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Original Article

QUALITY OF AMOXICILLIN TRIHYDRATE/POTASSIUM CLAVULANATE TABLETS COMMERCIALLY AVAILABLE IN LIBYAN PHARMACEUTICAL MARKET

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ABSTRACT

Objective: The objective of this study was to compare the quality of the amoxicillin trihydrate/potassium clavulantae (co-clavimox) tablets those are locally available in Libyan pharmaceutical market manufactured by various pharmaceutical companies with United State Pharmacopeia (USP) standards.

Methods: The five popular brands (clavomid, augmentin, clavodar, clamoxin, and clavimox) of co-clavimox conventional tablet of 625 mg strength were chosen. The quality of commercial products was evaluated through the identification of the content of active pharmaceutical ingredients (APIs) using UV- Spectrophotometer.

Results: The results obtained showed that, the products clavomid, augmentin, and clavodar conformed to the USP standard limit for quantitative assay of active ingredients. Clamoxin passed the standard limit test with a slight deviation (<2%), while clavimox failed the test with values far below the acceptable range.

Conclusion: This study has been able to confirm that some generic brands of co-clavimox tablets available in the Libyan markets possess qualities below official recommendations. Therefore, there is an urgent need for constant monitoring of different brands of medications in the market to ensure their safety and quality.

Keywords: UV-spectrophotometer, Quality, Amoxicillin, Potassium clavulantae

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INTRODUCTION

Antibiotics are very sensitive bioactive agents have been used to treat microbial infections for more than 70 y [1, 2]. If not properly used as specified, the tendency that the organisms involved may develop resistance against them and render them less effective or ineffective [3–5]. Resistance towards the antibiotics can rapidly be promoted in cases of uses falsified or substandard antibiotic products. Falsified antibiotics are those that deliberately misrepresent their identity, composition or source. Substandard medicines are authorised therapies that fail to meet either their specifications or their quality standards, or both [6]. Both may contain high, low, or wrong active pharmaceutical ingredients (APIs) and lead to loss of income, longer hospital stays, severe infections and death [7, 8]. This has recently been observed in generic drugs related to augmentin-like medicines, containing potassium clavulanate (PC) and amoxicillin trihydrate (AT) as the active pharmaceutical ingredients [9].

AT [$C_{16}H_{19}N_3OS.3H_2O$, MW. 419.46], (fig. 1) is a semi synthetic antibiotic belongs to the broad-spectrum β-lactam penicillin, it is the most widely used penicillin in the world [10]. It is used since the 1970s to treat bacterial infections, such as mild respiratory; throat, skin, nose, urinary tract, and infections of the ears [11–14]. However, AT is susceptible to degradation by β-lactamases, and therefore, the spectrum of activity does not include bacteria which produce these enzymes [15].

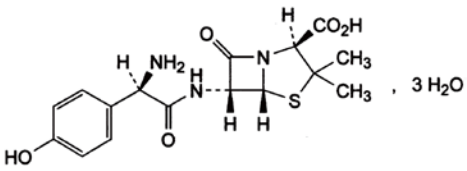

Fig. 1: Structure of amoxicllintrihydrate

On the other side, PC [$C_8H_8KNO_5$, MW. 273.3], (fig. 2) belongs to β-lactam inhibitors, which acts by preventing bacteria from destroying the action of AC and enhancing the spectrum range of AC [16, 17].

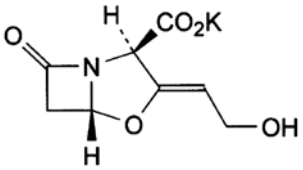

Fig. 2: Structure of potassium clavulanate

The combination of AT and PC give amoxicillin trihydrate/potassium clavulanate product (co-clavimox), which is the most successful antibiotic of the use of β-lactam antibiotics [13]. Co-amoxiclavis available in tablets, injectable, powder for reconstitution as suspension and oral solid dosage form. Although they are often considered 'twin drugs', they are different both in terms of safety profile and antimicrobial properties [18]. These two antibiotics act synergistically to produce the desired therapeutic effect and the efficiency depends on content of the active moiety in these dosage forms [9].

There are many and various analytical methods previously reported for assay of co-clavimox tablets which includes thin layer chromatography (TLC) [19-22], ultraviolet (UV) spectrophotometry [23, 24], titration [25], high-performance liquid chromatography (HPLC) [26–29], capillary electrophoresis (CE) [30], and infrared spectroscopy (IR) [31], in both British Pharmacopoeia (B. P) and United States Pharmacopoeia (U. S. P). Among then, HPLC is recommended for the analysis of co-clavimoxin pure forms and pharmaceutical preparations. However, this technique possesses some disadvantages such as requires high-cost equipment and analytical columns, requires high expertise skills to operate, makes use of large volumes of solvents as mobile phase, and it is a method of high maintenance cost. In addition, this method can be harmful to

the environment, since in most procedures that uses HPLC, was use toxic organic solvents, such as methanol and acetonitrile, as mobile phases [32, 33]. Recently, methodologies based on spectral analysis using UV radiation have experienced an amazing development and have been widely applied in various fields such as agricultural, food, pharmaceutical, and environmental sciences [34]. It allows the determination of very low concentrations of compound and the use of very small amount of sample, and at the same time to minimize the cost and time of the analysis. Therefore, the objective of this study was to evaluate the purity of some selected brands of co-clamimox tablets containing AT-500 mg and PC-125 mg those are available in Libyan Pharmaceutical Market susing the UV-spectrophotometric method.

MATERIALS AND METHODS

Sample collection

Five different commercial brands of co-climax tablets that contained AT500-mg and PC-125 mg were purchased from local pharmacies and were within the stated expiry date on pack (table 1).

Table 1: Brands of commercial co-clavimox tablets selected for this study

No.	Trade name	Manufacturer	Expire date
1	Clavimox	Pharco Pharmaceuticals, Egypt	12/4/2024
2	Clavomid	Remedica Ltd, Cyprus	17/11/2025
3	Clavodar	Dar AlDawa development and investment Co. Ltd, Jordan	18/6/2024
4	Clamoxin	Beloco Pharma, India	17/8/2024
5	Augmentin	GlaxoSmithk Ltd, Irland	23/8/2024

Reagents

The following regents were used in this study: AT 98.64% (analytical standard) from HiMedia Laboratories Pvt. Ltd (Maharashtra, India), PC 99.7% (analytical standard) from Vardhman Life Sciences Pvt. Ltd, (Maharashtra, India), and used without any further purification or treatment. Distilled water was generated in the laboratory at the Faculty of Pharmacy, Omer Al-Mukhtar University, Al-Bayda, Libya.

Apparatus

Tools used in this study were a thermo scientific genesys 10 series UV-Visible spectrophotometer loaded with a high-intensity xenon lamb and of a wavelength ranges from 190 to 110 nm, analytical balance (Sartorius AG) and ultrasonicator from Branson Ultrasonics Corporation (Danbury, CT, USA).

Preparation of AT and PC standard solutions

The preparation of standards and references solutions were done by the method described by Rajinder [15] with slight modification. A stock solutions of AT (9.536×10^{-3} M) and PC (7.318×10^{-3} M) were prepared by dissolving 400 and 200 mg AT and PC in 100 ml volumetric flasks with distilled water. These stock solutions were used to prepare the reference solutions by suitable dilutions with distilled water.

Preparation of AT and PC reference solutions

Aliquots of stock solution 0.10, 0.20, 0.30, 0.40 and 0.50 ml were transferred into a set of 10 ml volumetric flasks and volumes were completed to the mark with distilled water to produce solutions in the concentration range 9.536×10^{-5}–4.768×10^{-4} and 7.318×10^{-5}–3.959×10^{-4}Mfor AT and PC, respectively. Calibration graphs were constructed by plotting absorbance against the concentration of AT and PC.

Preparation of samples solutions

One tablet (claiming 625 mg) from each brand of co-clavimox (1–5) was weighed and finely powdered with a mortar and pestle. A quantity of the powder equivalent to 125 mg of PC and 500 mg AT of each brand of co-clavimoxwas dissolved in 100 ml volumetric flask with distilled water (Stock solution). This solution was filtered through Whatman No. 1 paper. Then, 0.30 ml of AT and 0.5 ml of PC were diluted to 10.0 ml with distilled water. Aliquots of these solutions were used for analysis [35].

Determination of wavelength maximum absorption (λ_{max})

A suitable wavelengths were required for the determination of AT and PC. The appropriate wavelengths for the determination of AT and PC were determined by wavelength scanning over the range 200-400 nm with a Genesy 10 series spectrophotometer.

Linearity and range

Linearity was studied by diluting stock standard solutions of AT and PC with distilled water to give a concentrations range of 9.536×10^{-5}–4.768×10^{-4} and 7.318×10^{-5}–3.959×10^{-4} Mfor AT and PC, respectively. The linearity was evaluated by linear regression analysis, which was calculated by the least square regression analysis [36, 37]. Calibration curves of absorbance vs. concentration were plotted and regression line equations were determined. The range of solution has been decided according to statistical analysis of regression equation.

Statistical analysis

All the collected data was treated in Microsoft office excel 2013 and the mean rates of AT and PC concentrations in different samples were compared using the student test (the T test). This test was used within a sill significance of 5% to express the means comparison of samples under same conservation conditions.

RESULTS AND DISCUSSION

Estimation of detection wavelength (λ_{max})

It was found that the absorption maximum (λ_{max}) of AT and PC in distilled water were observed at 282 nm and 294 nm, respectively (fig. 3), which are in good agreement with the literature values of a maximum between 271–313 nm [15, 37].

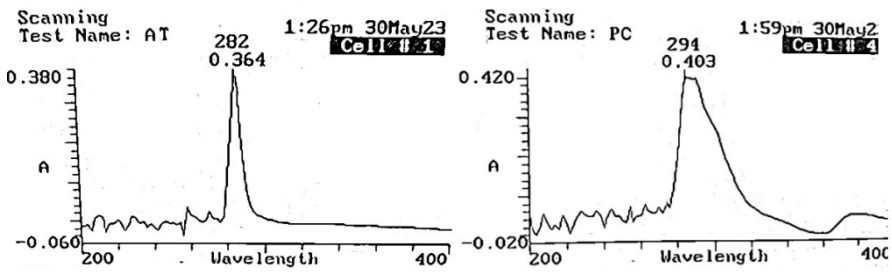

Fig. 3: UV-spectrum showing absorption maximum of AT and PC

Preparation of AT and PC calibration curves

Five different reference solutions of AC (9.536 x 10^{-5}, 1.907 x 10^{-4}, 2.861 x 10^{-4}, 3.814 x 10^{-4}, 4.768 x 10^{-4} mol/l) and PC (7.318 x 10^{-5}, 1.464 x 10^{-4}, 2.195 x 10^{-4}, 2.927 x 10^{-4}, 3.959 x 10^{-4} mol/l) were taken and the absorbances of these solutions were measured against distilled water as blank at a wavelength of 282 nm and 294 nm for AT and PC, respectively (table 2). Calibration curves of AT and PC were constructed by plotting concentration versus absorbance and regression equations were calculated (fig. 4).

Determination results linearity calibration curves

Calibration curves obtained were evaluated by its correlation coefficients (R^2). Values of R^2 close to 1 indicate a stronger linear relationship between x and y [20]. In this study, the absorbance of AT and PC solutions in the ranges of 9.536 x 10^{-5} to 4.768 x 10^{-4} and 7.318 x 10^{-5} to 3.959 x 10^{-4} mol/l were linear with correlation coefficients (R^2) of 0.999 and 0.997, respectively.

Table 2: Data for the standard curves of AT and PC

Reference solutions	No.	Concentration (mole/l)	Absorbance measured (mean±SD)
	1	9.536 x 10^{-5}	0.159±0.0002
AT	2	1.907 x 10^{-4}	0.312±0.0002
	3	2.861 x 10^{-4}	0.467±0.0007
	4	3.814 x 10^{-4}	0.642±0.0008
	5	4.768 x 10^{-4}	0.801±0.0010
	1	7.318 x 10^{-5}	0.107±0.0001
PC	2	1.464 x 10^{-4}	0.267±0.0002
	3	2.195 x 10^{-4}	0.421±0.0005
	4	2.927 x 10^{-4}	0.571±0.0007
	5	3.959 x 10^{-4}	0.743±0.0009

SD-Standard deviation; all the values are presented as mean±SD, n = 3

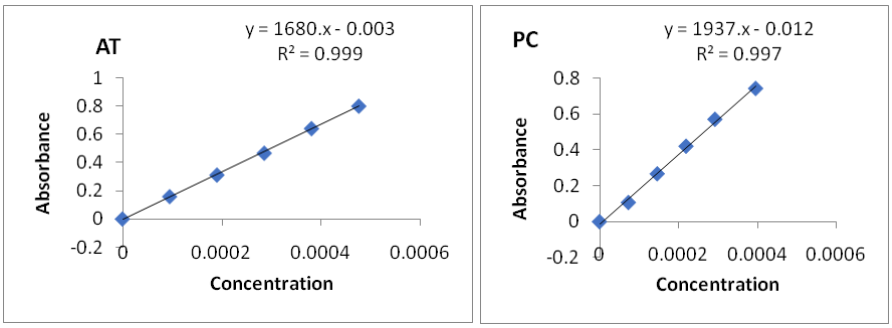

Fig. 4: Calibrations curves of AT and PC reference solutions

Quantitative analysis of Co-amoxiclv marketed products

The absorbances of the AT and PC in the five different samples of co-clavimox tablets (clavimox, clavomid, clavodar, clamoxin and augmentin) were analyzed at a wavelength of 282 and 294 nm, respectively, and the results obtained with spectra shown in fig. 5, 6.

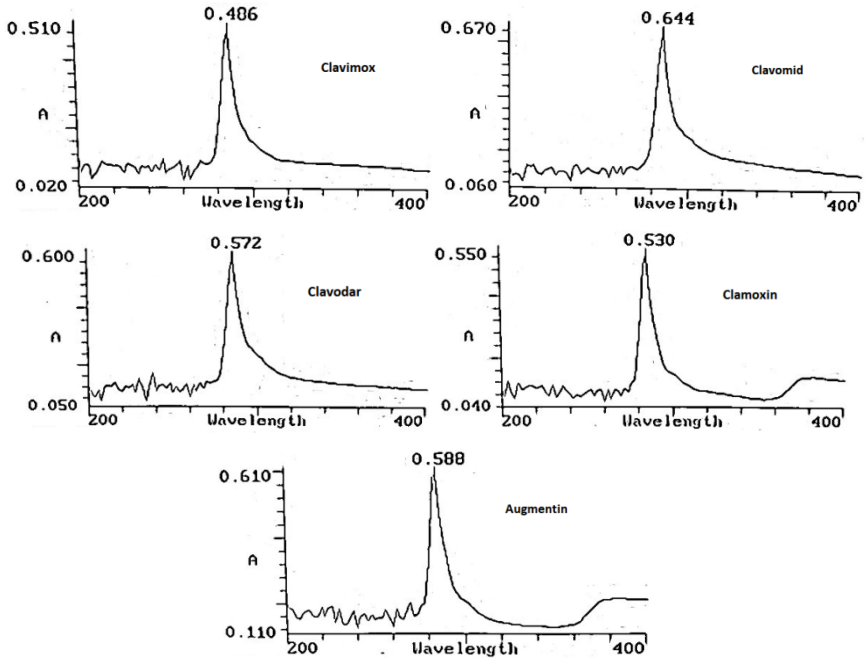

Fig. 5: UV absorbance spectra of AT in the five brands of co-clavimox tablets at 282 nm

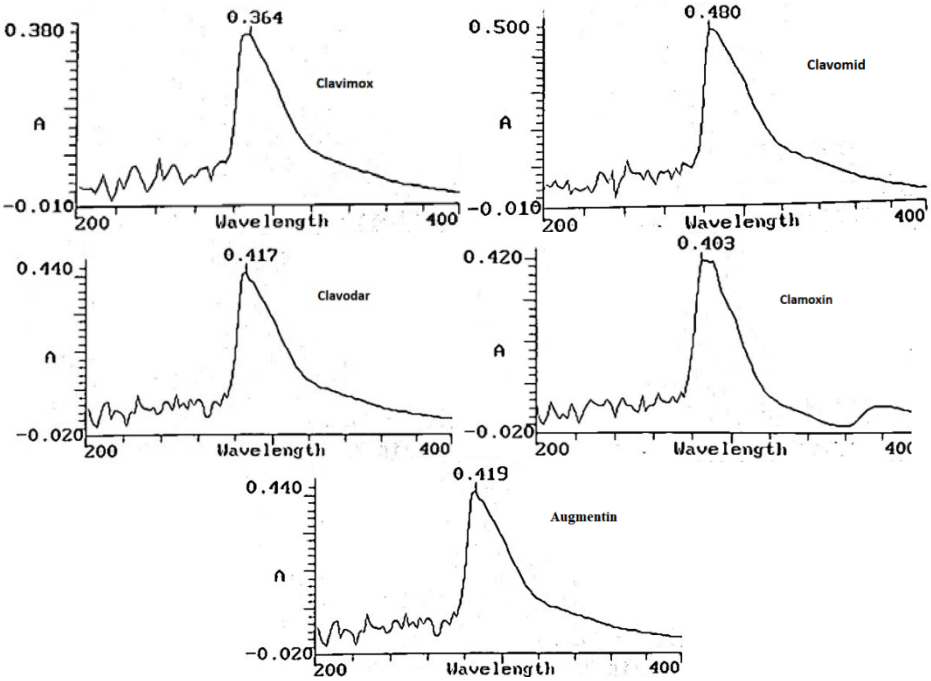

Fig. 6: UV absorbance spectra of PC in the five brands of co-clavimox tablets at 294 nm

The results of the quantitative analysis five brands of the co-clavimox tablet were expressed as a percent of drug present within tablets and are shown in table 3. Amongst the six brands tested, clavomid a product of Remedica Ltd company (Cyprus) exhibited the highest concentration of AT than other products as contained the equivalent of 107.6% AT. The lowest concentration was observed in clavimox, a product of Pharco Pharmaceuticals Company (Egypt) that contained the equivalent of 81.3% AT. However, the recorded concentrations of AT within tablets were decreased in the order of: Clavomid (Remedica Ltd, Cyprus, 107.6%)>augmentin (GlaxoSmithk Ltd, Irland, 98.3%)>clavodar (Dar Al-Dawa development and investment Co. Ltd, Jordan, 95.3%)>clamoxin (Beloco Pharma, India, 88.6%)>clavimox (Pharmaceuticals, Egypt, 81.3%). Statistically, clavimox exhibited lower concentration of AT than other drugs ($p<0.05$), but the mean differences among the other drugs were not significantly ($p<0.05$) different. According to USP–NF [38] co-clavimox tablets should contained AT and PC within 90%–120% of the labeled amounts. In comparison with USP-NF ranges, three brands contained acceptable amounts of active ingredients; one brand passed the standard limit test with a slight deviation (<2%), while the last brand failed the test with values far below the acceptable range.

Table 3: Content of AT and PC in the five different brands of co-clavimox tablets

	Brand name	Absorbance (mean±SD)	Amount found (mean±SD, mg	Label claim (mg)	Potency (%)
AT	Clavimox	0.486±0.0003	406.6±1.76	500	81.3
	Clavomid	0.644±0.0006	537.9±3.42	500	107.6
	Clavodar	0.572±0.0003	476.4±2.87	500	95.3
	Clamoxin	0.530±0.0005	443.2±1.76	500	88.6
	Augmentin	0.588±0.0005	491.4±2.87	500	98.3
PC	Clavimox	0.364±0.0002	106.1±0.0002	125	84.9
	Clavomid	0.480±0.0004	138.8±0.0004	125	111.1
	Clavodar	0.417±0.0002	121.1±0.0003	125	96.8
	Clamoxin	0.403±0.0001	117.1±0.0003	125	93.7
	Augmentin	0.419±0.0003	121.6±0.0003	125	97.3

SD-Standard deviation; all the values are presented as mean±SD, n = 3

On the other hand, the highest concentration (111.1%) of PC was observed in clavomid (Cyprus), whereas lowest concentration (84.9%) observed in clavimox (Egypt). The overall results of concentration of PC amongst the tested drugs were decreased in the order of: clavomid (111.1%)>augmentin (97.3%)>clavodar (96.8%)>Clamoxin (93.3%)>Clavimox (84.9%). Statistically, clavimox exhibited lower concentration of PC than other drugs ($p<0.05$), but, there were no statistically significant differences ($p<0.05$) in mean values in between clavomid, augmentin, clavodar and clamoxin, respectively. In comparison with USP-NF range for assay of tablets, all the studied drugs contained PC within 90%–120% ranges except clavimox with value below the acceptable range.

This study indicated that the product clavimox from Pharco Pharmaceuticals Company (Egypt) did not comply with official standards by having little strength. This brand, when used in therapy can cause therapeutic failure and hence leading to drug resistance. Thus, more efforts need to be done to control the supply of substandard drugs, which have major economic and health effects.

Based on the finding of this study, UV spectroscopy is a simple, low cost, reproducible and accurate method which is suitable for analysis of potassium clavulantae and amoxicillin trihydrate in pharmaceutical formulations. There are several possible limitations in this study which can be improved in future research. First, there is a lack of prior studies for the analysis of potassium clavulantae and amoxicillin

trihydrate using UV spectroscopy thus; there is a need of further studies to assess the quality of co-clavimox using UV spectroscopy. In addition, the method employed for this study requires validation in future study in order to verify the analytical method for routine quality control test on marketed pharmaceutical formulation.

CONCLUSION

The product clavimox from Pharco Pharmaceuticals Company (Egypt) did not comply with official standard (90–120% limits for content). The recorded concentrations of AT within tablets were, clavomid 107.6% (Cyprus), augmentin 93.3% (Irland), clavodar 95.3% (Jordan), clamoxin 88.6% (India), and clavimox 81.3% (Egypt). Whereas the recorded concentrations of PC, clavomid (111.1%), augmentin (97.3%), clavodar (96.8%), Clamoxin (93.3%), and Clavimox (84.9%).

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AUTHORS CONTRIBUTIONS

Both authors have contributed equally.

CONFLICTS OF INTERESTS

Declared none

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