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Original article

A Comparative Study Between Five Brands of Amoxicillin/clavulanic Acid (625 mg) Tablets Available in Libyan Drug Market

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ABSTRACT

Amoxicillin/clavulanic acid is a combination penicillin-type antibiotic used to treat a wide variety of bacterial infections. However, there are many Amoxicillin- clavulanic Acid brands marketed in Libya, with different quality and prices. The study was aimed to evaluate the quality of five commercial Amoxicillin- clavulanic Acid (625mg) products available in the Libyan market. This study was conducted to assess quality, all products were examined visually for their organoleptic properties, weight uniformity test, friability, hardness, disintegration test, dissolution test and IR were assayed. We carried out a physical comparison of all Amlodipine tablet products and assessed their quality. All the tested five brands were equivalent and complying with the official tests for weight variation, friability, disintegration and Hardness tests according to USP specifications. The friability test between 0.054% to 0.223%. All formulations were disintegrated between 1.57 to 9.04 minutes. Infra-Red (IR) spectroscopic investigations were revealed no any difference between brands and showed identical peaks compared to the reference. All the available brands in local Libyan pharmacies are having, with in the specified quality range and considerably, can be chosen according to good quality and cost, to improve the therapeutic benefit and patient compliance without interchangeability.

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INTRODUCTION

Amoxicillin Trihydrate (α-amino-hydroxybenzylpenicillin) is a semi synthetic, antibiotic [1]. Amoxicillin is in a class of medications called penicillin-like antibiotics. It works by stopping the growth of bacteria. It is a moderate spectrum, bacteriolytic, β-lactm antibiotics used to treat bacterial infections [2,3]. It is effective for bacterial infection, especially for Helicobacter pylori infection. Helicobacter pylori is a major causative agent of diseases such as Tonsillitis, Pneumonia, Bronchitis, Gonorrhea, ear infections, Genital, urethral infections in male/ females, stomach or duodenal ulcer and skin infection [4]. It is a combination consisting of amoxicillin and potassium clavulanate. It is specifically used for otitis media, streptococcal pharyngitis, pneumonia, cellulitis, urinary tract infections and animal bites. It is taken by mouth or by injection into a vein. also known as co-amoxiclav or amox-clav and Augmentin as brand names, is an antibiotic medication used for the treatment of a number of bacterial infections [5].

Amoxicillin is one of the most commonly prescribed antibiotics in children. Amoxicillin is available as a generic medication. In 2019, it was the 23rd most commonly prescribed medication in the United States, with more than 25 million prescriptions [6].
Amoxicillin Trihydrate (α-amino-hydroxybenzylpenicillin) is a semi synthetic, antibiotic [7]. Amoxicillin is in a class of medications called penicillin-like antibiotics.

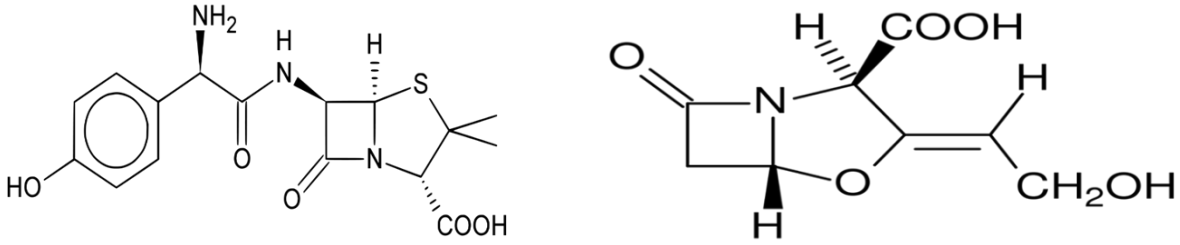

Figure 1. Chemical structure of Amoxicillin Trihydrate

Clavulanic acid, also known by its potassium salt form clavulanate, is FDA approved for clinical use in conjunction with amoxicillin to treat certain bacterial infections. This can be based on the source of the infection, Gram stain or culture and sensitivity results. The antibacterial activity of amoxicillin is not improved by clavulanic acid when used against bacteria that do not produce beta-lactamase. Therefore, indications for this drug combination only include patients suspected of infection with beta-lactamase producing bacteria. This combination has demonstrated efficacy in treating infections such as complicated and uncomplicated urinary tract infections, lower respiratory infections, sinusitis, otitis media and some skin and soft tissue infections caused by organisms such as H. influenzae, M. catarrhalis and S. aureus.
The amoxicillin/clavulanate combination should be considered before ceftriaxone for urinary tract infections to decrease the risk of re-infection and complications. Some off-label uses for amoxicillin/clavulanate include animal bites, impetigo, chronic obstructive pulmonary disease exacerbations, bronchiectasis and odontogenic infections [8].

MATERIALS & INSTRUMENTS

Materials

The brands of Amoxicillin/clavulanic acid tablets 625mg include: Augmentin® 625mg (SMITHKLINE BEECHAM LTD, UK), (Batch number: 5SVEV98BG). Clavimox® 625mg (PHARCO-PHARMACEUTICALS, EGYPT), (Batch number: 2201024. Amoclan® 625mg (HIKMA, JORDAN), (Batch number: 96568). Augmexiclav® 625mg (FUGEN HEALTHCARE LTD, INDIA), (Batch number: RH22010), Expiration-date 12-2024. Gloclav® 625mg (GLOBALPHARMA, UAE), (Batch number: P253)
For samples weighing an analytical balance Sensitive Balance "Sartorius" Germany, the hardness test was determined using Hardness tester "Pharma Test" type: PTB E, Germany, Disintegration Tester Disintegration apparatus "Pharma Test" type: PTZ, Germany, The Friability test was done by using Friabilator "Pharma Test" type: PTF E, Germany. All UV spectroscopic measurements were performed using UV spectrophotometer (Specord 200). IR Spectroscopy was done by using Infra-red spectrophotometer.

Study setting

The study was carried out in May 2022 at department of pharmaceutical science, University of Tripoli Alahalia (UTA) & Tripoli Centre of Drug & Food quality Control and specifications Tripoli/Libya.
We have subjected all five brands of Amoxicillin/clavulanic acid 625mg tablets include: (1) Augmentin® 625mg (UK), (2) Augmexiclav® (INDIA), (3) Clavimox® 625 mg (EGYPT), (4) Amoclan® 625mg (JORDAN) & (5) Gloclav® 625mg (UAE) compendia specification for visual inspection, uniformity of weight, hardness test, disintegration test as well as Infra-red spectroscopy.

Visual Inspection

Amoxicillin/clavulanic acid 625mg tablets were inspected visually and compared in respect to the visual characteristics including: color, clarity, shape and size.
The size in diameter of five tablets from each brand were measured and the average was taken [8] [9].

Uniformity of Weight

Twenty tablets of each formulation were weighted individually by using a Sensitive Balance, and the mean weight was calculated, and the percentage (%) deviation of the individual tablets from the mean was determined. according to United States Pharmacopeia (USP). Accepted limit: the weight of not more than two of tablets differ from mean weight by more than the percentage listed, and no tablet differs by more than double that percentage.

Hardness Test

The machine was calibrated and then one tablet was placed in its position. The machine turned on till the tablet breaks down and pressure applied was in Kg the same steps were repeated with other nine tablets. The average of ten reading was calculated to determine the crushing strength of tablets. The average of the ten readings was calculated [10]. Limit: force in kg must be within the range from 10 to 20 kg, and only one is allowed to be outside the limit.

Friability Test

A number of 10 tablets of each brand of amlodipine were weighted and placed in the Friabilator apparatus "Pharma Test" type: PTF E, Germany at 100 revolutions for 4 min. The tablets were deducted and weighed again then percent of weight loss was recorded. The friability of the tablets was then calculated using the following Formula:

$$\% \text{ Friability} = (\text{initial weight} - \text{final weight}) \div (\text{initial weight}) \times 100$$

Friability values are usually considered satisfactory when the product exhibits a weight loss of less than 1%.

Disintegration Test

The disintegration test was carried out by using Disintegration apparatus. Six tablets from each formulation were subjected to disintegration test. One tablet was placed in each of the six tubes of the basket. Then disks were added to each tube of the basket. The time taken for the last tablet to disintegrate completely was recorded in minutes. The disintegration time limit for uncoated tablet should be within 15 minutes, While for coated tablet should be disintegrated within 30 minutes according to the USP specifications.

Infra-red spectroscopy

Infrared spectra were obtained on IR spectrometer. The samples were prepared in KBr 10-15 mm diameter discs(1-2 mg of the substance to be examined was titrated with 300-400 mg of finely powdered and dried potassium bromide). IR Spectroscopy is used for recording spectra in the region of 650-4000 cm^{-1}

RESULTS AND DISCUSSION

Amoxicillin/clavulanic acid is a widely prescribed Antibacterial agents. Several brands of Amoxicillin/clavulanic acid tablets are available in the Libyan market leading to a confusion of their quality and prices. The objective of the present study is to make a comparative evaluation of five different brands of Augmentin which are commercially available in Libyan market. They were subjected to number of quality control tests to assess their biopharmaceutical equivalence. The branded products of Amoxicillin/clavulanic acid tablets evaluated for various physiochemical properties. The size of tablets was in the range of (19.61 to 21.11 mm in diameter) with all five brands. There is no significant difference between the batches of the brands as shown in Table 1.

The uniformity of weight for the five brands of gave values that compiled with USP specification and deviated less than 1.72 % from the mean value as shown in Table 2.

Table 1. Visual Inspection Test of Five brand of Amoxicillin/clavulanic acid 625 mg Tablets

No	Test	Gloclav	Augmoxiclav	Augmentin	Clavimox	Amoclan
1	Color	Off White	White	White	White	White
2	Clarity	Clear	Clear	Clear	Clear	Clear
3	Shape	Oval	Oval	Oval	Oval	Oval
4	Size (mm)	21.11 mm	20.03 mm	20.30 mm	19.61 mm	21.62 mm
5	Thickness	7.25mm	7.08mm	6.81 mm	5.74 mm	7. 73mm
6	Package	Blister pack	Blister pack	Blister pack	Blister pack	Blister pack
7	Tablet Types	Film coated	Film coated	Film coated	Film coated	Film coated

Table 2. Weight variation of five brands Amoxicillin/clavulanic acid 625 mg Tablets

Brand name	Results	Comment
Augmentin 625 mg (U/K)	1.28%	Pass
Clavimox 625mg (EGYPT)	1.72%	Pass
Amoclan 625 mg (Jordan)	1.05%	Pass
Gloclav 625mg (UAE)	1.11 %	Pass
Augmexiclave 625mg (India)	1.43%	Pass

The result of tablets friability test showed that all the brands tested had impressive friability values ranging 0.054% to 0.223% w/w According to USP, no batch should have a friability value greater than 1% w/w as showed in Table 4. Using hardness tester, the strength of the tablets was tested. The Hardness of the tablets was to pass this test and the range was between 10.35 kg to 14.42 kg of five brands according to USP specifications. This test is correlated to disintegration of these tablets, which is revealed the strength of tablets and the role of disintegrates materials, as shown in Table 3 [11].

Table 3. The Hardness test of five brands of Amoxicillin/clavulanic acid 625 mg Tablets

Brand name	Force in kg	Comment
Augmentin 625 mg (U/K)	13.34	Pass
Clavimox 625mg (EGYPT)	14.42	Pass
Amoclan 625 mg (Jordan)	11.84	Pass
Gloclav 625mg (UAE)	10.35	Pass
Augmexiclave 625mg (India)	14.00	Pass

Table 4. Friability test of five brands of Amoxicillin/clavulanic acid 625 mg Tablets

Brand name	Results	Comment
Augmentin 625 mg (U/K)	**0.073%**	**Pass**
Clavimox 625mg (EGYPT)	**0.072%**	**Pass**
Amoclan 625 mg (Jordan)	**0.054%**	**Pass**
Gloclav 625mg (UAE)	**0.223%**	**Pass**
Augmexiclave 625mg (India)	**0.099%**	**Pass**

The observed disintegration times for all the brands of Amoxicillin/clavulanic acid 625 mg investigated was less than 30 min. The fastest disintegration tablets were of Augmexiclave® 625mg brand was 1.57 minute, while the slowest brand was Augmentin® 625mg 9.04 minutes. The various brands could have employed different disintegrates to improve the penetration of aqueous liquids as shown in Table 5.

In fact, this attempt is done for quality purposes to improve the solubility and bioavailability of pharmaceutical drugs into the blood stream. The IR spectra revealed an investigation of the physical-chemical properties of the drug substance, alone and in combination with excipients of five different brands. Assessment of possible compatibilities between the drug and different excipient is an important part of formulation.

All the spectra were compared for shifting of major functional peaks and for the loss of functional peaks, if any. Amide group band (3500-3118 cm-1), Imine group band (1690-1640 cm-1), Carbonyl amide group band (1680-1630 cm-1), Carboxylic group band (1730-1700 cm-1) are shown in the spectra.

Table 5. Disintegration time of five brands of Amoxicillin/clavulanic acid 625 mg Tablets

Brand name	Results	Comment
Augmentin 625 mg (U/K)	9.04 min	Pass
Clavimox 625mg (EGYPT)	7.03 min	Pass
Amoclan 625 mg (Jordan)	6.55 min	Pass
Gloclav 625mg (UAE)	6.35 min	Pass
Augmexiclave 625mg (India)	1.57 min	Pass

When the spectra compared with the library, it was found out that, there was no shifting of functional peaks and no

overlapping of characteristic peaks and also there was no appearance of new peaks. No significant change in the IR spectra of Amoxicillin/clavulanic acid were observed, as shown in Figure 1.

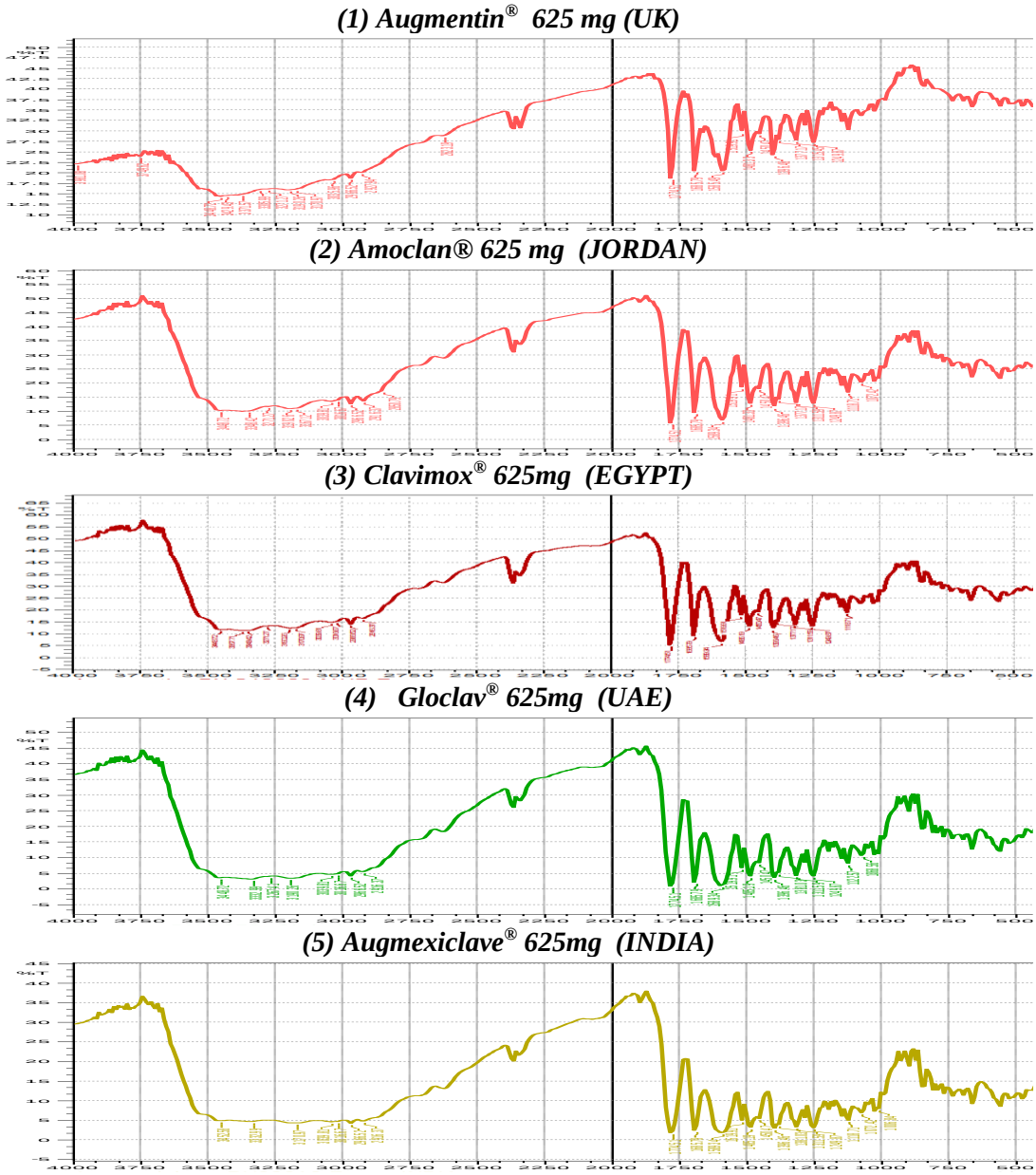

Figure 1. Spectra of provided by Amoxicillin/clavulanic acid 625 mg four brands & Drug reference of Augmentin® Tablet.

CONCLUSION

The evaluated Amoxicillin/clavulanic acid brands are available in local Libyan market fulfil criteria for drugs containing Amoxicillin/clavulanic acid active pharmaceutical ingredients. Moreover, the test products showed compatibilities between the drug and different excipient. But, by making fine tunings in the survey equivalence study, we found the best quality and cheap products, suggest more likely to improve the therapeutic benefit and patient compliance.

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Conflicts of Interest

The author declares that they have no conflict of interest.

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دراسة مقارنة بين خمس علامات تجارية لأقراص أموكسيسيلين/حمض الكلافولانيك (625 مجم) المتوفرة في سوق الأدوية الليبية

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المستخلص

أموكسيسيلين/حمض الكلافولانيك هو مضاد حيوي مركب من نوع البنسلين يستخدم لعلاج مجموعة واسعة من الالتهابات البكتيرية. ومع ذلك، هناك العديد من العلامات التجارية لحمض أموكسيسيلين- كلافولانيك المسوقة في ليبيا، بجودة وأسعار مختلفة. هدفت الدراسة إلى تقييم جودة خمسة منتجات تجارية من حمض الأموكسيسيلين-الكلافولانيك 625(ملغ) المتوفرة في السوق الليبي. لتقييم الجودة، تم فحص جميع المنتجات بصريًا لمعرفة خصائصها الحسية، وتم اختبار اختبار تجانس الوزن، والتفتيت، والصلابة، واختبار التفكك، واختبار الذوبان، واختبار الأشعة تحت الحمراء. أجرينا مقارنة فيزيائية لجميع منتجات أقراص أملوديبين وقمنا بتقييم جودتها. جميع العلامات التجارية الخمس التي تم اختبارها كانت متكافئة ومتوافقة مع الاختبارات الرسمية لتباين الوزن والصلابة والتفتيت والتفكك والاختبارات وفقًا لمواصفات USP. اختبار القابلية للتفتيت بين 0.54% إلى 0.223%. تم تفكك جميع التركيبات بين 1.57 إلى 9.04 دقيقة. كشفت التحقيقات الطيفية للأشعة تحت الحمراء (IR) عن عدم وجود أي فرق بين العلامات التجارية وأظهرت قمم متطابقة مقارنة بالمرجع. يمكن اختيار جميع العلامات التجارية المتوفرة في الصيدليات الليبية المحلية، ضمن نطاق الجودة المحدد وبشكل كبير، وفقًا للجودة والتكلفة الجيدة، لتحسين الفائدة العلاجية وامتثال المريض دون إمكانية التبديل.

الكلمات المفتاحية. أموكسيسيلين، حمض الكلافولانيك، التفكك، التفتت، الصلابة والعلامات التجارية.