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Investigation of the Interchangeability between Cefuroxime Axetil Tablets Marketed in Palestine. Is there A Quality Reason behind the Price?

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ABSTRACT

According to Food and Drug Administration (FDA), therapeutically equivalent antibiotics is expected to have equivalent clinical efficacy and safety when used under the conditions of their labeling. However, any defect in the quality of an antibiotic may negatively affect its efficacy and safety and accordingly are considered a substandard drug. Cefuroxime is a semi-synthetic, broad-spectrum cephalosporin antibiotic intended for oral administration. Any quality defect in this product may cause inefficacy and future bacterial resistance. The aim of this study was to evaluate the quality and cost price of all commercial Cefuroxime axetil tablet products available on the Palestinian market (One brand and two generic products). A survey on the price of all commercial tablet products was conducted. To assess quality, all products were examined visually for their general appearance. They were tested for weight uniformity, friability, disintegration, and dissolution profile, and assayed for Cefuroxime content. The original brand was more expensive than the two locally produced generic products. Based on our testing procedure, all Cefuroxime tablet products were equivalent to the brand product. Although, the two generic products released more than 85% of their Cefuroxime content within 15 minutes, while the brand released only 74.5%. These results demonstrate that generic Cefuroxime tablets produced by local manufacturers are often comparable *in vitro* to the brand product and have lower price. Accordingly, we encourage our physician to prescribe the local product since they may be interchangeable and have same safety and efficacy profile.

Keywords: Cefuroxime Axetil, Tablet, Analysis, Interchangeability, Price.

INTRODUCTION

Cefuroxime axetil is a second generation cephalosporin with a broad-spectrum antibacterial activity intended for oral (PO) administration. It is (RS)-1-hydroxyethyl(6R,7R)-7-[2-(2-glyoxylamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate, 7-(Z)-(O-methyloxime), 1-acetate 3-carbamate (Fig. 1). Cefuroxime acts by interfering with the peptidoglycan synthesis of the bacterial cell wall resulting in inhibition of the final transpeptidation needed for the cross-links (1). It is effective against wide range of microbes including Aerobic Gram-positive Microorganisms, Aerobic Gram-negative Microorganisms and Spirochetes (2).

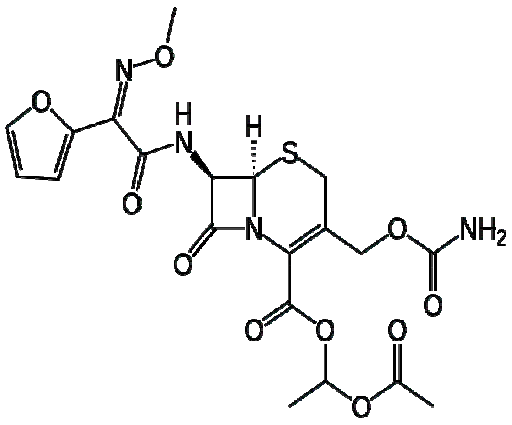

Figure (1): Chemical structure of cefuroxime axetil.

Cefuroxime axetil has a good pharmacokinetic behavior such that it is well absorbed from gastrointestinal (GI) tract and is rapidly hydrolyzed in the intestinal mucosa and blood to cefuroxime. Peak plasma concentration was reported to range between 2 to 3 hours after PO administration. With regards to its elimination manner, cefuroxime is excreted unchanged (about 95%) by glomerular filtration and renal tubular secretion with a terminal elimination half-life of 1.5 hour (3). In addition, cefuroxime is widely distributed in the body fluids. It has the capacity to pass through the placenta and is excreted with milk in lactating mother. Approximately, 33% of cefuroxime is bound to albumin (4). However, the pharmacokinetic data could be influenced by food administration. The extent of cefuroxime systemic absorption is enhanced when taken with food as its absolute bioavailability rises to reach approximately 50%.

Nevertheless, Finn and co-workers demonstrated that despite this alteration in absorption, the clinical effects and antibacterial activity were not affected by food intake at the time of tablet administration (5). Likely to other antibiotics, cefuroxime may interfere with oral contraceptive efficacy because of decreases estrogen re-absorption (6). Although the desired therapeutic effect that Cefuroxime gives as antibiotic, it like other medicines causes some side effects such as diarrhea , feeling or being sick, stomachache, headache, dizziness and penicillin allergic patients have a 5% to 10% incidence to have a cross-hypersensitivity reaction to cephalosporins (7). Cefuroxime axetil is marketed in Palestine under three trade names (Zinnat®, Zinex® and Zinaxim®).

It is formulated either as an oral solid dosage form such as film-coated tablets containing 250 or 500 mg of Cefuroxime or as oral suspension containing 125, 250 mg of the same API. During the development of generic dosage forms, pharmaceutical scientists play an important role in the selection of excipients and manufacturing process. In fact, these two factors have huge impact on the final quality and therapeutic outcomes of the obtained products. Wrong selection of these factors will result in substandard products. One of the most important problems that facing antibiotics is the growing resistance of microorganism due to the irrational use of these antibiotics or due to substandard quality of the produced dosage forms containing antibiotics. Therefore, regularly, investigations of the quality of medicines in the pharmaceutical market are crucial. Such aspects may include the extent of availability of counterfeit pharmaceuticals in the local market and to what extent generics were comparable to the originator (branded) medicine. The quality of pharmaceutical products might be assessed by visual examination, quantitative and qualitative identification pharmacopoeial analysis. Ideally, analysis of pharmaceutical products starts during manufacturing and continues after registration and marketing. However, only few countries have regulatory authorities that analyze pharmaceutical products before and after registration (8).

The quality of oral tablets and other drug dosage forms must be built in during different stages of production, testing, storage and distribution (9). However, the quality of end product is not guaranteed. The essential qualities of good compressed tablet are characterized by a number of specifications. These include the appearance, size, shape, thickness, weight, homogeneity, stability, hardness, dissolution time, and disintegration time. All such qualities are designed to ensure a safe, therapeutically, effective oral solid dosage form. Official QC tests for tablets or Compendial tests (i.e., pharmacopeial) include; uniformity of content of the API (i.e., Uniformity of weight & Content uniformity), disintegration test, dissolution test and friability test.

However, there are other tests that are frequently applied to tablets for which there are non-pharmacopoeial requirements but will form a part of manufacture's owner product specifications. These non-compendial tests include color, shape, tablet thickness, tablet hardness and tablet volume. Accordingly, this study was conducted in order to evaluate the quality of commercially Cefuroxime axetil tablet products available

on the Palestinian market and to assess if there any justification for their market price.

MATERIALS AND METHODS

Chemicals and reagents

All chemicals and reagents including Cefuroxime axetil powder, hydrochloric acid, potassium chloride and monobasic ammonium phosphate were kindly supplied by Jerusalem Pharmaceuticals Co. Ltd. (Ramallah, Palestine). HPLC-grade and analytical grade methanol was obtained from Fisher Scientific (Loughborough, UK). The purified water used for preparing solutions and mobile phase was obtained from water system (Stilmas, Italy). The examined tablets were purchased from the local market in just the same way that the patient might have bought them from a community pharmacy. All products have a labeled Cefuroxime content of 500 mg. All tested products were within their shelf lives and were manufactured within the same period (i.e., March 2016). A list of the tested products is shown in Table 1.

Table (1): A list of the tested commercial tablets of cefuroxime axetil available on the Palestinian market.

Product	Physical appearance	Classification	Manufacturing date (Expiration period)	Price USD /10tablets
A	Oblong biconvex caplet shape	Local	March 2016 (3 years)	10.5
B	Oblong biconvex caplet shape	Local	March 2016 (3 years)	10.5
C (reference)	Oblong biconvex caplet shape	Imported (brand)	March 2016 (3 years)	14

Methods and instrumentations

All methods used to determine the quality of the tablet products were conducted according to the United State Pharmacopeia (10). All tests were performed within product expiry dates. Before starting the study, the Palestinian Medicines Index (PMI) and the Israeli Medical Index (MEDIC, 2013 edition) were consulted to determine the brands which are currently available on the Palestinian market. Uniformity of dosage unites was assessed according to the following procedure: a set of 10 tablets was chosen randomly and weighed individually using high sensitivity analytical balance (Erweka, Germany). The weight variation was assessed by weighing 20 tablets individually for all of the tested products. The average weight and the standard deviation were determined and the percentage deviation from the mean of each tablet was calculated. The USP acceptance criteria for weight variation test is "Not more than two of the individual weights deviates from the average weight by more than 5% and none deviates by more than 10%. Hardness test was performed on 10 tablets by simultaneously measuring the thickness (mm), length (mm), width (mm) and crunching strength or hardness (N) using a hardness tester (Erweka TB24, Germany). For the purpose of determination of the volume of each product, the displacement method was used. A 25-mL calibrated graduated cylinder in 0.1 mL divisions was employed using a silicon oil as a soaking solvent. Five tablets of each of the tested product were immersed and the observed change in oil level was obtained, afterwards, the average volume was calculated.

Tablet disintegration time was also assessed, the test accomplished by introducing 6 tablets into the tubes of the rack assembly of a disintegration tester (Erweka ZT 320, Germany). The assembly was suspended in 1000 mL simulated gastric fluid (SGF) pH 1.2 maintained at 37°C and the apparatus was operated for a specified time until no fragments of un-dissolved tablets observed on the sieve of the apparatus. The device was set for raising and lowering in the basket in the immersion fluid at constant frequency rate between 29 and 32 cycles per minute. Drug release studies were performed according to the

USP apparatus II paddle method using a dissolution apparatus (Erewka, Heusenstamm, Germany). The paddles were rotated at 55 rpm and the temperature was kept at 37 ± 0.5 °C. Dissolution vessels were filled with 900 mL of SGF. All SGF was prepared using 0.07 N hydrochloric acid. Samples were withdrawn at 15 and 45 minutes, filtered, diluted as appropriate and measured at 278 nm using Ultra violet (UV) Spectrophotometer (Shimadzu UV 1700).

All chromatographic experiments were performed using a High performance liquid chromatography (HPLC) system (Dionex - UltiMate 3000 LC System, USA) consisting of a pump, auto-sampler injector and a UV detector. All LC parts were controlled by Chromeleon® version 6.80 (Dionex). Separations were done on a reversed phase column using the LC method described earlier in accordance to the USP procedures (10); the method provided a quantitative determination of the content of Cefuroxime axetil as API in the tested medicines. However, a brief description for standard preparation was shown here; "Transfer about 30 mg of Cefuroxime axetil to a 25 mL volumetric flask, dissolve in methanol, dilute with Methanol to volume, and mix. Promptly transfer 10.0 mL of this solution to a 50 mL volumetric flask and then dilute with 0.2 M MAP to volume, and mix". The area under the peak (AUP) from the chromatogram was obtained for this standard solution and then was used to determine the content of Cefuroxime in the tablets.

Related substances examined in accordance to British Pharmacopeia (BP) (11) in which the LC method used as described under assay. The method was performed by preparing test solution to dissolve tablet substance equivalent to 10 mg of cefuroxime axetil in to the mobile phase and dilute to 50 ml with the mobile phase. Reference solution (*1*) prepared by diluting 1 ml of test solution to 100 ml with the mobile phase, for reference solution (*2*) heat 5 ml of test solution at 60° for 1 h to generate the Δ3-isomers and for reference solution (*3*) expose 5 ml of test solution to ultraviolet light at 254 nm for 24 h to generate E-isomers. Reference solution (*4*) prepared by dissolving 10 mg of cefuroxime axetil in the mobile phase and dilute to 50 ml with the mobile phase. Inject 20 µl each of reference solutions (*1-4*) and chromatograms recorded at 278 nm with a flow rate of 1.5 ml/min. Percentage content of the related substances calculated from the areas of the peaks in the chromatogram by the normalization procedure.

RESULTS

Only three different commercial products of Ceferuxime tablets (500 mg/tablet) are available on the Palestinian pharmaceutical market (two locals and one brand). They were classified into brand and locally produced products and they were analysed for price to public. The results showed that both local products had same cost price and was approximately 33% less expensive than the original brand (Table 1). This may raise a question about the quality of these products and if the can be interchangeable or not.

In fact, according to FDA, products evaluated as therapeutically equivalent can be expected to have equivalent clinical efficacy and safety when used under the conditions of their labeling. However, these products may differ in the following characteristics: shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, and preservatives), expiration date/time, and, sometimes may have different labels. Therefore, if these products are substituted, there is a potential for patient confusion due to differences in color or shape of tablets. Moreover, inability to provide a given dose using a partial tablet if the proper scoring configuration is not available, or decreased patient acceptance of certain products because of flavor or taste. There may also be better stability of one product over another under adverse storage conditions, or allergic reactions in rare cases due to a coloring or a preservative ingredient, as well as differences in cost to the patient (12).

Accordingly, visual quality was used to examine and to evaluate the organoleptic properties due to the impact of these properties on patient compliance. The appearance of tablets of the selected brands was elegant and their color, size, texture were consistent with no sign of defects in all tested tablets. In fact, no one of the tested commercial prod-

ucts had one of the above advantages on the other.

Regarding the instrumental and compendial inspection, our data as expected showed that weight variation was found to be within the pharmacopeial limits. The deviation from the average weight results revealed that products A, B and C had the following range limits (97.68 - 102.50%), (96.75 - 102.97%) and (99.21 -104.25%) respectively in which no tablet was out of the USP allowed limit (i.e. NMT 5%). Table 2 provides a summary of the some quality tests.

Table (2): Weight variations, product's dimensions and hardness tests.

Product	Average weight ± (mg) RSD%	Thickness (mm)	Length (mm)	Width (mm)	Estimated Volume (cc)	Tablet hardness mean ± SD
A	937.4 ± 2.56	6.77 ± 0.08	19.11 ± 0.02	9.14 ± 0.06	0.95	16.10 ± 3.50
B	1247.3 ± 0.82	8.14 ± 0.02	20.31 ± 0.22	9.78 ± 0.08	0.95	19.18 ± 0.85
C	912.2 ± 1.32	5.78 ± 1.3	19.63 ± 0.01	8.31 ± 0.03	0.87	23.51 ± 1.20

Tablet hardness, tablet thickness and length results of the different tested products were also assessed and our findings were reported in Table 2. The size of the tablet was estimated to assess swallowing problems which represents a persistent challenge especially in elderly individuals and patients who have dysfagia or have experienced an oesophageal ulceration after tablet or capsule swallowing. The time required for complete disintegration of all tablets containing Cefuroxime (500 mg) was tested according to the pharmacopeial guidelines. The results demonstrated that time for disintegration of both formulations A and C was about 1 minute. However, the time needed to disintegrate product B was about 2 minutes. The percentage of dissolved CA in each product was determined at 2 time points particularly, 15 and 45 minutes according to the USP monograph. The test was performed using dissolution apparatus II as described earlier. The result showed that all products passed this test in the first stage of dissolution testing. The USP acceptance criteria of tablets labeled to contain the equivalent of 500 mg cefuroxime state that "Tolerances: not less than 50% (Q) of the labeled amount is dissolved in 15 minutes and not less than 70% (Q) is dissolved in 45 minutes". Where, Q, is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labeled contents. The percentages of drug release in all examined units were more than 55 and 75% at 15 and 45 minutes respectively (Table 3).

Table (3): Dissolution and disintegration time results of all Cefuroxime axetil tablets on the Palestine market.

Product	Disintegration time	Dissolution Average % of dissolved CA	
	USP Limit (NMT 15 min)	15 min.	45 min.
A	1	74.5 ± 5.5	91.8 ± 4.6
B	2	88.0 ± 3.1	100. 1 ± 1.5
C	1	93.15 ± 1.6	96.18 ± 2.2

The amount of Cefuroxime in each tablet of the examined pharmaceuticals was determined using the HPLC method. The estimated percentages per labels, from the assay, together with their relevant statistical analysis, are shown in Table 4. The USP 2014 specifies a range of 90 -110% of the stated amount of Cefuroxime tablets. Accordingly

all of the tested tablets were complies with the USP specifications. In addition, the obtained results pertaining related substances were summarized in Table 4.

Our findings suggest that all of the tested products met the pharmacopoeial specifications regarding related substances. Figure 2 shows a representative chromatogram of related substances test under the chromatographic conditions explained earlier.

Table (4): Assay and related substances results of the tested products with their statistical parameters.

Product	Average Assay (%) ± SD (n = 10)	Related substances (%)			
		Δ3-isomer	E 1 enantiomer	E 2 enantiomer	Other impurities
Pharmacopeial limit	90-110%	NMT 2.0%	Sum NMT 1.5%		NMT 1.0%
A	98.51±0.52	0.9	0.2	0.1	0.49
B	98.57±0.44	0.9	0.1	0.1	0.16
C	97.38±0.91	1.3	0.0	0.0	0.1

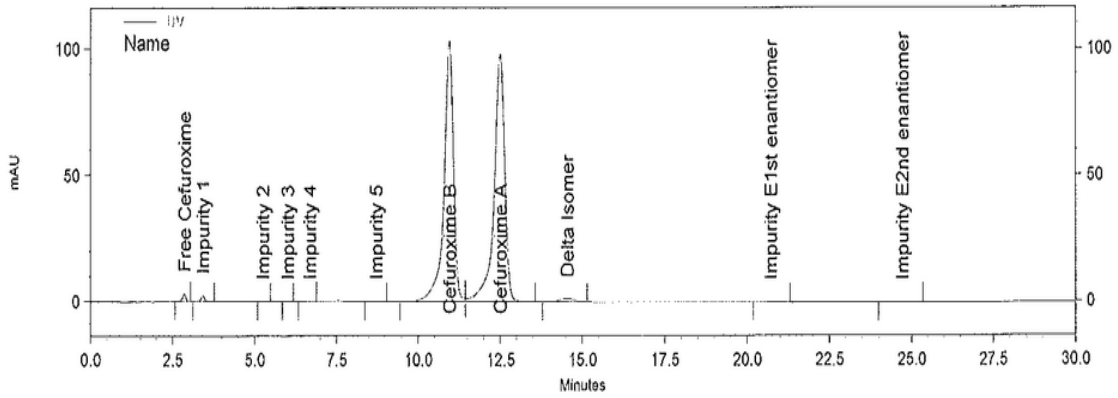

Figure (2): obtained chromatogram for related substances test.

DISCUSSION

Palestine relies under the Israel occupation and this impact negatively on many aspect of Palestinian occupation, especially the economic side. In fact, Palestine is considered a low income country. However, many patients try to not save many when the issue is related to medication. According to local community pharmacists and physicians, patients usually prefer imported drugs since they believe that these products have superior therapeutic effect and safety than the locally produced products. Many of these patients can pay a higher price for brand products despite the poor economic circumstances of many of them. Many of care providers also have this belief and sometimes encourage patients to buy the brand products. The objective of this study was to survey Cefuroxime tablet products available on the Palestinian pharmaceutical market according to their price and to assess their quality according to pharmacopeial and non-pharmacopeial standards in order to identify if these products could be interchangeable.

Quality control tests and specifications for some of the experimental part of the current study are given in pharmacopoeia. The most important for these are; weight uniformity, the drug release in terms of tablet disintegration and drug dissolution, resistance of tablets to fracture in terms of friability and hardness testing of the product. Previous studies have shown alarming serious levels of substandard medicines in some Arab and developing countries (8, 13-15). Indeed, the major aim of the research project was to investigate if the local medicines are comparable with the imported products and hence, their interchangeability may be granted. The Palestinian Ministry of Health (MOH) and the Department of Drug Control and Registration (DDCR) are the regulatory authorities that grant marketing authorization for branded and generic drug products. Ac-

cording to the current regulation (16), a product has to satisfy the compendial requirements for safety, purity and quality according to either the USP or the British Pharmacopeia (BP). Additionally, a bioequivalence study is required to show that the generic is bioequivalent to the brand name drug according to the USA Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) (17, 18). The Palestinian regulatory authorities recognize and accept properly conducted studies performed *in vitro* to support *in vivo* data (19). The result showed low price (one third less) of Cefuroxime local product comparable the original brand. In fact the cost of original brand exceeds the local products about 4 USD for each box of course therapy. This large price represents a negative impact on the economical situation of both patients and Palestinian MOH. A visual QC examination was carried on all Cefuroxime tablet selected in this study for the purpose of evaluating their organoliptic properties (i.e., shape, size, color, texture and presence of black spots). In fact, these parameters play a very important role in patient's acceptance or compliance toward any dosage form. With regard to tablet strength, all the tested products passed the friability test demonstrating that these products do not lose Cefuroxime during the transportation or handling process. However, high tablet strength should not compromise disintegration in the stomach.

Besides, the tablet size may be associated with swallowing problems. In fact, the drug induced oesophageal ulceration is a serious problem and is due to a delay in the passage of the tablet or capsule because of their sticking in the oesophagus. Indeed, several recommendations were proposed to avoid this problem. Among these recommendations; the use of a low size tablets or capsules, taking appropriate body posture and drink at least 100 mL of water or other appropriate carrier.

Concerning dissolution, this test is used as a tool in order to ensure products quality and batch to batch variability. It is also used as an alternative tool for the assessment of *in vivo* bioequivalence. *In vivo* bioequivlence studies are conducted in healthy volunteers. These studies are costly, time consuming and involve subjecting healthy volunteers to risks of side effects. However, today regulatory agencies like the FDA and the EMEA allow the replacement (waiver) of *in vivo* bioequivelence studies by *in vitro* dissolution testing especially for class 2 drugs (highly soluble, highly permeable. Accordingly the *in vitro* dissolution test is used to predict the in vivo absorption of the drug product, by means of *in vivo/in vitro* correlations (IVIVC). The dissolution of the drug from oral solid dosage forms is essential for drug bioavailability, especially for slightly water soluble drugs such Cefuroxime. For this reason, dissolution studies can give an idea of the amount of drug available for absorption after oral administration (19, 20). Drugs with poor dissolution profiles will not be sufficiently available in the body system to produce the desired therapeutic response (21). The dissolution profiles of all tested brands were performed in Simulated gastric Fluid (SGF) and they were found to be comparable. More precisely the average release of cefuroxime in SGF from the local was greater than 85% after 15 minutes while the brand released about 74.5 % of its content after same time and both local showed almost better drug release after 45 minutes than the original bran which may encourage us to conclude that the quality of these two local products are of high standard.

CONCLUSIONS

The obtained results indicated that all of the examined products were in accordance with the pharmacopeial specifications. The local products showed little significant differences compared to the original brand. However, the price of the brand is higher than the locally produced generics. Our findings signify that generic Cefuroxime tablets produced by local manufacturers are often comparable in vitro to the innovator product (even have better drug release) and have lower costs. According to the above mentioned findings, the local pharmaceutical products containing cefuroxime axetil showed comparable *in vitro* testing with the originator. Hence, we should take in our consideration that the national pharmaceutical industry need care-providers and inhabitants to be confident in their products, since they

showed high quality standard with about 33% save on the cost of each product.

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CONFLICT OF INTERESTS

The authors report no conflicts of interest in this manuscript.

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