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In-vitro quality evaluation of different products of amoxicillin-clavulanate potassium tablets

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ABSTRACT

Amoxicillin- clavulanate potassium is a broad spectrum antibiotic used in the management of most bacterial infections. World-wide, it is manufactured and marketed by different companies. The innovator brand, Augmentin, is expensive, hence the need to substitute them with much cheaper generic brands. Moreover, the quality of different products of the combination is not guaranteed. The object of this study was to evaluate the quality of five common products of amoxicillin-clavulanate potassium 625mg tablets marketed in Gondar town. Assessment of their quality were done by the evaluation of the physicochemical characteristics such as uniformity of weight, thickness, diameter, friability, hardness, disintegration time and assay of the products against pharmacopoeial standards and in comparison with the innovator brand. All branded tablets met the standards for acceptance. All brands have the weight uniformity, thickness and diameter within the specification. However, tablets from B2 & B3 have a significant difference in thickness with the innovator; and all brands have a significantly higher diameter than the innovator. All brand tablets have sufficient crushing strength and TS. However, B2 has higher TS, and B4 has lower TS than the innovator. All brand tablets have less than 1% friability. All tablets contain Amoxicillin and Clavulanate potassium within the stated standard range of 90-110%. However, B1 is with the highest, whereas B5 is with the lowest content. In conclusion, all the brands met the minimum requirements of the specifications in the standards. Moreover, there was no extended deviation between the innovator and other brands under investigation in many of the parameters.

Key Word: Amoxicillin, Clavulanic acid, Augmentin, Brands, Innovator, Quality evaluation.

INTRODUCTION

Amoxicillin belongs to the class of medications called penicillin-like antibiotics. The penicillins belong to the beta-lactam group of antibiotics[1], which are the dominant class of agents currently used for the chemotherapy of bacterial infections worldwide. Amoxicillin acts by inhibiting the synthesis of bacterial cell walls[2]. It inhibits cross-linkage between the linear peptidoglycan polymer chains that make up a major component of the cell wall of Gram-positive bacteria[3]. It is usually the drug of choice within the class because it is better absorbed following oral administration and it is resistant to gastric acid[4].

Amoxicillin (Fig.1) is susceptible to degradation by beta-lactamase-producing bacteria, and so may be given with Clavulanic acid to decrease its susceptibility[5]. Clavulanic acid (Fig.2), a β-lactamase inhibitor[6], is added to amoxicillin to inhibit β-lactamase and increase the anti-bacterial effect of amoxicillin. It is, however a less potent antibacterial agent as compared to amoxicillin[6]. Cla-vulanic acid has a similar structure to the beta-lactam antibiotics but binds irreversibly to the beta-lactamase enzymes[7]. Amoxicillin and Clavulanic acid combinations are available in oral solid dosage form, powder for reconstitution as suspension and injectable. These two drugs act synergistically to produce the desired therapeutic effect. Their potency depends on the content of the active moiety in these dosage forms[5].

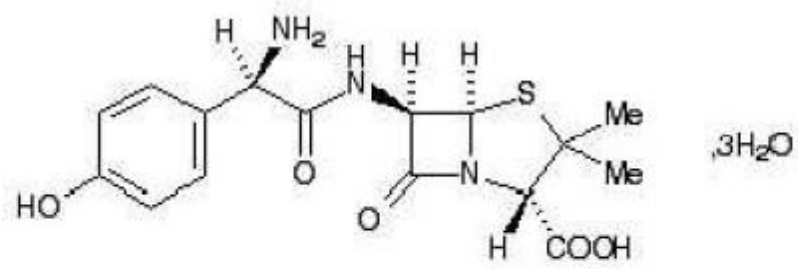

Fig: 1. Amoxycillin trihydrate

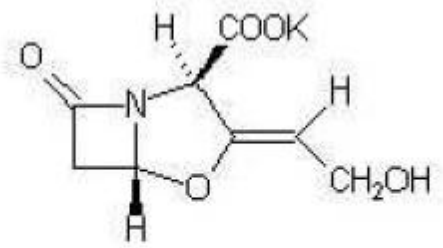

Fig: 2. Potassium clavulanate (derivative of Clavulanic acid)

The combination of amoxicillin with the β-lactamase inhibitor, clavulanic acid (clavulanate potassium) has, for over two decades, effectively extended the spectrum of activity of the semi-synthetic oral aminopenicillin to include β-lactamase-producing, penicillin resistant pathogens, in an era of rapidly developing antimicrobial resistance[8]. Amoxicillin/clavulanic acid is a widely used oral therapy that is effective in the treatment of the most common infections encountered in general practice[9, 10]. It is now most commonly used for the empirical treatment of bacterial respiratory tract infections and acute otitis media[11]. This combination is also used as a broad spectrum antibiotic for the treatment of a wide range of bacterial infections, including upper and lower respiratory tract infections and infections of the skin and soft tissue structures[5].

The introduction of generic drug product from multiple sources into the health care delivery system of many developing countries was aimed at improving the overall healthcare delivery systems in such countries. However, this has been accompanied by a variety of problems of which the most critical is the widespread distribution of fake and substandard drug products. The need to select one product from among several generic drug products of the same active ingredients during the course of therapy is a cause of concern to a healthcare practitioner. The first stage in ascertaining the therapeutic equivalence of any drug product involves ascertaining the chemical

and biopharmaceutical equivalence of such drug products[12].

Drug products that are chemically and biopharmaceutically equivalent must be identical in strength, quality, purity as well as content uniformity, disintegration and dissolution rates[13]. The need to ensure that the generic and branded drug products are pharmaceutically and therapeutically equivalent cannot be over emphasized. Variable clinical response in the same dosage form of a drug product supplied by different manufacturers has been reported; therapeutic inequivalences have been reported from the use of some generic brands of drug products such as tolbutamide[14, 15].

Therapeutic equivalence of medicines is determined through the evaluation of the chemical and biopharmaceutical equivalence[12]. The medicines must be identical in strength, quality, and purity in the same dosage form for the same route of administration[16, 17]. Dissolution profile of oral medications is of great importance: significant variation within the generics is a pointer to deficiency in drug formulation and the delivery system which can ultimately affect the therapeutic effect of the medicine. Dissolution test is known to be an important parameter in predicting the *in-vivo* bioavailability of most oral preparation [17, 18].

Antibiotics are very sensitive medicines and are used in the management of microbial infections. If not properly used as specified, the tendency that the microbes involved may develop resistance against them and render them ineffective is very high. Resistance towards the medicines can equally be developed in cases related to fake antibiotic products, where they are under dosed. This has recently been observed in generic drugs related to Augmentin-like medicines, containing amoxicillin and clavulanic acid and it's derivatives as the active ingredients[19]: primary reason for embarking on this study.

The present study

Medicines must be safe, effective and of acceptable quality and should be used rationally in order to produce the desired effect. They can be dangerous if there is no adequate control over their manufacture, storage and distribution or their use by the patient. During the past few decades, tremendous advances have been made in pharmaceutical technology and science. As a result, a large number of preventive and curative medicines are now available to fight diseases. Similarly, sophisticated and highly sensitive methods have been developed to ensure the quality of drugs. Unfortunately, however, despite all the advances made, concern about the quality of drugs has not abated [20].

Drug quality is currently receiving renewed international attention[21]. Over the past decade, there has been an increase in public awareness of the existence of counterfeit and substandard drugs, which have been increasingly reported in developing countries where drug regulations are ineffective. Although practically all types of pharmaceutical products have been shown to be involved, the existing data suggest that anti-infectious agents, particularly antibiotics and antiparasitic agents are the most counterfeited products in developing countries[22, 23].

Patients in Ethiopia commonly complain over the efficacy towards some brand of Amoxicillin-Clavulanate tablet products and they are rushing to more expensive European brands instead of another country products. Frequent observation of therapeutic failures of medicinal products, especially the generics necessitates regular review and study of medicine circulating in the Ethiopian drug market and developing countries at large. Moreover, the perception of the people among different brands has created an ambiguity even if they are expected to contain the same active ingredient. Hence, the objective of this study is to assess and compare the physicochemical properties of five products of amoxicillin-clavulanate tablets available for use in Gondar town, using known compendia.

METHODS AND MATERIALS

Materials

Five brand products of Amoxicillin/Clavulanate 625 mg tablets (Coded as B1, B2, B3, B4 and B5) were purchased from reputable pharmacies in Gondar town. B1 is the innovator brand known as Augmentin. It was used as a standard to compare the other four brands with it. The study was performed within the three fourth expiration dates of the products. Freshly prepared distilled water was used at every step of the project where necessary. All the reagents and the buffer used were analytical grades.

Methods

The experimental study design was conducted based on BP and USP monographs. Five common brand products of Amoxicillin/Clavulanate 625 mg tablets available in different drug retail outlets in Gondar town were taken by simple random sampling technique. Compendial and non-compendial tests were performed to assess the quality of these products against pharmacopoeial standards and also in comparison with the innovator brand (Augmentin). These tests include weight uniformity, thickness, diameter, hardness (crushing strength), tensile strength, friability, disintegration time and assay.

Weight of tablets

Twenty tablets were randomly selected from each batch and assessed gravimetrically on an individual basis using an analytical balance (Mettler Toledo, PR 203, Switzerland). The mean weight as well as standard deviation was calculated.

Thickness and Diameter of tablets

The thicknesses and diameter of the tablets were measured using sliding caliper scale (Nippon Sokutei, Japan). The results were expressed as the mean of three determinations.

Crushing strength

The load required to break the tablet (crushing strength) at room temperature into two equal halves was determined by the application of a diametrical force using a hardness tester (Schleuniger, 2E/205, Switzerland). The results were expressed as the mean of three determinations.

Tensile strength

The tensile strengths (*T*) of the normal tablets were determined at room temperature by diametrical compression using a Schleuniger hardness tester (Schleuniger, 2E/205, Switzerland) and by applying the equation:

$T = 2F/\pi dt$ (2.11)

Where, *T* is the tensile strength of the tablet (kg/cm^2), *F* is the load (MN) needed to cause fracture, *d* is the tablet diameter (m) and *t* is the thickness (m). All results were expressed as the mean of triplicate determinations.

Friability testing

To evaluate the friability of the tablets from each batch, ten intact tablets were randomly selected, dedusted and weighed. The tablets were then placed in an Erweka Friabilator (ERWEKA type TAR-20, Germany) and subjected to its tumbling actions at 25 rpm for 4 min. Afterwards, the tablets were once again dedusted and reweighed to determine the percentage loss of weight.

Disintegration tests

Six tablets from each batch were tested for disintegration times in distilled water at 37 ± 2 °C using a Disintegration Apparatus (CALEVA, G.B. Caleva Ltd., UK) USP,NF 27/30. The disintegration time was taken to be the time at which no granule of any tablet was left on the meshes of the apparatus[24].

Assay of the Tablets

Determination of Amoxicillin and clavulanate Potassium tablets were done by HPLC method. The assay was carried out using official monograph of Amoxicillin and clavulanate tablet as reported in the USP HPLC method, revision bulletin of March 1, 2009[25].

RESULTS AND DISCUSSION

Weight uniformity, thickness and Diameter

Uniformity of weight, thickness and diameter are indications of the amount of API in a batch of tablets. If weight, thickness or diameter of tablets in a batch varies, there will be variations in disintegration and dissolution. The compendium specification for uniformity of weight states that for tablets weighing more than 324 mg, weights of not more than two tablets should deviate from the average weight by more than 5%[24]. Weight uniformity, thickness and diameter of tablets are given in Table 1. Based on the result, the weight of the brand tablets ranges from1. 112 to 1.361g. All the brands met the compendium specification for weight uniformity. All the brands have a significant difference in weight with the innovator brand (p= 0.000). Brands B2, B3 and B5 have significantly higher, whereas B4 has significantly lower weight than the innovator.

All the tablets have a thickness and diameter ranges of 6.970 to 8.003mm and 10.233 to10. 813

mm, respectively. Comparison of the thickness of the bands shows that B4 and B5 have no significant difference with the innovator (p=0. 185 and p=0. 0682, respectively). However, B2 has a significantly lower and B3 has a significantly higher value than the innovator (p=0. 000 and p=0. 002, respectively). All the brands have a significantly higher diameter than the innovator brand.

Table 1. Weight, thicknesses and Diameter of the different Brands of Amoxicillin- Clavulanate 625mg tablets.

Brands	Weight (g) (mean ± SEM)	Thickness (mm) (mean ± SEM)	Diameter (mm) (mean ± SEM)
B1	1.153 ± 0.017	7.777 ± 0.028	10.233 ± 0.007
B2	1.361 ± 0.013	6.970 ± 0.026	10.813 ± 0.012
B3	1.187 ± 0.014	8.003 ± 0.015	10.650 ± 0.006
B4	1.112 ± 0.017	7.830 ± 0.017	10.397 ± 0.020
B5	1.218 ± 0.027	7.853 ± 0.012	± 0.007

Crushing strength, tensile strength and friability

Crushing strength and TS show the ability of tablets to withstand pressure or stress during handling, packaging and transportation. They are used to assess its resistance to permanent deformation. Furthermore, the mechanical strength of a tablet determines the disintegration time and the rate of dissolution. As the concentration of the binder increases, the mechanical strength increases [26]. The crushing strength, tensile strength and friability of the brand tablets are shown in Table 2.

The result indicates that the crushing strength and TS of the tablets range from 177.667 to 342.033N and 1.390 to 2.891 Kg/cm^2, respectively. Their comparison showed that B2 has a significantly higher TS than the innovator (p=0. 001) and; B3, B4 & B5 have a significantly lower TS than the innovator (p=0. 000, 0.004 & 0.002, respectively).

Friability is another measure of the mechanical property of tablets with compendia specification of less than 1% [25]. It is especially important because the tablet is subjected to various abrasive motions during production and use[27]. All the brands met the compendia specification for friability and there was no any significant difference with the innovator (p>0.05). This suggests that all the brands keep the tablets intact and withstand abrasive motions during handling and transportation.

Table 2. Crushing strength, Tensile strength and Friability of the different Brands of Amoxicillin-Clavulanate 625mg tablets.

Brand Code	Crushing Strength (N) (Mean ± SEM)	Tensile strength (Kg/cm^2) (Mean ± SEM)	Friability (%) (Mean ± SEM)
B1	337.833 ± 3.420	2.704 ± 0.016	0.009 ± 0.000
B2	342.033 ± 0.567	2.891 ± 0.012	0.007 ± 0.000
B3	255.100 ± 5.558	1.906 ± 0.039	0.008 ± 0.000
B4	177.667 ± 27.400	1.390 ± 0.215	0.009 ± 0.000
B5	230.600 ± 18.966	1.740 ± 0.142	± 0.000

Assay and Disintegration tests

The assay and disintegration time of the different Brands of Amoxicillin-Clavulanate 625mg tablets is depicted in Table 3. Assay of API is one quality parameter that assure the presence and content of Amoxicillin and Potassium clavulanate in the brand tablets. All the brands had contents of claimed API within the USP requirement of 90-110%. However, B1 is with the highest whereas B5 is with the lowest content. This

indicates that all the brands are manufactured under the pharmacopoeia specifications.

Disintegration is another crucial step in the release of drugs from immediate release dosage forms. The rate of disintegration is directly proportional to the rate of dissolution[28]. All the brand tablets met the pharmacopoeia DT requirements of less than 15 minutes. The DT of the brand tablets ranges from 4 to 12 minutes. This difference may result in difference in dissolution rate and release profile of the tablets. B2 and B3 have no significant difference in DT with the innovator (p= 0.482 & p= 1.00, respectively). However, B4 has a significantly shorter DT; and B5 has a significantly longer DT than B1 (p= 0.002 for both). This indicates that B4 may have high dissolution rate than B5.

Table 3. The disintegration time and assay of the different Brands of Amoxicillin-Clavulanate 625mg tablets

Brand Code	Disintegration Time (Minute) (mean ± SEM)	Amoxicillin Assay (%)	Clavulanate Potassium Assay (%)
B1	8.000 ± 0.577	101.22	99.45
B2	8.500 ± 0.289	97.76	95.66
B3	8.000 ± 0.000	98.24	95.23
B4	4.000 ± 0.000	99.35	97.04
B5	12.000 ± 0.000	94.82	94.62

CONCLUSION

The physicochemical evaluation the brands show that all of them met both the compendia and non-compendia standards for acceptance. Tablets in all brands have the weight uniformity within the specification. However, B2 & B3 have significant difference in thickness with the innovator; and all the brands have significantly higher diameter than the innovator brand.

All the brand tablets have sufficient crushing strength and TS to withstand the mechanical shocks during transportation, handling and storage of the tablets. However, B2 has higher TS and B4 has lower TS than the innovator. All the brand tablets met the pharmacopoeial specification of less than 1% friability. All the brand tablets contain Amoxicillin and Clavulanate potassium within the stated standard range of 90-110%.

In conclusion, all the brands met the minimum requirements of the specifications in the standards. Moreover, there was no extended deviation between the innovator and other brands under investigation in many of the parameters. From the data it is also possible to recommend the prescribers to reconsider brands before prescribing costly brands while there are no supportive physicochemical parameter differences.

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