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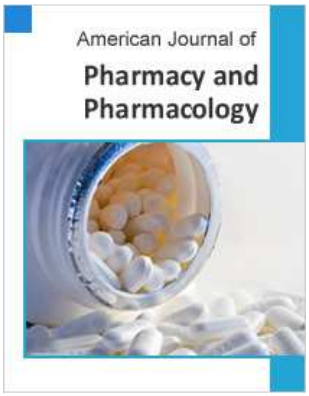

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Pharmaceutical Evaluation of an Augmentin Brand Manufactured in Different Countries

Mohamed N. El Attug[1, *], Amal Ammar[1], Serag Tunsi[1], Sohail Elmjrab[1], Shukri Al-Sharif[1], Abdulmonem Gobassa[2], Emhemmed Elgallal[2]

[1]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Tripoli, Tripoli, Libya
[2]Department of Drug Control, Centre for Food and Drug Control, Gurgi, Tripoli, Libya

Email address
elattug@gmail.com (M. N. El Attug), m.elattug@uot.edu.ly (M. N. El Attug)

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Abstract
Physicians often continue to prescribe brand-name drugs from the country of origin of the inventor to their patients even when less expensive of same brand drugs that are manufactured in different countries are available, despite it has been made by the same company. Some national authorities attract the inventors to establish their business and manufacture these brands to offer a cheaper brand drug than which made in country of origin to their citizens. Unfortunately Physicians in general and in Libya in particular tend to prescribe brand-name drugs which made in country of origin of the inventor, even without evidence of their therapeutic superiority. The objective of this project was to evaluate and compare the physicochemical equivalence and efficacy of different tablets of Augmentin® brand, that are available in Libyan local market, this brand is manufactured by GSK company in five different countries as; United Kingdom, Turkey, Greek, Ireland and Malta, the patients conscious about the selection of safest, effective as well as economical medicine. The proposed study has been performed to provide the evidence to the physicians and pharmacists that there is no superiority between among these products despite are manufactured in different countries, when they select the drugs for their patients. The physical parameters i.e. weight variation, thickness, hardness, disintegration, dissolution, potency (Antimicrobial susceptibility), as well as chemical assay were considered during the present study. All of these products had contents compatible with that required by Pharmacopeias and the dissolution profiles for all the drugs showed more than 92% of the active ingredient dissolved within 30 minutes. All drugs were approved with regard to tablets weight uniformity, thickness and hardness where the RSD % are between 0.74 % - 1.69 %, 0.35 % - 0.51 %, and 7.0 % - 8.9 %, respectively. The disintegration time of all samples also proved satisfactory, had completely disintegrated in less than 14 seconds.

1. Introduction

Amoxicillin / Clavulanic acid or co-amoxiclav is an antibiotic useful for the treatment of a number of bacterial infections. It is a combination antibiotic consisting of Amoxicillin trihydrate, a β-lactam antibiotic, and potassium clavulanate, a *β*-lactamase inhibitor. This combination results in an antibiotic with an increased spectrum of action

and restored efficacy against amoxicillin-resistant bacteria that produce *β*-lactamase. Amoxicillin is chemically defined as (*2S, 5R, 6R*)-6- {[(*2R*)-2- amino- 2- (4-hydroxyphenyl)- acetyl] amino} -3,3-dimethyl -7-oxo-4-thia-1azabicyclo [3.2.0] heptane-24-carboxylic acid.

Augmentin® tablet contain a combination of Amoxicillin trihydrate (Amox.) (Fig. 1A) and potassium Clavulanate (Clav.) (Fig. 1B)

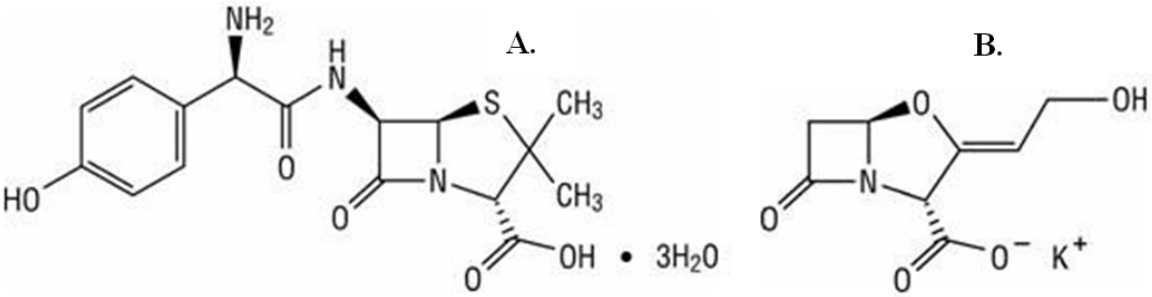

Fig. 1. *Chemical structure of Amoxicillin (A) and Clavulanic acid (B).*

Amoxicillin (Amox.) is a semi synthetic antibiotic with *in vitro* bactericidal activity against Gram-positive and Gram-negative bacteria. Amoxicillin is, however, susceptible to degradation by beta-lactamases, and therefore, the spectrum of activity does not include organisms which produce these enzymes. Clavulanic acid (Clav.) is a beta-lactam, structurally related to the penicillins, which possesses the ability to inactivate some beta-lactamase enzymes commonly found in microorganisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid-mediated beta-lactamases frequently responsible for transferred drug resistance. The formulation of amoxicillin and clavulanic acid in AUGMENTIN® protects amoxicillin from degradation by some beta-lactamase enzymes and extends the antibiotic spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin [1, 2]. It is on the World Health Organization's List of Essential Medicines, a list of the most important medications needed in a basic health system [3].

It is also used to prevent bacterial endocarditis in high-risk people having dental work done, to prevent Streptococcus pneumonia and other encapsulated bacterial infections in those without spleens, such as people with sickle-cell disease, and for both the prevention and the treatment of anthrax [4].

The United Kingdom recommends against its use for infectious endocarditic prophylaxis [5]. These recommendations have not appeared to have changed the rates of infection for infectious endocarditic [6].

Quality of the drug according to the modern definition requires that the product contain the quantity of each active ingredient claimed on its label within the applicable limits of its specifications, contain the same quantity of active ingredient from one dosage unit to the next, be free from extraneous substances, maintain its potency, therapeutic availability and appearance until used, and upon administration release active ingredient for full biological availability [6].

Many developing countries do not have an effective means of monitoring the quality of generic drug products in the market. This results in widespread distribution of substandard and/or counterfeit drug products. It was in view of this fact that WHO issued guidelines for global standard and requirements for registration, assessment, marketing, authorization and quality control of generic pharmaceutical products [8, 9].

If available, affordable, of good quality and properly used, drugs can offer a simple, cost-effective answer to many health problems. Despite the obvious medical and economic importance of drugs there are still widespread problems with lack of access, poor quality, and irrational use [10]. This study was conducted to evaluate the physical parameters i.e. weight variation, thickness, hardness, disintegration, dissolution, potency (Antimicrobial susceptibility), as well as chemical assay were considered during the present study and determine the *in vitro* activity of Augmentin against common and important bacterial isolates i.e *E.coli* and *Staphylococcus aureus* because these Gram ***-ve*** and Gram ***+ve*** organism are present in the environment everywhere due to which human come in direct contact with these organism and suffering from respiratory tract, gastrointestinal tract and urinary bladder infection.

2. Material and Methods

2.1. Material

2.1.1. Reagents & Solutions

All chemicals used were of analytical grade and used without further purification, Methanol, and Monopotassium phosphate (KH_2PO_4) in preparing buffer, Triethylamine, Orthophospheric acid for pH control of the buffer, standard used are Amoxicillin Trihidrate with Purity 85.7% were obtained from Fluka analytical company, and lithium clavulanate with purity 97% was obtained from European Directorate for the quality of medicines &health care European Pharmacopoeia (Ph.Eur.). Potassium bromide (KBr) for infrared spectroscopy was from BDH Company. All solutions were prepared by using ultrapure MilliQ-water (Millipore, Milford, MA, USA) and were filtered with a 0.2

µm membrane filter syringe (Dassel, Germany).

All samples were weighed using Sartorius CP64 Analytical balance (Sartorius incl). Antibiotic HiVeg assay medium No. 1 {seed Hi Veg agar}{antibiotic Hi Veg assay medium A},Soybean casein digest medium {Tryptone soya Broth} from Hi medium laboratories Pvt. Ltd, and using two type of bacteria negative bacteria *Escherichia coli* (ATCC- 25922) and positive bacteria *Staphylococcus aureus* (ATCC- 29213).

2.1.2. Samples (Generic Drugs)

Augmentin® (Amox/Clav) 500/125 mg Tablet made by GSK Pharmaceutical company.

Table 1. *Information about Augmentin products.*

Sample	Product Name	Manufacture Site
1	GSKU	UK
2	GSKI	Ireland
3	GSKT	Turkey
4	GSKG	Greek
5	GSKM	Malta

2.2. Equipments

2.2.1. Liquid Chromatographic System and Conditions

The assay of Augmentin carried on by using the method currently prescribed in the USP31-NF26 2008 [11] and was performed on Prominence UFLC (Model SPD-20A Shimadzu Corporation, Kyoto, Japan).system consisting of a LC quaternary pump (Model SPD-20AD Shimadzu Corporation, Kyoto, Japan), an auto injector Model SIL-20ACHT Shimadzu Corporation, Kyoto, Japan), a UFLC UV-VIS detector (Model SPD-20AV Shimadzu Corporation, Kyoto, Japan) The column temperature was maintained by using oven (Model CTO-20AC Shimadzu Corporation, Kyoto, Japan). Data acquisition was supported by (LC Solution software version 1.25, Shimadzu Corporation, Kyoto, Japan). The stationary phase used for the separation of Augmentin was XSELECT CSH C18 (250 x 4.6mm ID, 5 µm) made by Ireland with a column guard (50 x 4.6 mm ID, 2.7 µm) (SUPLECO Analytical, Bellefonte, USA), the mobile phase used for analysis of Augmentin was delivered with Flow Rate 1.0 mL/min. The amount of sample will be injected 5 µL, The Colum oven temperature was maintained at 30 ºC, the UV detector wave length 230 nm.

2.2.2. Instruments for Non-Official (Physical) Test

The non-official tests were done by various instruments as friabilty tester (ERWEKA® TAR220) for friabilty test, tablet combination tester (ERWEKA® TBH425 WTD) for hardness, diameter, thickness, weight tests, disintegration apparatus (ERWEKA® Model ZT320) for disintegration test, dissolution test unit (ERWEKA DT600) for dissolution test, Fourier Transform Infra-Red Spectroscopy (IR Prestige 21) for identification by IR, Data acquisition was supported by (IR Solution software version 1.4, Shimadzu Corporation, Kyoto, Japan). Incubator memmert; (Model 30-750), Oven memmert Model 3033 for microbiological tests.

2.3. Methods

2.3.1. Stranded Preparation

A reference solutionsof Amoxicillin was prepared by dissolving 50 mg of Amoxicillin trihydrate British Pharmacopeia Chemical Reference Standard (BPCRS) in 100 mL of volumetric flask dissolved in water, a Reference solutions of Clav. Was prepared by dissolving 20 mg of Clav. Reference (BPCRS) in 100 mL of water in volumetric flask.

Weight the 23.4 mg of KH_4PO_2 and dissolved in 3.0 L of water in volumetric flask to prepare the buffer, after that measure the 1900 mL of the buffer with measurement cylinder and add to it a 100 mL of methanol to prepare the mobile phase after that the mobile phase read to use.

For potency test the standard can be preparing by weight 57.15 mg of the Amoxicillin trihydrate standard with 16.25 mg lithium clavulanate as Clavulanic acid both are dissolved in 50 mL of the buffer.

The buffer solution will preparing by weight and dissolved 13.6 g from dibasic potassium phosphate added to 4 g of monobasic potassium phosphate in 1000 mL of purified water.

Media is used in the assay Antibiotic HI Veg assay medium by taken the weight 3.05 mg from the medium and put in conical flask that has 100 mL of purified water and keep in the steam sterilizer from Raypa Company.

2.3.2. Preparation of Inoculum

Live and fresh culture of *Staphylococcus aureus* and *Escherichia coli* were used against the drug. Cultures were grown in soya bean casein digest broth for 24 hours at 37 ^{0}C. After the incubation period cultures were inoculated into 100 mL of antibiotic medium.

2.3.3. Samples Preparation

A 20 tablets were weighed to measure the average weight and grinded it well. a 50 mg equivalent Amox in 100 mL of volumetric flask dissolved in water, a 10 mL of the solution were added to 100 mL of volumetric flask and diluted by mobile phase (95 mL of buffer: 5 mL of Methanol) to produce a 50 µg/mL final concentration of working sample solution.

The Preparation of sample for potency test each tablet is weighed and calculated into the final stock of (1 mg/mL and 0.25 mg/mL) of amoxicillin and Clavulanate, respectively. Transfer the weighed sample quantity into 100 mL of buffer solution and allowed to dissolve completely.

2.3.4. Assay of Content of Active Ingredient

Different products were tested during the assay by LC method according to USP 31-NF 26 [11]. 50 µg/mL of Amox. Under the condition of the chromatography system as shown in (Table 2).

(Fig. 2 and 3). Show typical chromatogram of Amoxicillin and of Clavulanic acid (BPCRS).

Table 2. *Chromatographic conditions, assay of content by USP 31-NF26 method* [11].

Mobile phase	**Buffer :Methanol (95:5 v/v)**
Elution	Isocratic: 100%
Column Temp	30 °C
Flow rate	1 mL/min
Detection (UV)	230 nm
Injection vol.	5 µL

In this test amount of drug in the dosage form is determined. A number of units from products are selected at random and assay procedures are carried out then the results obtained must be within the prescribed percentage limits [12-14]. It is to assure the presence of the required amount of active ingredient (Fig. 4) shows typical chromatograms overlay of five Augmentin products. More variation could lead to ineffectiveness therapeutic drug level or overdosing which lead to toxicity [15].

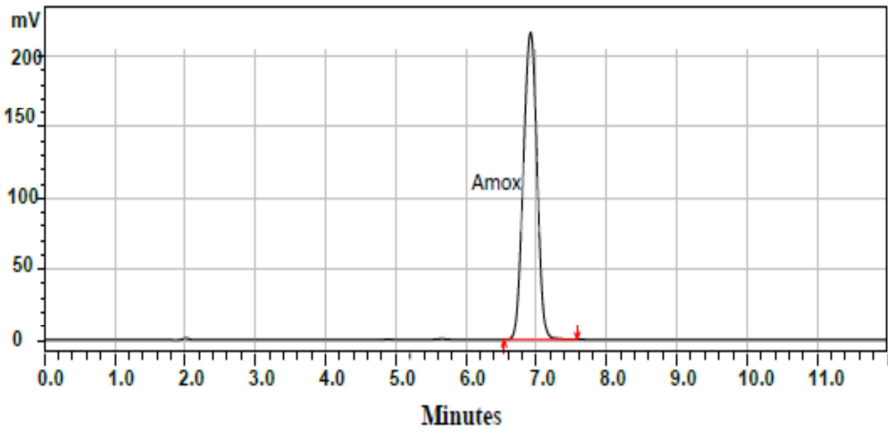

Fig. 2. *Typical chromatogram of Amoxicillin (BPCRS).*

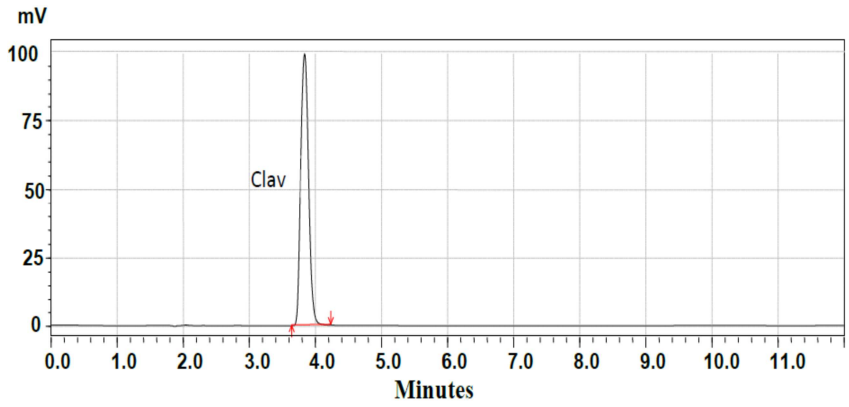

Fig. 3. *Typical chromatogram of Clavulanic acid (BPCRS).*

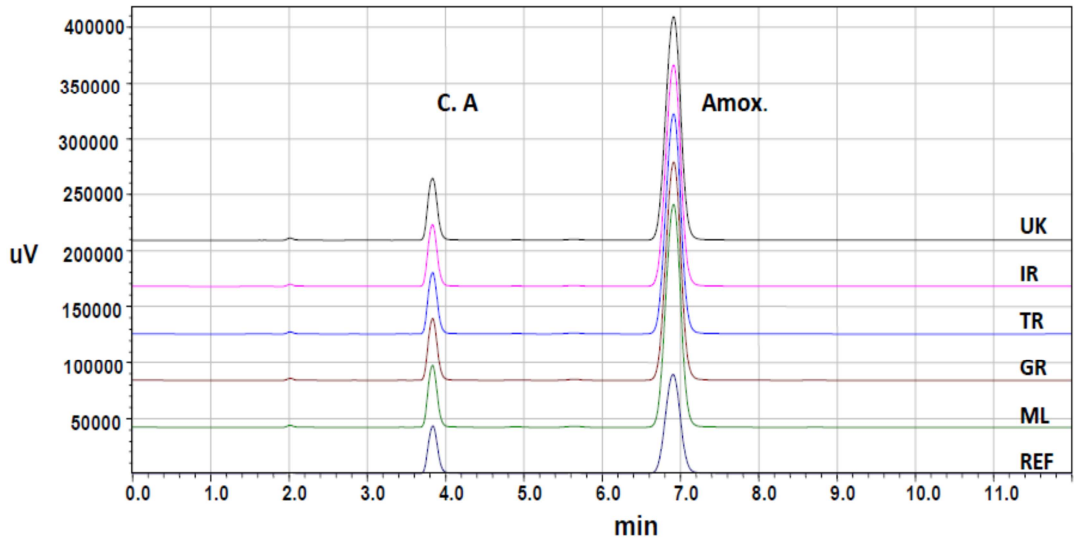

Fig. 4. *Typical LC chromatograms overlay of five Augmentin drugs.*

2.3.5. Dissolution Test

Dissolution test is the measurement of the proportion of drug dissolving in a stated time under standardized conditions *in vitro* [16]. To ensure availability of drug for absorption. Drug dissolution testis routinely used to provide critical in vitro drug release information for both quality control purposes, to assess batch-to-batch consistency of solid oral dosage forms such as tablets, and drug development, to predict in vivo drug release profiles. Since the dissolution of drug is considered to be an essential step in the absorption process, the availability of drug for absorption from a dosage form largely depends on the drug dissolving in gastrointestinal fluids [17].

Also to predict in vivo bioavailability, the prediction of in vivo bioavailability of most oral drugs depends mostly on the in vitro dissolution studies. Ideally, dissolution tests should provide data to distinguish good and bad products formulations, batches especially when operating conditions are optimal [18]. Chromatographic condition for determination the drug dissolved after certain time as shown in (Table 3).

Table 3. *Chromatographic conditions for dissolution by USP31-NF26 method* [11].

Mobile phase	Buffer :Methanol (95:5 v/v)
Elution	Isocratic: 100%
Column Temp	30 °C
Flow rate	1 mL/min
Detection (UV)	230 nm
Injection vol.	5 µL

2.3.6. Uniformity of Weight Determination

The tablet weight routinely measured to ensure that a tablet contains the proper amount of drug [19]. It is the test used to measure the uniformity of total mass of tablet "active ingredient and excipient in the batch. High variability of dose may cause toxicity or insufficient therapeutic drug level [15]. Also to ensure that the tablets in each lot are within the appropriate size range [8].

2.3.7. Diameter and Thickness Measurements

The physical dimensions of the tablet along with the density of the materials in the tablet formulation and their proportions, determine the weight of the tablet. The diameter and thickness express the size of tablet [19].

2.3.8. Hardness Test

Tablet hardness is usually expressed as the force required break-down the tablet [20], it is the test to measure the solidity of tablet to stand post operation procedure such as packing, storaging or handling. Although there is no official test for tablet hardness (it is non-compendia test), this property must be controlled during production to ensure that the product is firm enough to withstand handling during packaging and transporting without breaking, chipping or crumbling. Hardness may affect tablet friability and disintegration time. It usually affects drug dissolution and release, and it may affect bioavailability [21].

2.3.9. Disintegration Test

The disintegration test is provided to determine whether tablets or capsules disintegrate within the prescribed time when placed in a liquid medium at the experimental conditions [21]. Complete disintegration is the state in which any residue of the unit, except fragments of insoluble coating or capsules shell remaining on the screen of the test apparatus or adhering to the lower surface of the disk, if used, is a soft mass having no palpably firm core [21]. The disintegration provides drug particles with an increase surface area within the gastrointestinal tract and is the first important step toward solution, so this test is important to ensure the disintegration and discharge the drugs to the body fluids for dissolution [16]. It is used as a guide to formulator in the preparation of an optimum formula, and as an in process control test to ensure lot to lot uniformity [22]. It is the test used to measure the time of tablet disintegration.

2.3.10. Infrared (IR)

It is pharmacopeial test used for identification of compounds by detecting of the functional groups in it. IR analysis based upon a comparison of sample IR spectrum with that of reference standard as will be shown in Fig. 5. Which were acquired by (IR Solution software version 1.4, Shimadzu Corporation, Kyoto, Japan).

The IR test has been done by preparing the substance (Augmentin products) and the Amoxicillin and Lithium clavulanate reference substance (**BPCRS**) by the same procedure and record the spectra between 4000-650 cm^{-1} (2.5-15.4 µm) under the same operational conditions [12]. The transmission minima (absorption maxima) in the spectrum obtained with the Augmentin products correspond in position and relative size to those in the spectrum obtained with the Amox. and Clav. (BPCRS).

2.3.11. Antimicrobial Susceptibility (Potency) Tests [11]

The Antimicrobial susceptibility test of the antibiotic been used to demonstrate the efficiency of the drug. Under suitable condition the ratio of the dose that inhibits the growth of suitable and susceptible microorganisms. Cylinder-Plate Assay method is used to demonstrate the potency of the drug. 0.1 mL of live fresh microbial culture of *Staphylococcus aureus and Escherichia coli* was added to the 100 mL of each sterile medium. After pouring into the rectangular petridish. Plates were allowed to solidify and make the wells. After that prepared stock solution of standards and samples were inoculated in defined wells. Plates were incubated at 37^0C for 24 hours. After the appropriate incubation plates were observed for the zone of inhibition depending on the diffusion of the antibiotic from a vertical cylinder through a solidified agar layer in a petridish or plate to an extent such that growth of the added microorganism is prevented entirely in a circular area or zone that called Zone of Inhibition

around the cylinder containing the antibiotic solution. A clear zone of inhibition against both strains was observed. By comparing the width of *Escherichia coli* strains zone which has less zone width than that of the *Staphylococcus aureus* strains zone as will be shown in Fig. 6.

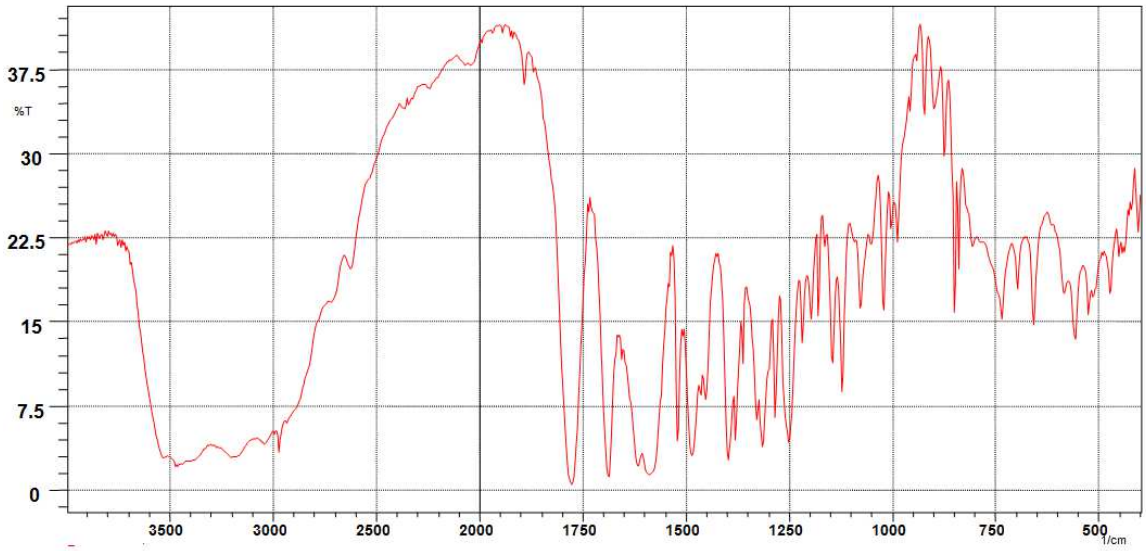

Fig. 5. *Typical IR spectra of amoxicillin trihydrat and lithium Clavulanate (BPCRS).*

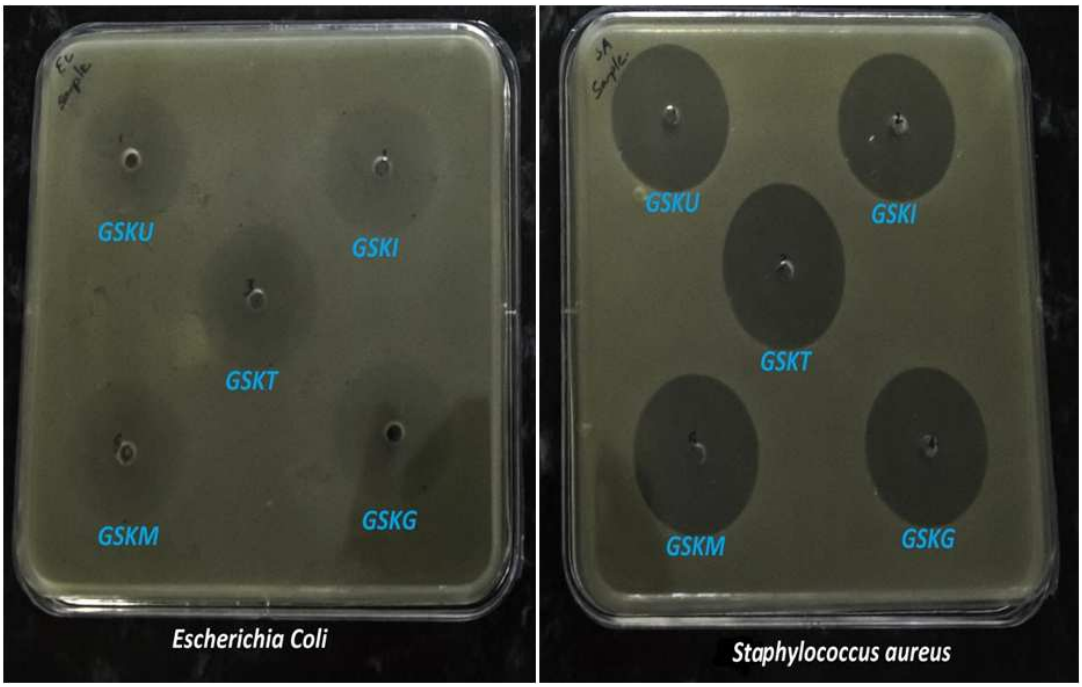

Fig. 6. *The inhibition zone of the five Augmentin sample (GSKU, GSKI, GSKT, GSKG, GSKM) on the both type of the bacteria.*

3. Results and Discussion

3.1. Results

The quality control tests results for the different formulations are summarized in (Tables 4, 5 and 6).

All official tests were carried out according to USP 31-NF 26 (2008) [11]. For the assay of average weight, since the values found were higher than 250 mg, each unit could vary by not more than (NMT) ± 5 % around the average, with a tolerance of two tablets outside this limit, and none could deviate more than 10 % from the nominal value. Thus all drugs were approved.

The thickness test for all the tablets analyzed (Table 4). All drugs were approved with regard to tablets thickness, the RSD % of tablets thickness is between 0.35% -0.51%.

The tablet hardness for all tablet analyzed in the (Table 4) all drug were approved with regard to tablet hardness the RSD % of tablet hardness is between 7.0% - 8.9 %.

The disintegration time of all samples also proved satisfactory, as all tablets had completely disintegrated in less than 14 Seconds. The results of these tests are presented in

(Table 4).

Table 4. *Non official (Physical) tests.*

Product Name	Weight mg (± RSD)	Diameter mm (± RSD)	Thickness mm (± RSD)	Hardness N (± RSD)	Disintegration Sec.
GSKU	1081.45 ± (1.20)	20.03 ± (0.25)	7.13 ± (0.37)	429.40 ± (8.9)	11.17
GSKT	1066.43 ± (1.69)	20.02 ± (0.14)	6.96 ± (0.43)	401.70 ± (8.5)	13.15
GSKG	843.64 ± (1.45)	18.43 ± (0.18)	6.67 ± (0.41)	349.00 ± (8.8)	10.20
GSKI	1064.69 ± (1.48)	19.99 ± (0.18)	7.04 ± (0.51)	423.20 ± (8.7)	12.46
GSKM	1076.47 ± (0.74)	20.01 ± (0.19)	7.09 ± (0.35)	445.30 ± (7.0)	12.22

(Table 4) presents the results for dosage unit content, uniformity and the dissolution profiles. All of the five analyzed samples had contents compatible with that required by USP, mean content ranging from 90.0 to 120.0% for Amox and Clav. Dissolution profiles for all the drugs showed more than 95 % of the active ingredient dissolved within 30 minutes was the recommended not less than (NLT) 85 % for Amox and 80% for Clav.

The different tests results were as following.

3.1.1. Official (Pharmacopeial) Results

The results for Official tests are presented in (Tables 5 and 6).

(i). Content of Active Ingredient

The dose content uniformity was tested by the method of weight variation. Ten tablets were weighed, accurately and individually, in each sample. From the content test result, the active content in each unit was calculated, presuming homogeneous distribution of this component in the formulation. Results were expressed as percentage of declared quantity and its relative standard deviation (RSD %).

(ii). Dissolution

The dissolution profiles of the products (released drug) being tested against the amoxicillin and Clavulanic acid references (BPCRS). Since all the drugs showed more than 92 % of the active ingredient dissolved within 30 minutes. (Tables 5).

Table 5. *Determination of Amoxicillin & Clavulanic acid content (Assay) and (Dissolution) test.*

Product Name	% Content of Amox.	% Dissolution of Amox.	% Content of Clav.	% Dissolution of Clav.
GSKU	97.65	98.21	104.89	103.44
GSKT	96.34	98.76	98.88	105.89
GSKG	96.59	96.76	99.44	101.22
GSKI	95.26	96.85	100.22	103.76
GSKM	97.52	92.98	101.96	100.01

3.1.2. Non Official (Pharmacopeial) Results

The results for non-official tests are presented in (Tables 5 and 6).

(i). Weight Uniformity

Twenty tablets from each sample were individually weighed on an analytical balance the result is shown in (Table 6).

Table 6. *Uniformity of weight*

Product Name	Min weight (mg)	Max weight (mg)	Average weight (mg)	RSD (%)
GSKU	1056.2	1095.3	1081.45	1.20
GSKT	1039.7	1098.8	1066.43	1.69
GSKG	830.9	859.2	843.64	1.45
GSKI	1041.4	1088.3	1064.69	1.48
GSKM	1061.5	1089.3	1076.47	**0.74**

(ii). Hardness

Although there is no official test for hardness, this property need be controlled to ensure that the product is firm enough to withstand handling without breaking or crumbling and not so hard that the disintegration time is prolonged.

All drugs were approved with regard to hardness since this parameter was found to be above 340-450 N, as shown in (Table. 4). A force about 40 N is the minimum requirement for satisfactory tablet.

(iii). Disintegration

The immersion liquid for this test was water at 37 ± 1ºC. Six tablets of each sample were assessed, the disintegration time of all samples also proved satisfactory, as all tablets had completely disintegrated within 14 Seconds as shown in (Table 4).

(iv). Infrared (IR)

The matching of the product's IR data against *Amoxicillin trihydrat and Lithium Clavulanate (BPCRS)* IR data were obtained more than 95 %. Therefore all products are comply regards to the IR matching test.

(v). Antimicrobial Susceptibility (Potency) Test

Based on the Antibiotics-Microbial Assays (USP 31)[11] we performed the assay for the drug component of Amoxicillin Clavulanic acid 500 mg/125 mg. Cylinder-plate Assay method was performed for the samples and standards. The

results as shown in the (Tables 7, 8 and 9).

Table 7. *Zone of Inhibition of Samples.*

Product Name	Zone of Inhibition against avg.(mm) Escherichi coli	Zone of Inhibition against avg.(mm) Staphyl. aureus
GSKU	26.62	29.41
GSKT	**28.47**	29.74
GSKG	26.81	**30.10**
GSKI	26.79	29.06
GSKM	27.29	29.87

* Concentration of Amox./Clav. [*0.02µg/0.005µg*] (*20 µL*)

Table 8. *Zone of inhibition of standard.*

Well Number	Zone of Inhibition against avg.(mm) Escherichia coli	Zone of Inhibition against avg.(mm) Staphyl. aureus
1	28.92	34.34
2	28.19	35.75
3	30.40	35.09
4	30.11	36.04
Average	29.40	35.30

* Concentration of Amox./Clav. [*0.02µg/0.005µg*] (*20 µL*)

Table 9. *Mean difference from the standards.*

Well Number	Difference against (mm) Escherichia coli	Difference against (mm) Staphy. aureus
GSKU	**2.78**	5.89
GSKT	0.93	5.56
GSKG	2.59	5.20
GSKI	2.61	**6.24**
GSKM	2.11	5.43

* Concentration of Amox./Clav. [*0.02µg/0.005µg*] (*20 µL*)

A clear zone of inhibition against both strains was observed. By comparing the width of *Escherichia coli* strains zone which has less zone width than that of the *Staphylococcus aureus* strains zone. By looking to the inhibitory activity of five products as shown in in (Table 7), the product that made by GSK in United Kingdom (GSKU) has the lowest inhibitory activity (26.62 mm) while the product that made in Turkey (GSKT) has highest inhibitory activity (28.47 mm) against *Escherichia coli*, moreover the product that made in Ireland has the lower inhibitory activity (29.06 mm), while product that made in Greek has the higher inhibitory activity (30.10 mm) against *Staphylococcus aureus*.

3.2. Discussion

The results presented in (Tables 4, 5 and 6) indicate that all the analyzed drugs attain standards of quality recommended by official compendia United states Pharmacopeia (USP), British pharmacopeia (BP) and European Pharmacopoeia (Ph. Eur.) [11, 12, 23]. Since it is common for drug tablets to vary in weight, mechanical resistance and disintegration characteristics (besides the design, thickness, diameter and size specific to each drug), these properties must be controlled during manufacturing, to ensure the expected appearance and therapeutic efficacy of the product. The assay of uniformity of mass is used to check homogeneity among the units of the sampled batch. Tablets of different weights may differ in quality parameters, including the content of active ingredient [24, 25].

Tablets are also subject to mechanical shocks during production, packing, storage, transportation, distribution and handling. For this reason, they should possess a certain level of mechanical resistance. High friability (i.e., low capacity to withstand friction) means that the drug is more likely to suffer mechanical erosion, which may cause loss of the active ingredient and thus compromise its efficacy. Hardness is related to friability, but also to disintegration and dissolution speed. A very hard tablet may exhibit an increased dissolution time [24-27].

As shown in (Table 4), all the products were approved in respect of their hardness and thickness. The physical assay on disintegration is related to the capacity of solid pharmaceutical forms to release their active ingredients, because before their solubalization the tablets must disintegrate into small particles, increasing the contact surface with the dissolution medium and favoring absorption and bioavailability of the drug [27, 28].

The results of dosage assays presented in (Table 5) showed that the average content of Amox. and Clav. among the analyzed products ranged from 90.0 % to 120.0 %. Product made in Ireland showed the lowest content of Amoxicillin, while Product made in Greek showed the lowest content of Clavulanate, since its average content was 99.44 %, this

deviation still maintained the drug content within the interval of 90.0 % – 120.0 % (United states Pharmacopeia) [11].

The dissolution study may be performed by collecting only one aliquot from the bath after 30 minutes, in which not less than 80 % and 85 % of the Clavulanate and Amoxicillin, respectively must be dissolved in the dissolution medium after this interval.

This reinforces the importance of assessing whole dissolution profiles in order to determine pharmaceutical equivalence, as well as in routine quality control. Despite the great advances in the last decade, these results confirm the need for tighter legislation and inspection regarding the quality drugs already on the market, which when implemented will further enhance the quality of drugs available in the Libyan market, besides increasing the availability of drugs from various sources.

All drugs were approved with regard to their disintegration time were (10.20 - 13.15 sec.) and the product made in Malta (GSKM) has the lowest RSD % (0.74% and 0.35%) of weight uniformity and tablet thickness, respectively, as shown in (Tables 4 and 6).

The safety and efficacy of drug was determined by means of content assay and microbial susceptibility test. The amount of Amoxicillin and Clavulanate in different products was between 90.0 % - 120.0 % that make it sure that the amount of active ingredient in each product complies the pharmacopeial limits. Whereas the effectiveness is confirmed by the inhibitory activity of five products against both strains that were better or similar to that of product made in country of origin GSKU.

4. Conclusion

As a Conclusions all tested products of same brand of Augmentin (625 mg) tablets manufactured by same company in different countries, were complied with the specific requirements for quality control tests of pharmcobias [11, 12], namely, the uniformity of weight of tablets, disintegration, dissolution, assay and anti-microbial potency.

This project has been carried out to conduct a comparison of various Augmentin tablet (625 mg) manufactured by same company in different countries by using non official and official methods (United states Pharmacopeia, British pharmacopeia, and European Pharmacopoeia [11, 12, 23]. By looking to the analytical techniques that are used in the evaluation these products in our project it has been found that all products are comply with the specifications for content (90.0 % - 120.0 %). and dissolution test not less than 80 % and 85 % of the Clavulanate and Amoxicillin, respectively. All the products are comply with the limits for the hardness, uniformity of weight and thickness uniformity tests and their efficacy as (anti-microbial potency).

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