assessed per batch of multisource Tegretol®. Hardness measurements recorded at zero time acted as reference points to track the change in hardness values upon storage in three different conditions. After storage; hardness values showed a significant increase for all batches especially for those stored under accelerated conditions ($p < 0.05$). For batches stored under normal and cold conditions almost equally increased hardness values were obtained, yet, the obtained values significantly differ than those measured at zero time ($p < 0.05$). Higher hardness values were noticed among Egyptian Tegretol® batches compared to Saudi Arabian batches. In addition, in one batch Saudi T1 capping during hardness measurement test was noted. This could be explained by polymorphic transformation of CBZ in this batch. However, all batches were accepted as they lied within the acceptance range (4-10 Kp) determined according to the specifications of USP 2019. Moreover, a statistically significant difference between batches of Egyptain Tegretol® and Saudi Arabian Tegretol® was attained ($p < 0.05$).

Tablet Friability and Stability

Figure 8 demonstrates the results for tablet friability of multisource Tegretol® measured at zero time and after storage in normal, accelerated and cold conditions. An initial weight of 277.01 mg was observed in Egyptian Tegretol® batches with a % friability of 0.331. A comparable % friability of 0.321 was noticed among Saudi Arabian Tegretol® batches with a little increased initial weight of 380.71 mg. It was found that the % friability decreased in both sources of Tegretol® after storage in the three different conditions. Hence, the lowest % friability was obtained by batches stored under accelerated conditions. Despite the similar % tablet friability; a statistically significant difference was noted regarding the initial weights of both sources after storage, where the Egyptian source of

Table 5: Total Impurity content of multisource Tegretol® tablets before and after storage

Source (n = 50)	*Zero time*	*After six months storage*			*Acceptance limit[a]: ≤ 0.5%*	*p-value*
	Mean % content at 25°C/45% RH	*Mean % content at 25°C/45% RH*	*Mean % content at 45°C/75% RH*	*Mean % content at 10°C/15% RH*		
Egy Tegretol®	0.091	0.108	0.146	0.097	accepted	< 0.05
Saudi Tegretol®	0.110	0.135	0.188	0.115	accepted	< 0.05

[a]acceptance limit is determined according to the specifications of USP

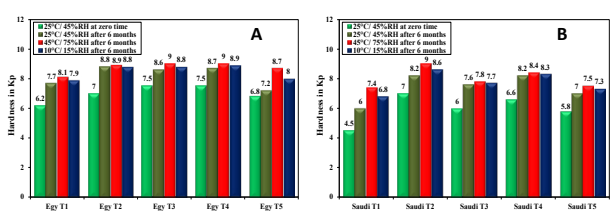

Figure 7: Mean Hardness variability of multisource Carbamazepine tablets before and after six months storage: A: Egy Tegretol® and B: Saudi Tegretol®

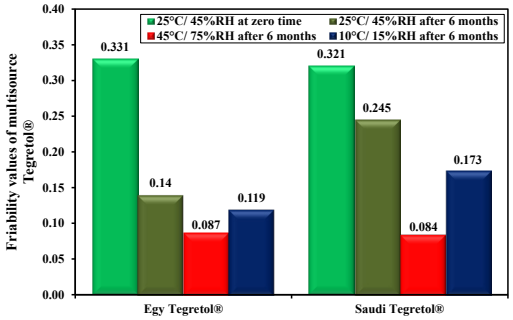

Figure 8: Mean Friability variability of multisource Carbamazepine tablets before and after six months storage

Tegretol® batches weighed 279.25 mg while Saudi Arabian batches weighed 284.37 mg. This reflects the higher tendency of Saudi Arabian Tegretol® to absorb moisture than Egyptian Tegretol®. For batches stored under cold conditions; Saudi Arabian batches showed a relatively higher % friability of 0.173% compared to 0.119% of Egyptian source. However, Saudi Arabian Tegretol® tablets weighed 264.80 mg which was significantly lower than the weight of Egyptian Tegretol®, 275.33 mg. This finding indicated that Egyptian batches are more affected by cold conditions in contrast to Saudi Arabian batches that are more affected by high temperature degrees and high humidity. For batches stored under normal conditions; Saudi Arabian batches revealed higher % friability (0.245%) with a final weight of 281.42 mg than Egyptian batches with 0.140% and 277.12 mg, respectively. This ensures that Saudi Arabian Tegretol® batches are mainly affected by the influence of high temperatures and humidity than lower ones, while Egyptian Tegretol® has low stability in cold conditions. Collectively, all batches of multisource Tegretol® measured at Zero time and after storage were accepted as they showed percent friability lower than the acceptance limit (≤ 1.5%) determined by the USP 2019.

Inter-source Variability in Tablet Thickness

Table 6 shows that a non-statistically significant difference ($p > 0.05$) was indicated regarding the thickness of multisource Tegretol® tablets assessed at Zero time and after storage under either, normal, accelerated or cold conditions. Similar thickness values of 0.365 cm ($p > 0.05$) were obtained by Egyptian and Saudi Arabian Tegretol® when tested. However, a slight increase in thickness value was noted for batches stored under accelerated conditions to obtain a value of 0.369 cm ($p > 0.05$).

Efficacy of Treatment

Inter-subject variability in Tegretol® concentration per time after one month

The results revealed that all patients receiving multisource Tegretol® showed a minimum concentration (Cmin) after one hour of administration, followed by a gradual increase till reaching a maximum plasma CBZ concentration (Cmax) after eight hours (tmax) of administration and by 12 hours a gradual decrease in CBZ plasma concentration was started. However, the level of plasma CBZ varied among patients. For patients receiving Egyptian Tegretol®, the highest values for maximum plasma CBZ levels obtained, was 14.70 and 14.50 µg/mL identified by patients' number P6 and P2, respectively. For Saudi Arabian Tegretol®, a highest value of 14.00 µg/ml was recognized as CBZ (Cmax) by patients' number P20 and P27, also a concentration of 13.60 µg/mL in patient number P16. The ANOVA test ensured that the within-subject variations noted in patients receiving either Egyptian or Saudi Arabian Tegretol® were considered as statistically insignificant ($p > 0.05$). In addition, it's worth mention, that all patients administrating Saudi Arabian Tegretol® guaranteed higher CBZ plasma levels on average than patients receiving Egyptian source. However, no statistical significance was noticed for inter-brand variability according to ANOVA test (Figure 9).

Inter-subject variability in Tegretol® concentration per time after six months

A Cmin was shown after one hour of administration, followed by a gradual increase till reaching a Cmax after eight hours (tmax) of administration and by 12 hours a gradual decrease in CBZ plasma concentration was started. However, the level of plasma CBZ after six months of administration was higher than that observed after one month of administration in all groups receiving either Egyptian or Saudi Arabian Tegretol®. Thus, the obtained difference was statistically significant only for patients receiving Saudi Arabian Tegretol® ($p < 0.05$), while a statistical insignificance was noted for patients taking Egyptian Tegretol® ($p > 0.05$) according to ANOVA test. Hence, a statistical significance was evident for inter-brand variability (Figure 10).

Table 6: Mean thickness values of multisource CBZ tablets before and after storage under different conditions

Source [a]	*Zero time 25°C/45% RH*	*After 6 months at 25°C/45% RH*	*After 6 months at 45°C/75% RH*	*After 6 months at 10°C/15% RH*	*p-value*
	Thickness in cm	*Thickness in cm*	*Thickness in cm*	*Thickness in cm*	
Mean Egy Tegretol®	0.365	0.365	0.369	0.365	> 0.05
Mean Saudi Tegretol®	0.365	0.365	0.369	0.365	

[a]50 tablets measured per brand source

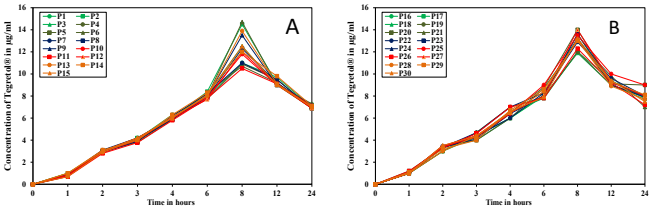

Figure 9: Inter-subject variability of time-concentration graph of multisource Tegretol® after one month of administration: A: Egy Tegretol® and B: Saudi Tegretol®

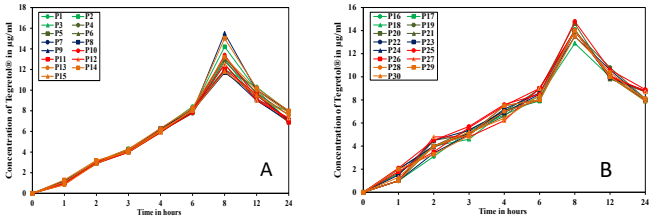

Figure 10: Inter-subject Variability of Time-Concentration graph of multisource Tegretol® after six months of administration: A: Egy Tegretol® and B: Saudi Tegretol®

Blood Sodium Level after Administration of Multisource Tegretol®

Results of blood sodium levels of patients along the treatment period with multisource Tegretol® are shown in Figure 11. The initial blood sodium level was measured for all patients as a reference point to track changes in blood sodium level in response to Tegretol® administration. All patients under study were free of diseases that are known to possibly affect the blood sodium level, to limit any confounding factors. The initial blood sodium level of all patients was within the normal range (135–145 mEq/L). After one month of Tegretol® administration; the results revealed that patients taking CBZ may suffer from decreased blood sodium levels. Some patients experienced relatively statistically significant low blood sodium levels of 136.6 mEq/L and 136.4 mEq/L ($p < 0.05$) after administration of Egyptian Tegretol® for one month. In contrast, a statistically significant decrease in blood sodium level was seen among patients taking Saudi Arabian Tegretol®, where the observed values were borderline blood sodium levels of 135.5, 135.3, 135.4 and 135.0 mEq/L ($p < 0.05$). The drop in blood sodium level was more prominent in patients receiving Saudi Arabian Tegretol® compared to patients taking Egyptian Tegretol®, proofing inter-subject variability towards CBZ administration. After six months of Tegretol® administration; a marked decrease in blood sodium level was evident. The majority of patients taking Egyptian Tegretol® showed statistically insignificant ($p > 0.05$) results of low to borderline blood sodium levels in response to Tegretol® treatment. Although, two patients (P1) and (P14) experienced statistically significant drop in their blood sodium level, their recorded values were out of the normal range; 133.9 mEq/L ($p < 0.05$) and 133.8 mEq/L ($p < 0.05$), respectively. Similar cases with a statistically significant drop in blood sodium level were noticed among patients receiving Saudi Arabian Tegretol®, however the amount decreased was greater ($p < 0.05$). Collectively, the drop in blood sodium level was more prominent in patients receiving Saudi Arabian Tegretol® compared to patients taking Egyptian Tegretol®, proofing inter-subject variability towards Carbamazepine administration.

Correlation between Blood Sodium Level and Cmax of Multisource Tegretol®

Correlations established between blood sodium levels and Cmax of multisource Tegretol® ensure a strong negative relation, as any increase in Cmax value cause a decrease in blood sodium level as found in Figure 12. After six continuous months of Tegretol® administration, similar behavior was noted but with exaggerated significant decrease in blood sodium level. Thus, results illustrated in Figure 12 show higher correlation coefficient R2 value of 0.768 for correlation after six months than that calculated after one month with a R2 value of 0.6675; indicating that after six months of CBZ administration higher Cmax values were obtained causing the blood sodium level to significantly decrease, in contrast to the gradual decrease of blood sodium level recognized after one month of Tegretol® administration. Owing to that conclusion; a close monitoring for Cmax values is augmented for epilepsy patients treated with Tegretol® to avoid dangerous health conditions as Hyponatremia.

In-vitro In-vivo Correlation studies

Correlation between Cmax and dissolution at 60 minutes in four dissolution media

Results demonstrated in Figure 13, indicate a strong positive correlation between Cmax of Tegretol® batches and percent dissolved at 60 minutes in different dissolution media. The strongest correlation was observed for batches dissolved in 1% SLS dissolution medium owing to the high correlation coefficient R2 value of 0.5562 ($p < 0.05$). Relatively lower R2 values of 0.4962 ($p < 0.05$) and 0.4955 ($p < 0.05$) were noticed for batches dissolved in HCl/KCl Buffer (pH 1.2) and Phosphate

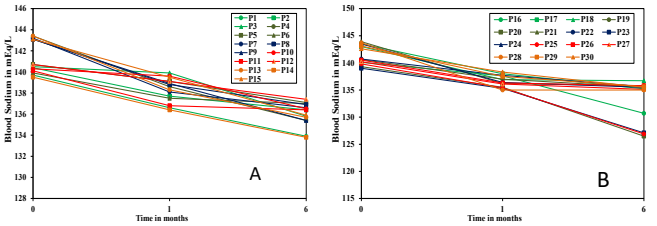

Figure 11: Inter-subject variability in blood sodium level after administration of multi-source Tegretol®: A: Egy Tegretol® and B: Saudi Tegretol®

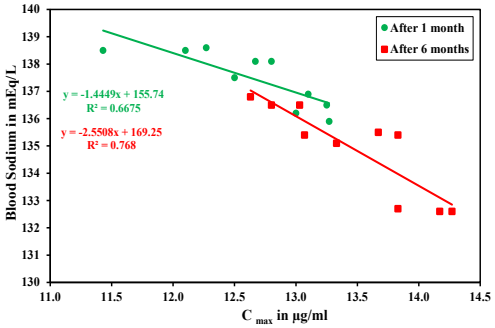

Figure 12: Correlation between Cmax of multisource Tegretol® and blood sodium level after one and 6 months of administration

Buffer (pH 6.8) dissolution media, respectively, yet statistically significant strong positive correlations were indicated. In contrast, the lowest calculated R2 value of 0.4887 ($p < 0.05$) was evident in Acetate Buffer (pH 4.5) dissolution medium, where a statistically significant strong correlation was considered.

Correlation between Cmax and %Dissolution Efficiency %D.E (0–90 min)

The results displayed in Figure 14, provided that a strong positive correlation between Cmax of Tegretol® batches and %D.E. in different dissolution media was proofed. The strongest correlation was evident for batches dissolved in Phosphate Buffer (pH 6.8) dissolution medium in response to the high correlation coefficient R2 value of 0.9015 ($p < 0.05$), instead of 1% SLS dissolution medium that provided the lowest R2 value of 0.5553 ($p < 0.05$), though a statistically significant strong positive correlation was considered in both dissolution media. Also, a strong positive correlation was seen for Acetate Buffer (pH 4.5) dissolution medium with a correlation coefficient R2 value of 0.7262 ($p < 0.05$). Furthermore, a relatively lower R2 values of 0.5657 ($p < 0.05$) was noticed for batches dissolved in HCl/KCl Buffer (pH 1.2), yet a statistically significant strong positive correlations was indicated. In conclusion, the values exerted by multisource Tegretol® batches for percent dissolution at 60 minutes were in direct relation to %D.E. of the same batches.

CONCLUSION

The comparative quality control tests and efficacy results generated in the present paper support the previous complaint from the physicians and patients that the efficacy of some multisource Tegretol® are different. Based on the study conditions, the results indicated that the multisource

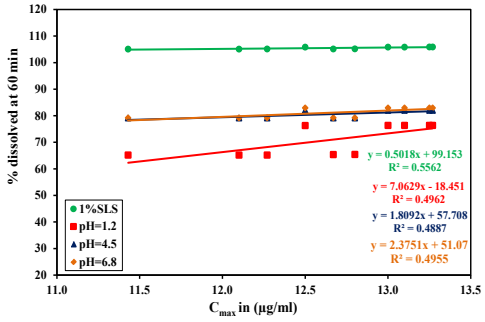

Figure 13: Correlation between Cmax of assessed batches and dissolution at 60 min in different dissolution media

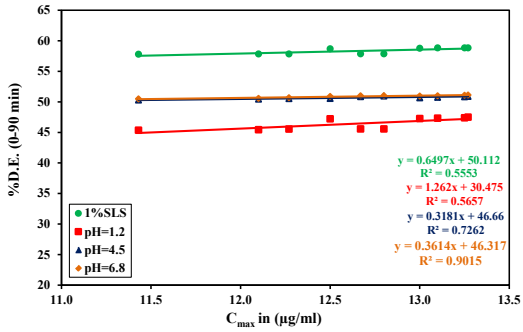

Figure 14: Correlation between Cmax of assessed batches and % D.E. (0-90 min) in different dissolution media

brand CBZ products investigated are not pharmaceutically, pharmacokinetically and pharmacodynamically equivalent to each other and should not be used interchangeably.

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AUTHOR CONTRIBUTIONS

Dr. Sarah Amer carried the pharmaceutical quality control tests and the clinical study. Dr. Sarah also helped in interpreting the results of pharmaceutical products bioequivalence analysis. Dr. Hany aid in designing and execution of a relevant clinical study and helped in interpreting results obtained from patients. Prof./Dr. Eshra supervised the developed study plan and aid in methodology development and framing the proper research questions. Prof./Dr. Eshra also helped in interpreting results and revising the thesis.

REFERENCES

1. Flicker F, Eberle VA, Betz G. Variability in commercial carbamazepine samples – impact on drug release. International Journal of Pharmaceutics. 2011;410(1–2):99–106. doi:10.1016/j.

ijpharm.2011.03.032
2. Specifications: Test procedures and acceptance criteria for new drug substances and New Drug Products. Handbook of Pharmaceutical Manufacturing Formulations. 2009;94–114. doi:10.3109/9781420081275-15
3. Li M, Qiao N, Wang K. Influence of sodium lauryl sulfate and tween 80 on carbamazepine–nicotinamide cocrystal solubility and dissolution behaviour. Pharmaceutics. 2013;5(4):508–24. doi:10.3390/pharmaceutics5040508
4. Morais JA, Lobato M do. The New European Medicines Agency guideline on the investigation of Bioequivalence. Basic & Clinical Pharmacology & Toxicology. 2010;106(3):221–5. doi:10.1111/j.1742-7843.2009.00518.x
5. Fortunato D. Dissolution method development for immediate release solid oral dosage forms. Dissolution Technologies. 2005;12(3):11–4. doi:10.14227/dt120305p11
6. Džodić PL, ivanovi LJ, Proti AD, Zeevi ML, Joci BM. Determination of carbamazepine and its impurities Iminostilbene and iminodibenzyl in solid dosage form by column high-performance liquid chromatography. Journal of AOAC INTERNATIONAL. 2010;93(4):1059–68. doi:10.1093/jaoac/93.4.1059
7. Abdelrahman MM, Abdelwahab NS. Analysis of carbamazepine, oxcarbazepine, their impurities, and non-labeled interfering substances by stability-indicating UPLC/ms/ms method: Studying the method's Greenness Profile. Chromatographia. 2018;81(11):1503 17. doi:10.1007/s10337-018-3623-0
8. Ghosal K, Ranu S, Billah M, Mondal S, Hoque M. Quality Control Studies on conventional carbamazepine tablets available in the Indian Drug Market. Dissolution Technologies. 2012;19(1):36–9. doi:10.14227/dt190112p36
9. Suryanarayanan R. Quantification of carbamazepine in tablets by powder X-ray diffractometry. Advances in X-Ray Analysis. 1991;417–27. doi:10.1007/978-1-4615 3744-1_46
10. Davidson AG. A multinational survey of the quality of carbamazepine tablets. Drug Development and Industrial Pharmacy. 1995;21(19):2167–86. doi:10.3109/03639049509065899
11. Mittapalli PK, Suresh B, Hussaini SS, Rao YM, Apte S. Comparative in vitro study of six carbamazepine products. AAPS PharmSciTech. 2008;9(2):357–65. doi:10.1208/s12249008-9035-y
12. Labadie J. Forensic pharmacovigilance and substandard or counterfeit drugs. International Journal of Risk & Safety in Medicine. 2012;24(1):37–9. doi:10.3233/jrs-2012-0551
13. Stepone E, Survilaite A, Aniuliene R, Steibliene V. P.1.K.007 severity of anxiety and depression symptoms and health related quality of life among women with stress urinary incontinence. European Neuropsychopharmacology. 2015;25. doi:10.1016/s0924-977x(15)30454-5
14. Kara A, Rosania, MS, Julie G, Pharmacy Leaning Network. August 2019
15. Kara A, Rosania, MS, Julie G, Pharmacy Leaning Network. January 2020
16. Elmaadawi AZ, Singh N, Reddy J, Nasr SJ. Prescriber's guide to using 3 new antidepressants: Vilazodone, levomilnacipran, vortioxetine. Current Psychiatry. 2015 Feb 1;14(2):28-35.
17. Mroueh L, Boumediene F, Jost J, Ratsimbazafy V, Preux P-M, Salameh P, et al. Self-reported attitudes about medication in Lebanese people with epilepsy. Epilepsy &Behavior. 2019;98:80–7. doi:10.1016/j.yebeh.2019.06.028
18. Hassib ST, Hashem HMA, Mahrouse MA, Mostafa EA. Determination of four antiepileptic drugs in plasma using ultra-performance liquid chromatography with mass detection technique. Biomedical Chromatography. 2018;32(8). doi:10.1002/bmc.4253
19. Leitinger M, Trinka E, Zimmermann G, Granbichler CA, Kobulashvili T, Siebert U. Epidemiology of status epilepticus in adults: Apples, pears, and oranges — A critical review. Epilepsy & Behavior. 2020;103:106720. doi:10.1016/j.yebeh.2019.106720
20. Naguib IA, Elyazeed NA, Elroby FA, El-Ghobashy MR. Stability indicating spectrophotometric methods for quantitative determination of carbamazepine and its degradation product, iminostilbene, in pure form and pharmaceutical formulations. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 2019;214:21 31. doi:10.1016/j.saa.2019.01.080
21. Sardar K, Rashid MA, Khandoker MR, Khan A. Anticonvulsants and antidepressants in chronic pain management. Journal on Recent Advances in Pain. 2016;2(3):90–3. doi:10.5005/jp-journals-10046-0050
22. Kosjek T, Heath E, Andersen HR, Kompare B, Ledin A. Identification of carbamazepine's UV degradation products. InAQUAbase. Workshop on mitigation technologies: Eliminating trace organics during water treatment 2007 (pp. 40-41). Forum Environmental Sciences, RWTH Aachen University.
23. Yamamoto Y, Takahashi Y, Imai K, Ohta A, Kagawa Y, Inoue Y. Prevalence and risk factors for hyponatremia in adult epilepsy patients: Large-scale cross-sectional cohort study. Seizure. 2019;73:26–30. doi:10.1016/j.seizure.2019.10.013
24. Kabi A, Kaeley N, Bhatia R, Mohanty A. Carbamazepine-induced hyponatremia – a wakeup call. Journal of Family Medicine and Primary Care. 2019;8(5):1786. doi:10.4103/jfmpc.jfmpc_185_19
25. Alsaadi T, El Hammasi K, Shahrour TM, Shakra M, Turkawi L, Almaskari B, et al. Prevalence of depression and anxiety among patients with epilepsy attending the epilepsy clinic at sheikh Khalifa Medical City, UAE: A cross-sectional study. Epilepsy & Behavior. 2015;52:194–9. doi:10.1016/j.yebeh.2015.09.008
26. Kumar S, Sarangi SC, Tripathi M, Gupta YK. Evaluation of Adverse Drug Reaction Profile of antiepileptic drugs in persons with epilepsy: A cross-sectional study. Epilepsy & Behavior. 2020;105:106947. doi:10.1016/j.yebeh.2020.106947
27. Silva R, Almeida A, Bicker J, Gonçalves J, Carona A, Silva A, et al. Pharmacokinetic monitoring of Levetiracetam in Portuguese refractory epileptic patients: Effect of gender, weight and concomitant therapy. Pharmaceutics. 2020;12(10):943. doi:10.3390/pharmaceutics12100943
28. AkterA,BeghMZ,ParvezA,IslamF.QUALITYANALY SISOF DIFFERENT MARKETED BRANDS OF CARBAMAZEPINE AVAILABLE IN BANGLADESH. 2019
29. Roberti R, Casarella A, Iudice A, La Neve A, Beghi E, Capovilla G, et al. Appropriate use of generic and branded antiseizure medications in epilepsy: Updated recommendations from the Italian League Against Epilepsy (lice). Epilepsy & Behavior. 2021;116:107804. doi:10.1016/j.yebeh.2021.107804
30. Najafi MR, Najafi MA, Shayan-Moghadam R, Saadatpour Z, Ghadimi K. Comparison of the efficacy of Tegatard and Tegretol as a monotherapy in patients with focal seizure with or without secondary generalization. American Journal of Clinical and Experimental Immunology. 2020;9(4):58.
31. Das S, Jiang X, Jiang W, Ting TY, Polli JE. Relationship of antiepileptic drugs to generic brittleness in patients with epilepsy. Epilepsy & Behavior. 2020;105:106936. doi:10.1016/j.

yebeh.2020.106936
32. YamadaM,WeltyTE.Genericsubstitutionofantiepilepticdrugs: a systematic review of prospective and retrospective studies. Annals of Pharmacotherapy. 2011 Nov;45(11):1406-15.
33. Beran RG. Generic substitution and advice to patients –potential legal medicine consequences – from a (Australia) to U (United Kingdom or United States of America). Seizure. 2021;91:515–9. doi:10.1016/j.seizure.2021.03.016
34. Weitzel J, Erzkamp S, Langer K, Rose O. Effects of generic exchange of solid oral dosage forms in neurological disorders: A systematic review. International Journal of Clinical Pharmacy. 2020;42(2):393–417. doi:10.1007/s11096-020-01023-2
35. Sacks CA, Van de Wiele VL, Fulchino LA, Patel L, Kesselheim AS, Sarpatwari A. Assessment of variation in state regulation of generic drug and interchangeable biologic substitutions. JAMA Internal Medicine. 2021;181(1):16. doi:10.1001/jamainternmed.2020.3588
36. MEDINA-LOPEZ JR, Cedillo-Díaz LA, Hurtado M. In vitro equivalence study of different doses of carbamazepine reference tablets using USP Apparatuses 2 and 4. International Journal of Applied Pharmaceutics. 2019;291–5. doi:10.22159/ijap.2019v11i4.33174
37. Solon LG, Oliveira AI, Guerra GC, Soares LA, Araújo AA. Determination of carbamazepine in pharmaceutical formulations. Brazilian Journal of Pharmaceutical Sciences. 2010;46(3):509–13. doi:10.1590/s1984-82502010000300014
38. Pharmaguideline. Climatic Zones for stability studies [Internet]. [cited 2010 December]. Available from: https://www.pharmaguideline.com/2010/12/different-climatic-zones-for stability.html
39. Good manufacturing requirements for active pharmaceutical ingredients. Handbook of Pharmaceutical Manufacturing Formulations. 2009;79–80. doi:10.3109/9781420081275-13
40. Sharp RP, Havrda DE. Possible effect of refrigeration of warfarin on the international normalized ratio. Pharmacotherapy. 2002;22(1):102–4. doi:10.1592/phco.22.1.102.33509
41. García MA, Cristofoletti R, Abrahamsson B, Groot DW, Parr A, Polli JE, et al. Biowaiver monograph for immediate-release solid oral dosage forms: Carbamazepine. Journal of Pharmaceutical Sciences. 2021;110(5):1935–47. doi:10.1016/j.xphs.2021.02.019
42. Namazi MH, Yousefi ZK, Shirazi MG, Shaykholeslami M, Vakili H, Moatamedi MR, Safi M, Forotaghe AN. Comparison of the clinical efficacy of three brands of warfarin. Indian journal of pharmacology. 2004 Nov 1;36(6):360.
43. Zhang X, Boyert N, Mitro M, Tang X, Bowers K, McShane AJ. Development and validation of a free carbamazepine assay on an automated chemistry analyzer. The Journal of Applied Laboratory Medicine. 2020;5(2):357–62. doi:10.1093/jalm/jfz003

Appendix I

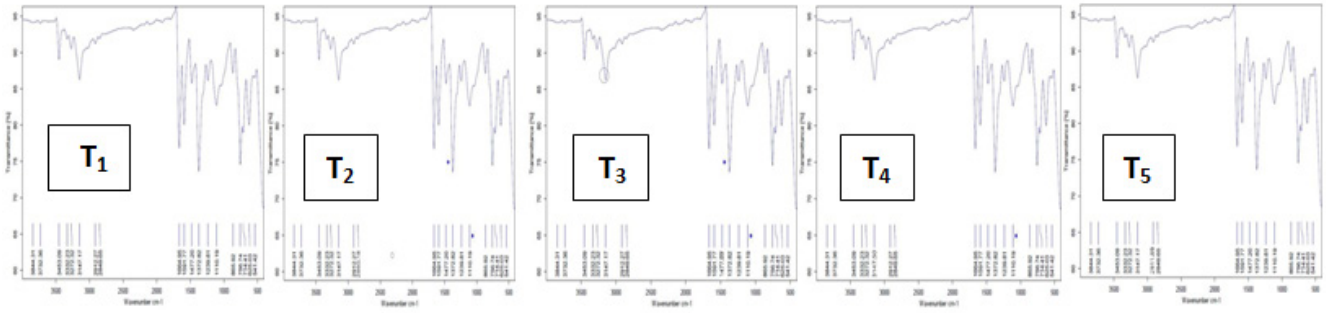

Figure 1: Infra-Red (IR) spectra for different batches of Egyptian Tegretol® tablets.

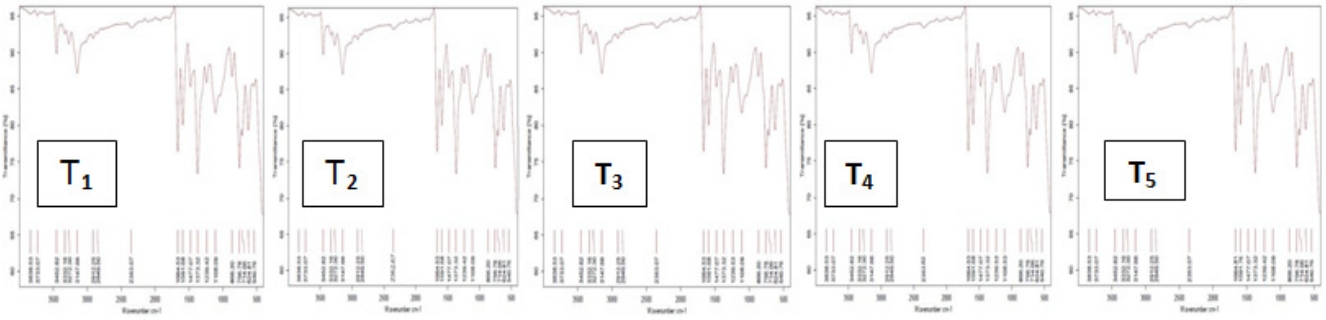

Figure 2: Infra-Red (IR) spectra for different batches of Saudi Arabian Tegretol® tablets