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COMPARATIVE ASSESSMENT OF THE PHYSICOCHEMICAL AND *IN-VITRO* BIOAVAILABILITY EQUIVALENCE OF CO-TRIMOXAZOLE TABLETS MARKETED IN TIGRAY, ETHIOPIA

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ABSTRACT

The availability of numerous brands of co-trimoxazole in our local market today places health professionals in a difficult situation of choice of a suitable brand or the possibility of alternative use. The aim of the study was to predict the physicochemical and *in-vitro* bioavailability equivalence of six brands of co-trimoxazole tablets marketed in Tigray, Ethiopia. Weight uniformity, friability, hardness, disintegration, assay and dissolution profile were performed using methods described in British and United State Pharmacopoeias and all these tablets passed compendial specifications. Statistical analysis (ANOVA) of thickness, weight and disintegration data showed a significant difference ($p<0.05$) between generic and innovator brands. Similarly, a significant difference was found between the mean % release of trimethoprim ($p<0.0002$) and sulfamethoxazole ($p<0.0001$) of the generic and innovator brands at the pharmacopoeia specified time, 60 min. These statistical results indicated that the brands were not equivalent with respect to their *in-vitro* release profile. All products showed a trimethoprim % release of greater than 85% within 15 min. Model independent approach of similarity factor (f_2) showed; generic brands C (f_2=33.71*)*, D (f_2=31.85*)* and E (f_2=36.33*)* were not bioequivalent with the innovator and so may probably not be used interchangeably. However, generic brands B (f_2=52.02*)* and F (f_2=77.55*)* were similar with the innovator and so may probably be used interchangeably. Results have shown that more than cost consideration and company reputation is required for day-to-day rational decision making in drug products sourcing.

INTRODUCTION: Generic drug prescribing and dispensing is frequently promoted as a means of lowering healthcare costs. The issue of bioequivalence of generic products to innovator drugs and the overwhelming proportion of substandard and counterfeit drugs in the market tends to affect this practice. Post-market monitoring, in which data about a product is collected and assessed after it had been granted marketing authorization of approved medicines has been employed to assess the quality, therapeutic effectiveness and safety of medicines. The data and information obtained could be used for product improvement, development of standards and regulations [1].

The importance of dissolution in quality assurance and regulatory science is well documented [2]. It therefore becomes apparent that sensitive and reproducible

dissolution data derived from physicochemically and hydrodynamically defined conditions are necessary in order to compare various *in- vitro* dissolution data and be able to use such results as a surrogate for possible *in- vivo* bioavailability, bioequivalence testing, and *in-vitro-in- vivo* correlations [3].

Though the problem is worldwide, Southeast Asia and Africa seem to be particularly plagued by counterfeited pharmaceuticals [4]. For example, a study done in Southeast Asia in 2001 showed that 38% of antimalarials on sale in pharmacies did not have any active ingredients [5]. In a WHO survey, 20-90% of antimalarial [6] and 28% of antibiotic [5] drugs failed quality specifications.

Penicillin, tetracycline, co-trimoxazole and chloramphenicol, are among the favored counterfeited antimicrobials [4]. There is no sufficient data to contemplate the nature and extent of the problem in Ethiopia. But few studies indicate the occurrence of poor quality paracetamol [7] and ciprofloxacin [8] dosage forms marketed in the capital, Addis Ababa.

Generic products are usually far cheaper than their branded (innovator) versions as generic manufacturers do not have the investment costs for the development of a new drug [9]. Like many other countries, there is a widely held belief that cost of pharmaceuticals is strongly correlated with their quality in Ethiopia.

However, the validity of this argument needs to be ascertained with data derived from research. In the local market, the price of the cheapest generic is 43 times lower than the most expensive brand of co-trimoxazole tablets. There is a growing concern about this situation. How can a patient know if buying a cheaper brand would be therapeutically effective or not?

The combination of trimethoprim (TMP) and sulfamethoxazole (SMX) in a 1:5 ratio, known as co-trimoxazole; has been used for the treatment of a wide variety of infections due to Gram-positive and Gram-negative organisms. The synergistic bactericidal effect of the combination is due to sequential blockade of bacterial enzyme systems associated with tetrahydrofolate synthesis [10].

Co-trimoxazole is reported to have a very high number of generics with very wide price margins amongst the antibiotic family of drugs marketed in Ethiopia. For the health care providers to use these brands interchangeably, the bioequivalence of these brands have to be ascertained [1].

Thus, the present study was carried out to evaluate the physicochemical and bioavailability equivalence of different brands of co-trimoxazole tablets marketed in Tigray, Northern Ethiopia; sourced from different pharmaceutical manufacturers in order to determine the appropriateness of their interchangeability.

MATERIALS AND METHODS:

Materials:

Instruments: A High Performance Liquid Chromatography (Shimadzu, LC/20A Series, Japan), a Pharma Test dissolution tester (Apparatus 2) (Pharma Test®, PTWS610, Germany), a Pharma Test hardness tester (Pharma Test®, PTB 311, Germany), a Pharma Test friability tester (Pharma Test®, PTFE, Germany), a basket-rack assembly LOGAN DST-3 disintegration tester (LOGAN Instruments Corp.), and an Electronic micro balance (Sartorius, Germany) provided by Addis Pharmaceutical Factory were used for the study.

Chemicals and Reagents: Acetonitrile HPLC grade (Sigma-Aldrich, Germany), Triethylamine HPLC grade (Fluka, Switzerland), Methanol (Sigma-Aldrich, Germany), Chloroform (Sigma-Aldrich, Germany), Isopropyl alcohol (Sigma-Aldrich, Germany), Diethylamine (Sigma-Aldrich, Germany), Glacial acetic acid (Sigma-Aldrich, Germany), Sodium hydroxide (Sigma-Aldrich, Sweden), Hydrochloric acid (Sigma-Aldrich, Germany) and double distilled and deionized Water were used in the study. TMP working reference standard, Batch number 20/001544 with purity of 99.5% and SMX working reference standard, Batch number 200911/01 with purity of 99.93% obtained from Addis Pharmaceutical Company were also used for the study.

Methods:

Sampling: Six brands of a double strength tablets containing 480 and 960 mg of one of the most widely used antibiotic, co-trimoxazole was evaluated.

The study was designed to collect samples at various levels of drug distribution chains, such as hospital pharmacies, private sector pharmacies and drug stores which are available in Tigray. Detail information on co-trimoxazole tablets included in the study is given in **Table 1**.

The drug samples were anonymously purchased in their original package as supplied by the manufacturers. Then the collected samples were taken to Addis Pharmaceutical Factory; and the physicochemical parameters of the tablets were analyzed as described in BP and USP [11-13].

TABLE 1: DETAIL INFORMATION ON CO-TRIMOXAZOLE TABLETS INCLUDED IN THE STUDY

Country	Brand	Code	Strength (mg)	Batch No	Mfg. Date	Exp. Date
Switzerland	Bactrim*	A	480	B2066	Apr-09	Apr-14
India	Bisepton	B	480	376	Oct-08	Oct-11
India	Cotreich	C	960	490336	May-07	May-12
Ethiopia	Cotri	D	480	3915	Jul-08	Jul-13
Ethiopia	Cotrimoxazole	E	480	30343	Mar-08	Mar-13
Cyprus	Deprim	F	480	45368	Oct-10	Oct-15

*= innovator product

Uniformity of Weight Test: The test for uniformity of weight for each brand of co-trimoxazole tablets was carried out as described in BP [11]. The weights of 20 tablets were determined individually using an electronic micro balance. The average weight for each brand as well as the percentage deviation from the mean value was calculated.

Hardness and Thickness Testing: Using forceps, four tablets were individually placed between the platens of integrated hardness, thickness and diameter tester. The four tablets were randomly selected from each brand and the resulting visual readings of tablet hardness and thickness were recorded. The thickness of product C (oblong tablet) was measured using Digital Caliper.

Friability Test: Ten tablets from each brand were dusted and weighed on the analytical balance. The tablets were placed in the drum of the friability tester and rotated at 25 rpm for four minutes (100 times) [12]. Thereafter they were removed; reweighed and the percent friability was determined [14].

Disintegration Test: Disintegration test was carried out according to specification given in BP [11]. A 900 ml beaker with 37 ± 0.5^{o}C water was prepared. Six tablets were placed into the basket-rack assembly and connected to the disintegration apparatus.

Assay of the Active Ingredients:

Chromatographic System: High performance liquid chromatography method was used for the assay according to USP specification [13]. A stainless steel column of Nucleosil 100 C18 (25 cm x 4.6 mm) packed with stationary phase of 5 µm particle size and UV detector at 254 nm was employed. A mixture of water, acetonitrile and triethylamine (700:200:1(v/v)) the pH of which was adjusted to 5.74 with sodium hydroxide and dilute glacial acetic acid was used as a mobile phase with flow rate of 1.5 ml/min; injection volume of 20 µl; and an ambient oven temperature.

Preparation of Samples: Twenty tablets of the sample was weighed and crushed to powder. A portion of the powder containing 32 mg of TMP and 160 mg of SMX was transferred to a 100 ml volumetric flask and the solution was then diluted with methanol to volume and filtered. Five ml of filtrate was transferred to a 50 ml volumetric flask and diluted with mobile phase to volume to get a working sample solution of 0.032 and 0.16 mg/ml of TMP and SMX, respectively. A similar standard working solution was also prepared. The content of both TMP and SMX in co-trimoxazole tablets were calculated from peak areas of the chromatograms of the test and reference standard solutions.

Dissolution Studies: The dissolution studies of all brands were carried out according to the USP specifications using a type II (paddle), operated at 75 r/pm. Six tablets selected at random from each sample were used simultaneously for the study. The dissolution medium was 900 ml 0.1N hydrochloric acid maintained at 37±0.5^{o}C. Five ml volume of leaching fluid was withdrawn at 10, 30, 45 and 60 minutes time intervals by replacing with the same volume of

dissolution medium. After filtration and appropriate dilution the concentration of each component was determined by using HPLC in similar fashion to the assay. The percentage dissolved of both TMP and SMX was tested statistically to ascertain differences among brands using one-way analysis of variance (ANOVA, p=0.05) while Dunnett's test was employed to ascertain where the difference arose with regard to the innovator products [1].

Data Analysis: Analytical data obtained from the experiments carried out were analyzed using GrahPad Instat 3 and GraphPad Prism 5 software programs for statistical and graphical comparisons. To compare the dissolution profiles of all generic and innovator brands, a one way ANOVA and model independent approach of similarity factor (f_2) was employed. The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in percent dissolution between the two curves and is calculated as [10,15]:

$$f_2 = 50 \log \left(\frac{100}{\sqrt{[1 + \frac{1}{n}\sum (R_t - T_t)]}} \right)$$

Where, n is the number of time points, R_t and T_t are the dissolution value of reference and test product at time t.

RESULTS AND DISCUSSION:

Uniformity of Weight Test: The results of weight variation test are depicted in **Table 2**. According to the specification outlined in BP [11], the test for weight variation where the strength is greater than 250 mg; the tablet passes the test if not more than two of the individual weights deviate from the average weight by more than ±5% and none deviated by ±10%.

All brands of co-trimoxazole tablets showed acceptable uniformity of weight as none had percentage deviation in weight greater than 5% as stipulated by the pharmacopoeia which agrees with similar works conducted in Turkey [10]. Application of ANOVA revealed significant differences among samples mean weights (p<0.0001), with the post hoc identifying for mean tablet weight difference between innovator and generic brands; similar to results reported for nifedipine tablets in Nigeria [16].

Friability Test: Adequate tablet hardness as well as reasonable friability is required for consumer acceptance [17]. The pharmacopoeia states that the friability value of tablets should be less than 1% [13] and as such all the brands of co-trimoxazole passed this friability specification (**Table 2**). Tablets with higher crushing strength showed low friability value similar to those ciprofloxacin hydrochloride brands conducted elsewhere [18].

Thickness and Hardness Test: Examination of tablet thickness gives insight as to the tablet tooling used by various manufacturers and results are indicated in **Table 2**. Similarly, mean hardness values of tablets of co-trimoxazole in this study are shown in **Table 2**. A force of about 5 kg/cm^2 is the minimum requirement for a satisfactory hardness of tablets [19]. Generally, all the studied tablets passed hardness and friability test specification of tablet dosage forms.

However, statistical analysis (ANOVA) of thickness (p<0.0001) and hardness (p<0.0091) data showed a significant difference among different brands. These differences in tablet sizes (weight, diameter and thickness) may actually have some negative psychological effects on clinicians and their patients since they could raise doubts on the general equivalence of the brands [16].

Disintegration Test: Disintegration is a crucial step for immediate release dosage forms because the rate of disintegration affects dissolution and subsequently therapeutic efficacy of medicine [9].

The mean disintegration times of different brands of co-trimoxazole tablets included in the study are shown in **Table 2**. Product B showed the highest disintegration time (6.24 min) which correlates with its low friability and high hardness values.

Differences between the means of disintegration times of generic and innovator brands, were statistically significant (p <0.05) similar to earlier reports on artesunate tablets [19].

Assay of Active Ingredients: The results for actual content of different brands of co-trimoxazole 480 and 960 mg tablets included in the study are depicted in **Table 3**. It is described that co-trimoxazole tablets should contain not less than 93.0% and not more than

107.0% of the stated amount [13]. All brands of co-trimoxazole tablets passed as per the USP specification. The highest and lowest TMP content was obtained 99.93 and 98.59% for product A and C, respectively. Similarly, the highest and lowest SMX content was obtained 101.25 and 100.01% for product D and C, respectively. Statistical comparison for mean difference of drug content indicated that with 95% confidence interval, there was no significant difference in the drug content among the different brands ($p > 0.05$); unlike the works reported on ciprofloxacin [8] and; lamivudine and zidovudine combination tablets [17].

Dissolution Studies: The official Pharmacopoeial specification is that not less than 70% of the stated drug amount should be contained by samples taken at 60 min [12, 13].

From the dissolution test results (**Table 3**), it can be observed that all samples showed a mean release of more than 70% before 60 min. However, the mean is not the only factor to be considered in the analyses of the results obtained from a dissolution test of solid dosage forms [17].

TABLE 2: OFFICIAL AND NON-OFFICIAL TABLET PARAMETERS OF DIFFERENT BRANDS OF CO-TRIMOXAZOLE TABLETS

Product	Thickness [a] (mm) ±SD	Hardness [a] (kg/cm^2) ±SD	Friability [b] (%)	Disintegration [c] (min) ±SD	Weight [d] (mg) ±SD	Mean % deviation
A	4.56±0.90	9.49±0.95	0.60	0.57±0.27	504.60±5.10	0.77
B	3.70±0.10*	13.20±6.63	0.13	6.24± 2.18*	532.19±11.13*	1.70
C	4.63±0.11#	8.68±1.63	0.4	5.32±0.19*	1046.72±6.53	0.38
D	6.69±0.03	14.97±1.77	0.38	3.72±0.50*	575.42±12.45*	1.97
E	5.99±0.10*	6.79±0.96	0.69	2.12±0.70#	572.821±2.50*	1.78
F	4.24±0.10*	12.44±1.25	0.08	1.04±0.28	620.54±6.41*	0.88
Limits		**>5 kg/cm^2**	**<1%**	**<15 min**		**<5%**

[a] (n=4), [b] (n=10), [c] (n=6), [d] (n=20), *=p<0.01, #=p<0.05, SD=standard deviation

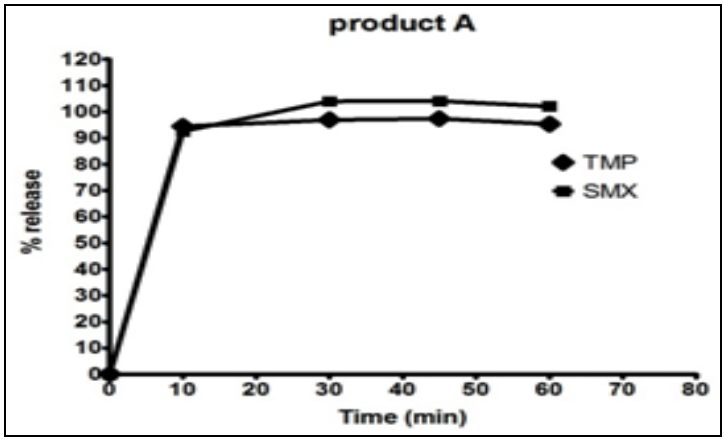
TABLE 3: ASSAY, % DISSOLVED AND F_2 VALUE AT 60 MIN OF CO-TRIMOXAZOLE TABLETS

Products	Assay ± RSD (%)		Dissolution ± RSD (%)		f_2 at 60 min for SMX	Similarity
	TMP	SMX	TMP	SMX		
A	99.93±0.88	100.74±0.59	95.30±1.50	102.12±1.27		
B	99.33±0.70	100.96±0.55	95.07±2.22	102.01±1.07	52.02	Yes
C	98.59±0.60	100.01±0.60	100.45±1.24	94.30±1.86	33.71	No
D	99.54±0.65	101.25±0.64	100.34±.09	99.45±2.25	31.85	No
E	99.50±0.69	100.36±0.64	96.59±5.01	102.48±3.56	36.33	No
F	99.39±0.53	100.56±0.59	102.25±3.14	104.81±2.742	77.55	Yes
Limits	**93-107 %**		**>70%**		**>50**	

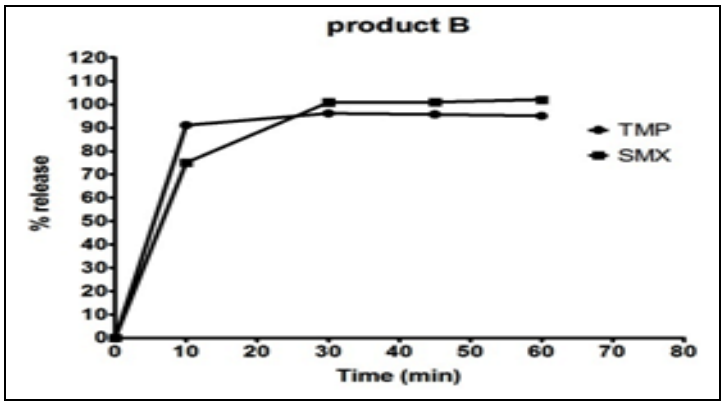
RSD = relative standard deviation, TMP = trimethoprim, SMX = sulfamethoxazole

The dissolution profile of each brand of co-trimoxazole is given in **Figure 1(A-F)**. Similarly, the trends of percent release (dissolution profile) of TMP and SMX for the six brands of co-trimoxazole tablets are shown in **Figure 2(A-B)**.

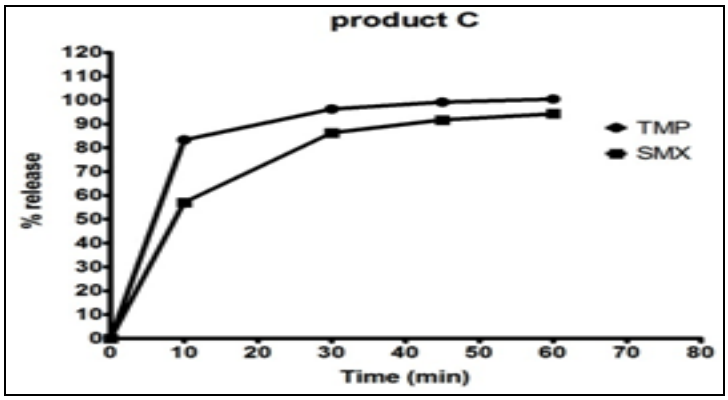
There was an immediate release and super imposable dissolution profile of TMP for all brands compared to SMX release and dissolution profile (**Figure 2(A-B)**). It was observed that products A and F with the smallest disintegration time 0.57 and 1.04 min, respectively showed fast percentage drug release that agrees with earlier works on ciprofloxacin tablets [8].



A



B



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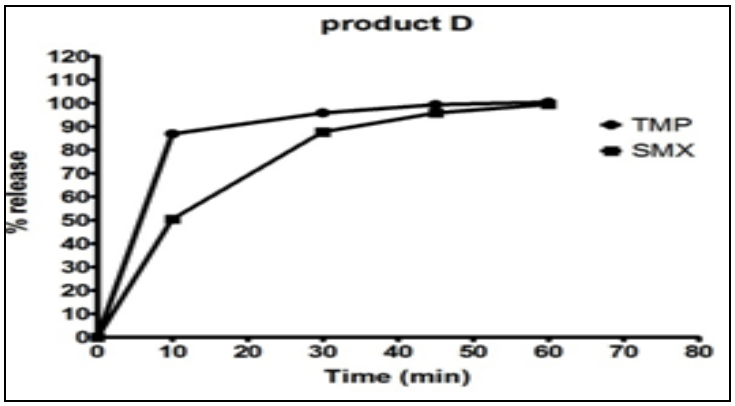
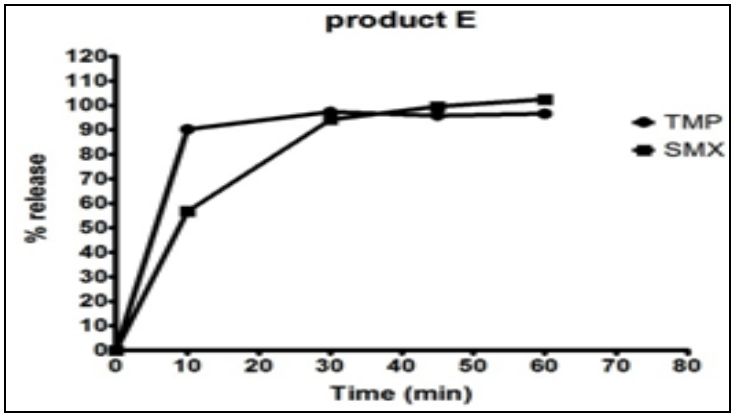
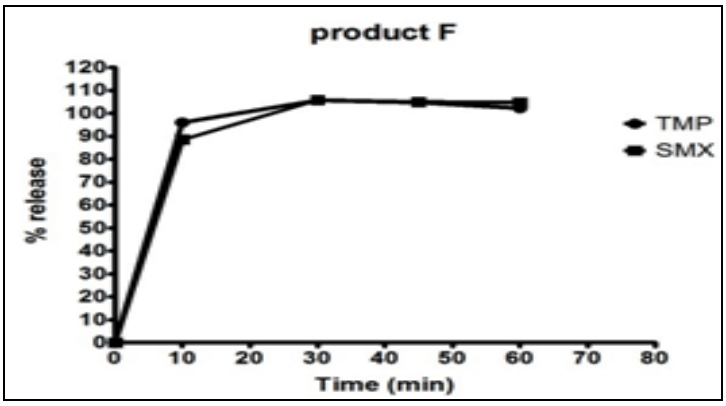


D

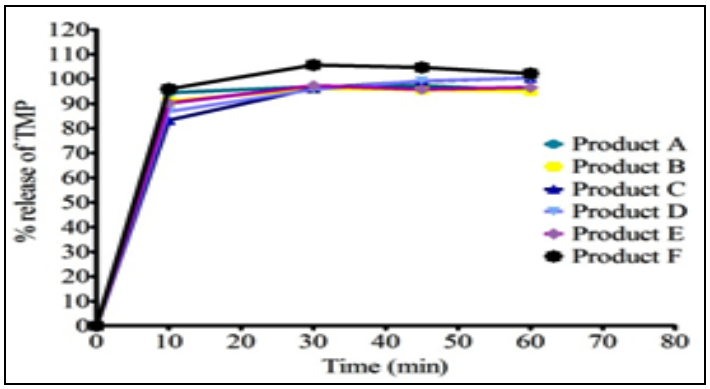


E



F

FIG. 1(A-F): DISSOLUTION TRENDS OF EACH PRODUCT OF CO-TRIMOXAZOLE TABLETS



A

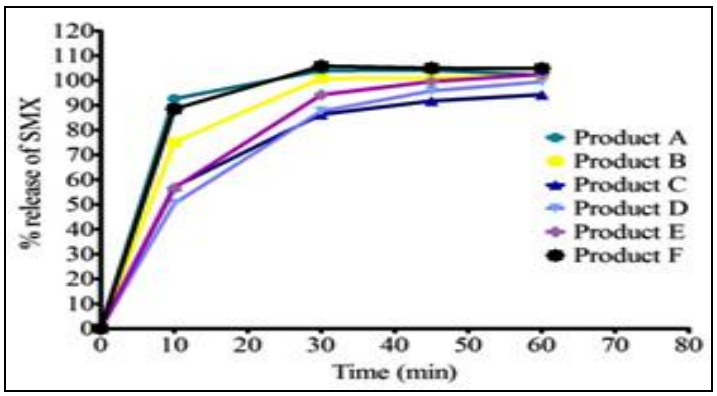


FIG. 2(A-B): PERCENT OF TRIMETHOPRIM (A) AND SULFAMETHOXAZOLE (B) RELEASED FROM SIX BRANDS OF CO-TRIMOXAZOLE TABLETS

One-way analysis of variance was undertaken for time points 10 and the pharamacopoeially specified time, 60 minutes. The results of ANOVA as shown in **Table 4 and 5** indicated that the percent dissolved was significantly different at the two time points at 0.05 level of confidence for both TMP and SMX. These statistical results indicated that the products of co-trimoxazole tablets were not equivalent with respect to their *in vitro* release profile; similar observation was made on ciprofloxacin [1, 8] and artesunate [19] in other works.

TABLE 4: RESULTS OF ANALYSIS OF VARIANCE AT TWO TIME POINTS FOR TRIMETHOPRIM RELEASE

Time (min)		Sum of squares	Df	Mean square	F-value	Sign. (p)
10	Between groups	1597	5	319.41	108.95	0.0001
	Within groups	87.948	30	2.932		
	Total	1685	35			
60	Between groups	268.6	5	53.72	6.981	0.0002
	Within groups	230.86	30	7.695		
	Total	499.45	35			

Df = Degree of freedom, Sign. = Significance

TABLE 5: RESULTS OF ANALYSIS OF VARIANCE AT TWO TIME POINTS FOR SULFAMETHOXAZOLE RELEASE

Time (min)		Sum of squares	Df	Mean square	F-value	Sign. (p)
10	Between groups	9628.30	5	1925.70	94.64	0.0001
	Within groups	610.30	30	20.34		
	Total	10239	35			
60	Between groups	396.5	5	79.31	14.63	0.0001
	Within groups	162.6	30	5.421		
	Total	559.2	35			

In order to ascertain the source of differences, pair-wise comparisons of the generic brands against innovator product, were performed by multiple comparisons using Dunnett's test and the outcomes at 0.05 levels are as shown in **Table 6**. Values above the critical value (2.66) indicate that the mean % dissolved difference was significant while values below the critical value indicate that the differences were not significant. Consequently, it can be inferred that the difference in TMP % dissolved for product B, C, D and E at 10 min were significantly different from the innovator product, while product F was not significantly different from the innovator product. Similarly, products C, E and F were significantly different from the innovator product, while product B and D were not significantly different from the innovator product in TMP % dissolved at 60 min.

TABLE 6: DUNNETT'S TEST FOR TMP AND SMX RELEASE OF THE PRODUCTS AT 0.05 LEVELS WITH CRITICAL VALUE 2.66[a]

Time (min)	Pair Comparison	Trimethoprim		Sulfamethoxazole	
		Mean Difference (% dissolved)	Significance	Mean Difference (% dissolved)	Significance
10	A vs B	3.40	3.44	17.55	6.74
	A vs C	11.14	11.27	35.50	13.63
	A vs D	7.62	7.71	42.17	16.19
	A vs E	17.80	18.00	35.87	13.77
	A vs F	-1.50	1.51	4.08	1.57
60	A vs B	0.58	0.36	0.11	0.08
	A vs C	-4.80	2.30	7.82	5.82
	A vs D	-0.94	0.58	-0.36	0.265
	A vs E	-4.70	2.93	2.67	1.98
	A vs F	-6.60	4.12	-2.69	2.00

[a] = Critical Value is obtained from a table of Dunnett's test; [b] = Mean difference is obtained by subtracting mean % dissolved of innovator from mean % dissolved of other brands

In the same way, the differences in SMX % dissolved for products B, C, D and E at 10 min were significantly different from innovator product, while product F was not significantly different from innovator product. At 60 min, only product C showed significant difference in SMX % dissolved from the innovator product. These results showed that product F had the least departure in SMX % dissolved from the innovator product, at the two time points. At the pharamacopoeially specified time, product C showed a significant difference from the innovator product, in both TMP and SMX % dissolved. It is worthy to note that the difference identified by ANOVA and the comparison performed by Dunnett's tests are statistical and not bioavailability equivalence [1]. To prove the bioequivalence of two or more drug products, a similarity in the rate and extent

to which the drug in the dosage form becomes available for absorption need be demonstrated [19]. In this study f_2 derived from dissolution profiles of the six brands of co-trimoxazole were used as estimators for bioavailability of TMP and SMX, hence their bioequivalence. Similarity factor f_2 is included as guidance on dissolution testing of immediate release solid oral dosage forms [15].

The high rate of dissolution of TMP (**Figure 2A**) precludes any possibility of bioavailability problem resulting from drug dissolution and hence justifies interchangeability among the six brands with regard to TMP. In cases where greater than 85% of drug is dissolved within 15 min, dissolution profiles are usually accepted as similar without further mathematical evaluation [19].

That means, all the six brands have the same bioavailability with regard to TMP. The rate of dissolution of SMX, however, did not meet the criterion of 85% dissolution and as such were subjected to further mathematical (f_2) evaluation to demonstrate bioequivalence (**Table 3**). On the contrary, another study [10] showed that more than 85% of the labeled amounts of both TMP and SMX in test and reference products were dissolved in 15 min and hence profile comparison with f_2 was unnecessary.

For two dissolution profiles to be considered similar and bioequivalent, f_2 should be between 50 and 100 [9, 15]. Therefore, the SMX dissolution profiles of products C (f_2 =33.71), D (f_2=31.85) and E (f_2=36.33) (as shown in **Table 3**) using the model independent approach (f_2) were not similar with innovator product and so may probably not be used interchangeably; similar results were reported on one brand of artesunate (f_2 = 23.8) [19], three brands of ciprofloxacin (f_2 = 17.6-25.8) [1] and three brands of methformin hydrochloride (f_2 = 24.5-39.4) [20].

On the other hand, the dissolution profiles of products B (f_2=52.02) and F (f_2=77.55) were similar and most probably bioequivalent with innovator product, and so may be used interchangeably as indicated by other works on two brands of ciprofloxacin in Nigeria (f_2 = 53.9 and 53.3) [1], six brands of ciprofloxacin in India (f_2 = 65.35 -77.33) [9].

Interestingly from this study, it was understood that price may not necessarily indicate the quality and effectiveness of a drug product as earlier pointed out in other studies [1]. Products B and F were sold at the price of 1.50 and 12.00 Birr per 10 tablets, respectively; but both are bioequivalent to the innovator product which was sold at about 65.00 Birr per 10 tablets at the local market.

On the other hand, products C, D and E, which were sold at a price of 2.50, 2.00 and 3.00 Birr per 10 tablets, respectively, were not bioequivalent with the innovator brand.

Therefore, our observation here was that the cheaper brands may or may not be bioequivalent with the innovator brand which further highlights the need to really characterize multisource medicines.

Results have shown that more than cost consideration and company reputation is required for day-to-day rational decision making in drug products sourcing.

CONCLUSION: Six brands of co-trimoxazole tablets have been subjected to analysis according to the monograph of BP and USP. Our results indicated that all brands of co-trimoxazole tablets included in this study were chemically equivalent. Statistical analysis (ANOVA) showed that there was significant difference in the mean drug release between the generic and innovator products; and the similarity factor (f_2) also showed that three of the generic products were not bioequivalent with the innovator brand.

This is significant in therapy where drugs are expected to not only conform to their label claims but also have satisfactory bioavailability. These findings support the need for activation of the regulatory rules with emphasis on post marketing evaluation of pharmaceutical products in order to monitor the safety, quality and efficacy of essential drugs in the country.

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