Quality and *in vitro* bioequivalence evaluation of different brands of amoxicillin + clavulanic acid (500 + 62.5) mg tablets distributed in Burkina Faso

Evaluation de la qualité et de la bioéquivalence in vitro de différentes marques de comprimés d'amoxicilline + acide clavulanique (500 mg + 62,5 mg) distribuées au Burkina Faso

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Abstract
In a previous study, we reported the evaluation of the physicochemical quality and in vitro bioequivalence of different brands of amoxicillin capsules 500 mg marketed in Burkina Faso. As our goal was to document the quality and biopharmaceutical performance of essential antibiotics marketed in resource-limited countries, we investigated here, the interchangeability with the originator of five brands of amoxicillin + clavulanic acid (500mg+62.5mg) tablets distributed in Burkina Faso. The physicochemical quality of the different brands was first verified according to the USP monograph. The comparative evaluation of the in vitro dissolution profiles was performed in three different pH environments (1.2 - 4.5 - 6.8) using statistical calculations of the difference (f_1) and similarity (f_2) factors. All brands of amoxicillin + clavulanic acid (500mg+62.5mg) tablets, including the originator, met USP specifications for weight uniformity, identification, content and dissolution of active ingredients. However, the similarity and difference factor values showed that two generic brands (B and E) did not have similar amoxicillin dissolution profiles to the comparator product in pH 4.5 media (f_1 = 23,54 and 17.02; f_2=35.96 and 46.90, respectively). Therefore, these two products cannot be used interchangeably with the originator. The other three generic brands were similar to the originator and can therefore probably be used interchangeably.
Key words: Amoxicillin, Clavulanic acid, Tablets, Quality, Dissolution, bioequivalence.
Résumé
Dans une précédente étude, nous avons rapporté l'évaluation de la qualité physicochimique et de la bioéquivalence in vitro de différentes marques de gélules d'amoxicilline 500 mg commercialisées au Burkina Faso. Notre objectif étant de documenter la qualité et les performances biopharmaceutiques des antibiotiques essentiels commercialisés dans les pays à ressources limitées, nous avons déterminer ici l'interchangeabilité par rapport au prínceps, de cinq marques de comprimés d'amoxicilline + acide clavulanique (500 mg + 62,5 mg) distribués au Burkina Faso. La qualité physicochimique des différentes marques a été d'abord vérifiée conformément à la monographie de la pharmacopée américaine (USP). L'évaluation comparative des profils de dissolution in vitro a été effectuée dans trois milieux de pH différents (1.2 - 4.5 - 6.8) en utilisant les calculs statistiques des facteurs de différence (f1) et de similarité (f2). Toutes les marques de comprimés d'amoxicilline + acide clavulanique (500mg+62,5mg), y compris le princeps, étaient conformes aux spécifications de l'USP pour les essais d'uniformité de masse, d'identification, de teneur et de dissolution des principes actifs. Cependant, les valeurs des facteurs de similarité et de différence ont montré que deux marques génériques (B et E) n'avaient pas des profils de dissolution de l'amoxicilline similaires à ceux du produit comparateur en milieu pH 4,5 (f1 = 23,54 et 17,02 ; f2=35,96 et 46,90, respectivement). Par conséquent, ces deux produits ne peuvent donc pas être utilisés de manière interchangeable avec le princeps. Les trois autres marques génériques étaient similaires au princeps et peuvent donc probablement être utilisées de manière interchangeable.
Mots clés : Amoxicilline, Acide clavulanique, Comprimés, Qualité, Dissolution, Bioéquivalence.

1. Introduction

Amoxicillin and clavulanic acid tablets are among the most widely used antibiotics in Africa. These are formulations combining an extended spectrum β-lactam (amoxicillin) and a potent beta-lactamase inhibitor (clavulanic acid). Clavulanic acid rapidly and irreversibly inhibits most beta-lactamases produced by gram-positive and gram-negative bacteria. As a result, this combination is active on a large number of bacteria, including those resistant to beta-lactamin, whether this resistance is acquired (staphylococcus aureus, gonococcus, Haemophilus influenzae, colibacillus, Proteus mirabilis) or natural (klebsiella, Proteus vulgaris, Bacteroides fragilis). The absorption profiles of the two components of this medicine are similar. Amoxicillin is very partially transformed in the body into penicillin acid. Clavulanic acid is partially converted to low molecular weight metabolites. Amoxicillin and clavulanic acid are eliminated mainly by the kidneys [1,2].

The combination of amoxicillin + clavulanic acid is included in the WHO [3] and Burkina Faso essential medicine lists [4]. It is used in particular in certain infections of the ENT sphere, of the skin, dental, bronchopulmonary (pneumonia), digestive, renal, urinary. Often, treatment with amoxicillin + clavulanic acid is given when an infection does not respond well to treatment with amoxicillin alone (or another antibiotic) or if it is severe, at risk of complications and/or affects fragile people (pregnant women, children, the elderly or chronically ill) [1].

Many studies reported cases of generic antibiotics that are not bioequivalent to the standard innovator drugs, such as ciprofloxacin [5], amoxicillin capsules [6-9] and amoxicillin + clavulanic acid [10]. The use of substandard amoxicillin + clavulanic acid can lead to increasing their resistance by certain bacteria.

Therefore, the quality monitoring and, in particular, the evaluation of the interchangeability of the different brands of amoxicillin + clavulanic acid used in the health programs is necessary, in order to better guarantee the health of our populations.

Amoxicillin and clavulanic acid are water-soluble drugs and have BCS Class I characteristics [11]. Therefore, the comparative in vitro dissolution test can be used for the assessment of its bioequivalence [11, 12].

2. Materials and Methods

2.1. Materials

Amoxicillin trihydrate and lithium clavulanate chemical reference substances and Prednisone 10 mg tablets USP reference standard were kindly donated by United States Pharmacopeia (USP, Rockville, USA). Sodium acetate trihydrate (crystalline powder) and anhydrous acetic acid were from Carlo Erba Reagents, Val-de-Reuil, France. Potassium chloride, sodium monobasic phosphate and methanol HPLC grade (99.9%) were obtained from Sigma-Aldrich, Germany. Hydrochloric acid (37% w/w) and phosphoric acid (PANREAC, Spain), dibasic potassium phosphate and sodium hydroxide (≥ 99%w/w) were purchased from Analar NORMAPUR® (VWR Chemical, USA). 0.1N hydrochloric acid was prepared from the 37% w/w concentrated solution. Distilled water was freshly prepared in the laboratory (Water Distiller Fur Labortechnik, Germany).

2.2. Selection of samples

Six brands of amoxicillin + clavulanic acid (500mg + 125mg) tablets, with a marketing authorization in Burkina Faso [13] and available at the time of the study were collected from wholesale distributors in the city of Ouagadougou. For a given brand, a sample of one batch with at least one year of validity remaining was taken. The batches of drugs were taken at random from the sampling site, taking into account the quantities available. During all stages of the study, the collected samples were maintained under the storage conditions specified by the manufacturer.

The comparator drug selected in this study was the originator product. It is Augmentin® 500 mg/62.5 mg tablet from Glaxo Wellcome (France), which has a marketing authorization [13] and was available in Burkina Faso at the time of the study. It was selected according to the recommendations of the WHO guidance on the selection of comparators of pharmaceuticals for the assessment of equivalence of multi-source drugs [14].

2.3. Physicochemical quality assessment

All samples (including the comparator product) were subjected to quality control testing in accordance with USP 43 monograph [15]. The tests performed were uniformity of weight, disintegration, dissolution, identification and assay of the active ingredient.

The identification and assay of amoxicillin and clavulanic acid content in tablets were performed in triplicate for each sample using a high-performance liquid chromatography chain equipped with a UV-Visible diode array detector (HPLC-DAD, Agilent 1200 Infinity Series, USA). A ZORBAX SB-C18 chromatographic column (250 x 4.6 mm, 5µm) was used. The mobile phase consisted of the dihydrogenophosphate buffer mixture pH 4.2 and Methanol (5:95 v/v) at an elution rate of 1.0 mL/min. The injection volume and detection wavelength were 5.0 µL and 220 nm, respectively. Identification of the active substances was performed by comparing the retention times of the major peaks of the sample solutions with those of the solutions of the USP reference chemicals. The standard

solution consisted of 1 mg/mL of USP amoxicillin reference standard and 62.5 µg/mL of USP clavulanate lithium reference standard. This standard solution was stored at 4°C and injected within 10 hours.
The dissolution tests were carried out with the paddle method using a Sotax® AT dissolution apparatus (France). The operating conditions used are described in Table 1. The concentrations of active ingredients released at 30 minutes were determined by HPLC at 220 nm under the same conditions as the assay.

2.4. Dissolution profiles determination

The same dissolution test conditions were used to determine the dissolution profiles, with some differences described in Table 1.
As recommended for the BCS-based "biowaiver" approach, the comparative in vitro dissolution test was performed in three dissolution media, namely pH 1.2 buffer (0.1 N hydrochloric acid), pH 4.5 acetate buffer, and pH 6.8 phosphate buffer [16]. These three media were prepared according to USP 43 [15].
Samples were taken at 15, 30, 45, and 60 minutes. The volume withdrawn at each time point was immediately replaced with the same dissolution medium to keep the dissolution volume constant throughout the test.
Table 1 below details the conditions used for dissolution testing and determination of active substance release profiles. Twelve units of tablets were used for the determination of the release profile of each sample.

Table 1. Operating conditions for the dissolution test of amoxicillin + clavulanic acid (500mg+62.5mg) tablet [16, 17].

Parameters	Operating conditions for the dissolution test	Operating conditions for the determination of dissolution profiles
Dissolution medium	Distilled water	Buffers pH 1.2- 4.5 and 6.8
Temperature of the dissolution medium	37.0°C±0,5°C	37.0°C±0.5°C
Volume of dissolution medium	900 mL	900 mL
Paddle rotation speed	75 rotations per min	75 rotations per min
Sampling time		15-30-45 and 60 min
Volume of dissolution medium collected at each time	10 mL	10 mL
Number of tests	06	12

2.5. Statistical analysis and results validation

Equipment and methods were validated in accordance with USP 43 general methods [17] and ICH Q2(R1) [18] recommendations, as descripted in our recent study [9].
The chemical reference standards of amoxicillin trihydrate and lithium clavulanate from USP were used for calibration and validation of the assays.
All results are expressed as mean ± standard deviation (SD).
The USP specification for amoxicillin and clavulanic acid content is 90.0-120.0% of the labelled amount. For the dissolution test, at least 85% of the indicated amount of amoxicillin and 80% of the indicated amount of clavulanic acid must release within 30 minutes [15].
For comparative dissolution study, if both products (test and comparator) demonstrate 85% dissolution in at least 15 minutes, the profiles are considered similar [16]. If not, the difference factor f_1 and the similarity factor f_2 were calculated. A value of f_2 less than 50 and f_1 greater than 15 indicates a difference between the dissolution profiles [16, 19, 20].

3. Results

3.1. Characteristics of the samples collected

A total of six (06) samples of different brands (5 multisource drugs and one comparator) of amoxicillin + clavulanic acid (500mg+62.5mg) tablets, all of which have a marketing authorization in Burkina Faso [13], were collected. For each sample, a minimum of 96 tablets from the same batch were collected. Table 2 presents the different information on these samples.

Table 2. Information on amoxicillin + clavulanic acid samples (500mg+62.5mg) collected.

Sample code	Batch number	Country of origin	Presentation/ Packaging	Manufacturing date	Expiry Date
Comparator	RN6J	France	Aluminum blister pack of 8 tablets/box of 24 tablets	Not mentioned	11/2023
A	22688	Germany	Aluminum blister pack of 8 tablets/box of 16 tablets	08/2021	08/2023
B	911653	India	Aluminum and PVC blister pack of 8 tablets/box of 16 tablets	12/2021	11/2023
C	KM7924	Austria	Aluminum blister pack of 2 tablets/box of 16 tablets	03/2022	02/2024
D	19361019	India	Aluminum blister pack of 8 tablets/box of 16 tablets	09/2021	02/2024
E	19368002	India	Aluminum blister pack of 8 tablets/box of 16 tablets	10/2021	09/2023

3.2. Pharmaceutical quality of different brands of amoxicillin + clavulanic acid tablets

The HPLC chromatograms of a sample of amoxicillin + clavulanic acid tablets are provided in Figure 1.

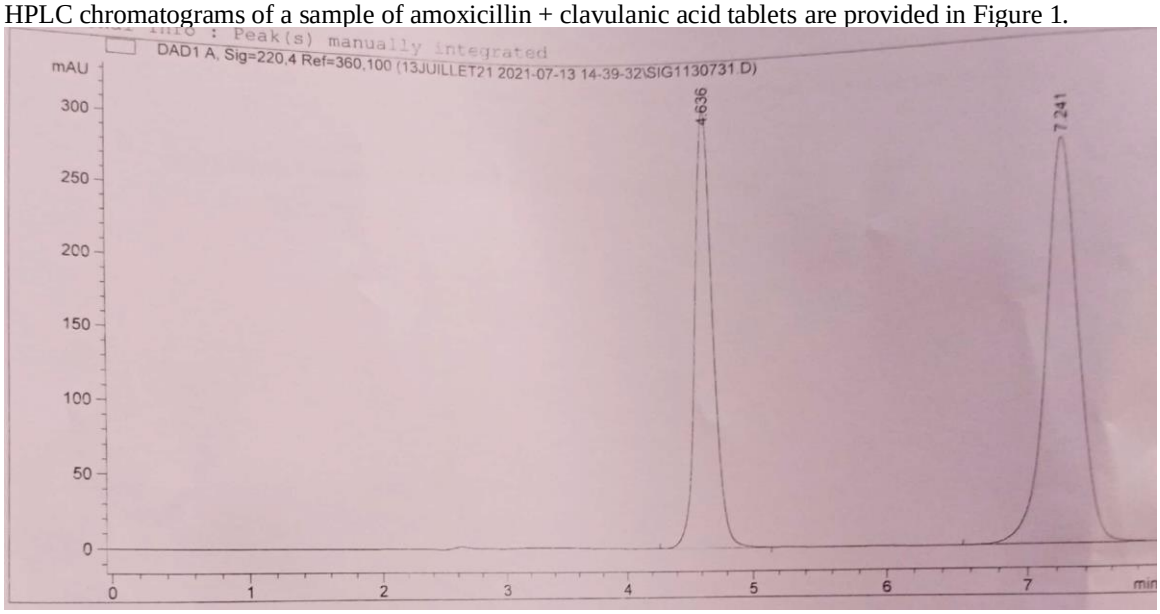

Figure 1. HPLC chromatograms of clavulanic acid and amoxicillin tablets at 220 nm.

Table 3 presents the results of the mass uniformity, content (%) and dissolution tests of the different brands of amoxicillin + clavulanic acid tablets. Each value represents the mean ± standard deviation.

Table 3. Results of pharmaceutical quality control of amoxicillin + clavulanic acid tablet samples

Sample	Mean weight (mg, Mean±SD)	Weight deviation (%)	Content (%) m/m (Mean±SD)		Dissolution in 30 min (%) m/m (Mean±SD)	
			Clavulanic acid	Amoxicillin	Clavulanic acid	Amoxicillin

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Comparator	784.75±11.29	3.00	90.59±1.31	115.05±0.02	101.48±5.11	110.13±1.53
A	877.51±9.71	3.00	102.03±1.97	112.57±0.35	95.15±3.14	108.44±0.66
B	1067.72±8.62	2.20	92.21±4.06	117.17±2,38	97,90±2,01	91.24±2.11
C	872.74±9.87	2.58	97.79±2.14	95.09±3.45	99.03±3.06	109.91±4.73
D	1064.87±8.82	1.81	91.07±2.53	115.78±0.15	97.81±1.27	100.22±1.72
E	1060.76±9.17	1.66	100.74±0.46	113.32±1.85	96.79±1.34	93.37±1.50
Specification	**-**	**≤ 5.00**	**90.00-120.00**		**≥ 80.00**	**≥ 85.00**

SD: Standard deviation

3.3. In vitro dissolution profiles of the different brands of amoxicillin + clavulanic acid tablets

Figures 2 and 3 show the comparative dissolution profiles of the different generics versus the originator.

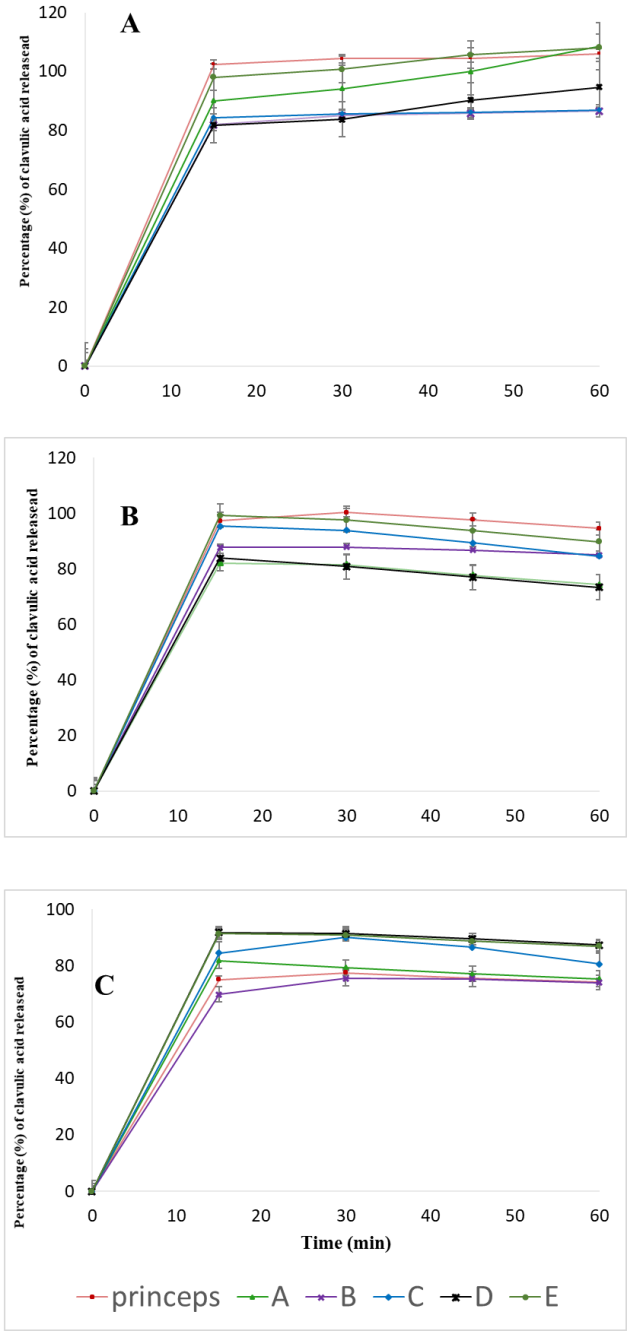

Figure 2. Clavulinic acid release profiles in pH 1.2 (A), 4.5 (B) and 6.8 (C) media from the different brands of amoxicillin+clavulanic acid (500mg + 62.5mg) tablets.

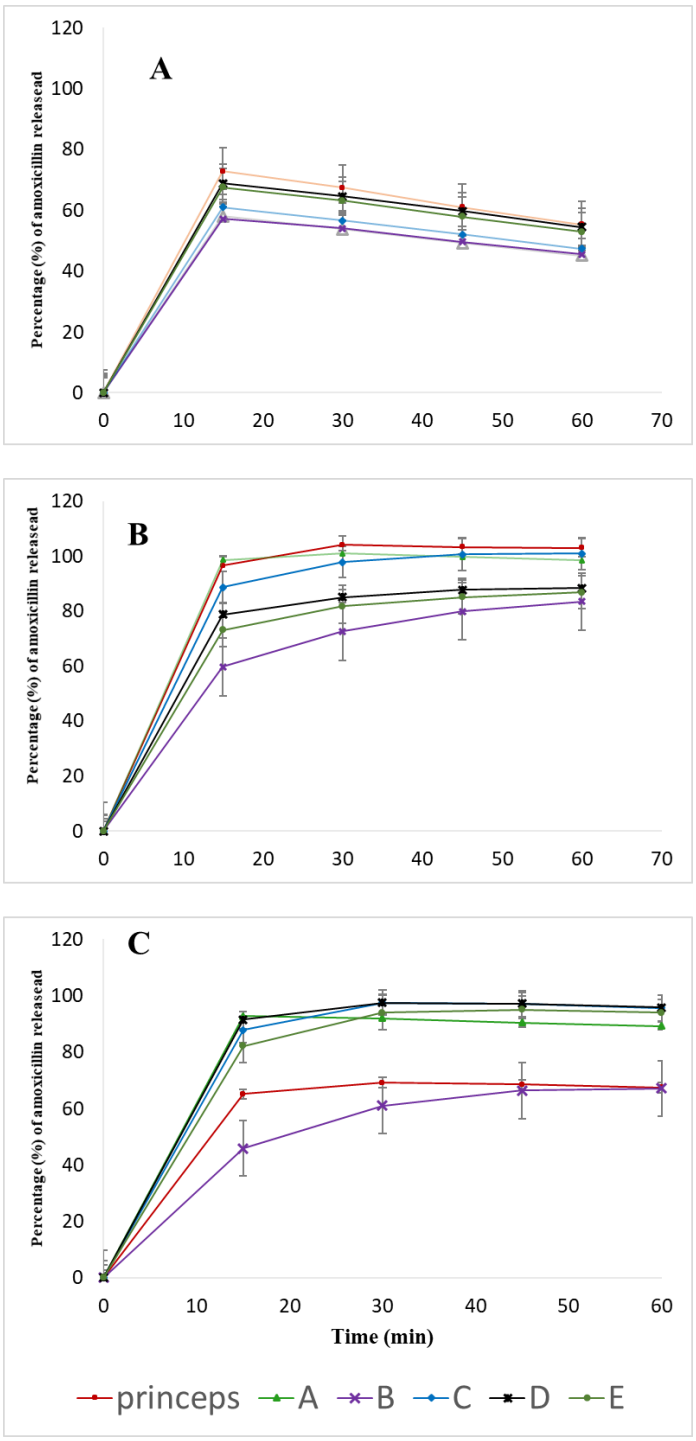

Figure 3. Amoxicillin release profiles in pH 1.2 (A), 4.5 (B) and 6.8 (C) media from the different brands of amoxicillin + clavulanic acid (500mg + 62.5mg) tablets.

3.4. In vitro dissolution profiles comparison

The results of the difference and similarity factor calculations are presented in Table 4 and 5.

Table 4. Similarity (f_2) and difference (f_1) factors for clavulanic acid release patterns.

Sample	pH 1,2		pH 4,5		pH 6,8		Similarity
	f_1	f_2	f_1	f_2	f_1	f_2	

A	NA	NA	NA	NA	8,14	64,73	Similar
B	NA	NA	NA	NA	10,12	58,22	Similar
C	NA	NA	NA	NA	10,62	59,35	Similar
D	NA	NA	NA	NA	14,32	52,95	Similar
E	NA	NA	NA	NA	14,56	53,43	Similar

NA = Not applicable

Table 5. Similarity (f_2) and difference (f_1) factors for amoxicillin release patterns.

Sample	pH 1,2		pH 4,5		pH 6,8		Similarity
	f_1	f_2	f_1	f_2	f_1	f_2	
A	13.59	54.52	NA	NA	7.49	60.04	Similar
B	14.45	55.34	23.54	35.96	3.60	79.65	Non similar
C	13.44	58.95	NA	NA	11.41	58.46	Similar
D	6.00	76.03	10.16	55.24	12.55	55.90	Similar
E	4.81	78.05	17.02	46.90	7.94	66.60	Non similar

NA = Not applicable

4. Discussion

All brands of amoxicillin + clavulanic acid tablets (500mg+62.5mg) met USP specifications for the physicochemical tests performed. The identification of active substances in the samples was done on the basis of HPLC peak retention times. The chromatograms obtained from the reference substances of amoxicillin and clavulanic acid were used as controls. Thus, the retention times of the major peaks of the samples correspond to those of the reference substances, i.e. 4.63 min ± 0.02 min for clavulanic acid and 7.19 min ± 0.08 min for amoxicillin. No difference of ±10% was observed, confirming the presence of the active substances in all samples. The analysis of the assay data shows that all samples collected, including the originator, had active ingredient contents in accordance with USP specifications (90.00 -120.00%). Finally, the 30-minute dissolution percentages of the different brands of amoxicillin + clavulanic acid tablets were also all in compliance and ranged from 91.00-110.00 for amoxicillin (≥ 85.00%) and from 95.00-101.00% (≥ 80.00%) for clavulanic acid.

Figures 2 and 3 show dissolution profiles with almost similar but not superposable shapes for all the different brands of amoxicillin + clavulanic acid tablets (500 mg + 62.5 mg). The dissolution of amoxicillin of the different products was rapid with a release of more than 85% of the labelled quantity in 15 min at pH 4.5 for 2/5 brands. The dissolution of clavulanic acid was also rapid with a release of more than 85% of the labelled amount in 15 min at pH 4.5 for all brands (6/6). This could partly explain the fact that the quality control dissolution test of this drug combination is performed in an aqueous medium (pH of approximately 5.11). In addition to the pH 4.5 medium, we note that clavulanic acid also dissolves very rapidly at pH 1.2. Overall, we note a less marked release in pH 6.8 for clavulanic acid and in pH 1.2 for amoxicillin. In our recent study on amoxicillin capsules [9], we also noted a less marked release of amoxicillin in pH 1.2 than in pH 4.5 and 6.8. As also noted concerning amoxicillin capsules, the release of amoxicillin after 60 minutes is not complete in pH 1.2, whereas in the other pH values, the active ingredient is totally released at the same time for most brands of amoxicillin + clavulanic acid tablets (500 mg + 62.5 mg).

Dissolution of clavulanic acid from the princeps was rapid with a release of more than 85% of the labeled amount within 15 min at pH 1.2 (>101.11%) and pH=4.5 (>94.49%). Clavulanic acid releases of more than 85% were also

observed within 15 minutes (when considering the data ranges), for products A, B, C, D, and E in pH 1.2 and pH 4.5 media. For all these brands, clavulanic acid is therefore considered to dissolve very rapidly since at least 85% of this active ingredient dissolved within 15 min. In these cases, the calculation of the similarity factor becomes unnecessary at these pH values. Indeed, the WHO states that if the comparator and test products dissolve very rapidly, i.e. at least 85% dissolution in 15 min or less, a profile comparison is not necessary [11]. At pH 6.8, since the comparator does not dissolve more than 85% of the labeled amount in 15 min, calculation of the similarity factor is necessary.

The same observation was made for the dissolution of amoxicillin in pH 4.5 (at least 85% of the dissolution in 15 minutes) with the originator and products A and C.

In the other cases, the difference factor (f_1) and similarity factor (f_2) were used to compare the in vitro dissolution profiles of the different brands of amoxicillin + clavulanic acid tablets (500 mg + 62.5 mg) multisource with the originator product.

The dissolution data from our study met the conditions for the application of the Fit Factor method. Indeed, the WHO recommends using data with less than 20% variance at the first time point and less than 10% variance at subsequent time points for the calculation of f_1 and f_2 [16]. This condition is met because the coefficients of variation of the release of active ingredients at the 15-minute point did not exceed 20%. For the other points, they were less than 10%.

The results show that the brands of amoxicillin + clavulanic acid tablets (500 mg + 62.5 mg) A, C and D, had similar release patterns of clavulanic acid and amoxicillin as the f_2 values were greater than 50 and the f_1 values were less than 15, regardless of the nature of the dissolution medium (Tables 4 and 5). However, for samples B and E, conforming similarity and difference factors were obtained with clavulanic acid in all pH media, while f_2 values below 50 and f_1 values above 15 were obtained for amoxicillin at pH 4.5. Thus, the latter two samples did not have similar amoxicillin dissolution profiles as the comparator product. These two products had lower and incomplete amoxicillin release rates within 60 minutes (83.41% and 86.85%, respectively). Therefore, they cannot be considered interchangeable with the originator.

We can therefore conclude that three of the five brands of multi-source amoxicillin + clavulanic acid tablets (500 mg + 62.5 mg) tested were similar to the comparator product and therefore can be used interchangeably. In a similar study, Olanrewaju et al. highlighted that out of six brands of amoxicillin + clavulanic acid tablets collected in Nigeria in 2012, one of them was not bioequivalent with the innovator brand [10].

Conclusion

Physicochemical quality and in vitro bioequivalence assessment of different brands of amoxicillin + clavulanic acid tablets (500 mg + 62.5 mg) distributed in Burkina Faso was conducted in compliance with WHO recommendations.

The results indicate the need to strengthen regulatory measures with a focus on post-marketing surveillance of pharmaceutical products. Similar evaluations should be conducted on a regular basis for all drugs used in the treatment of priority diseases in Burkina Faso.

Declaration of Competing Interest:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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