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QUALITY ASSESSMENT OF TEN BRANDS CO-TRIMOXAZOLE TABLETS COMPARED WITH THE ORIGINAL BRAND IN YEMENI MARKET

ABDULKARIM KASSEM ALZOMOR[*1], YASER AL-MADHAGI[2], NAHLAH MANSOUR NOMAN[1], AND LAMIA RASHAD AL-AKHALI[2]

1: Department of Pharmacy, Faculty of Medicine and health sciences, Thamar University, Republic of Yemen

2: Department of Pharmacy, Faculty of Medical sciences, Al-Nasser University, Republic of Yemen

***Corresponding Author: Abdulkarim K. Alzomor, Ph.D. Head of Department of Pharmacy, Faculty of Medicine and Health Sciences, Thamar University, Republic of Yemen; E-mail: alzomor1974@yahoo.com; Contact No.: +967773418635**

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ABSTRACT

The aim of this study is to evaluate the quality of sulfamethoxazole and trimethoprim (co-trimoxazole) as tablet marketed in Yemen. The results revealed that the local brands have equivalent results to the reference and within the limit of pharmacopoeia (90- 110%), the results of the dissolution test of the local brands within the limit of pharmacopoeia not less than (80%) except Batrim was nonequivalent to the reference and out the limit of pharmacopoeia, and the friability test results for local brands were equivalent to the reference and within the limit of pharmacopoeia (≤1%). Moreover the imported brands showed that the mean assay results were equivalent and within the pharmacopoeia limits (90-110%) and the dissolution test for results were identical to the reference and within the limit of pharmacopoeia not less than (80%), and the friability test results for imported brands were identical to the reference and within the limit of pharmacopoeia (≤1%) except Balkatrin was out of the limit of pharmacopoeia. Concisely, all

the selected brands of Co-trimoxazole tablet were equivalent and conformed to the pharmacopeial requirements except Batrim (in dissolution test) and Balkatrin (in friability test).

Keywords: Co-trimoxazole, quality, imported, local, tablet

INTRODUCTION

Its important to remember that the drugs are unlike other consumer goods in that they are crucial to meet the important objective of improving public health and so they should be treated in special way other than the other commodities. Their development, manufacturing, import, subsequent handling within the distribution chain and use require specialized knowledge and skills. Consequently, they should conformed to prescribed standards and their quality should be rigorously controlled. The standards are achieved through well-articulated Current Good Manufacturing Practice (cGMP). Maintaining cGMP will ensure the formulation of products of acceptable standards in contents of active ingredients, good physical and chemical stability and acceptable microbiological quality. Deviation from these standards attracts serious sanctions from the regulatory authorities[1].

Sulfamethoxazole belongs to the sulfonamides group of chemotherapeutics. Despite the availability of numerous antibiotics sulfonamides is still an important drug for therapeutic use, particularly in the treatment of acute urinary tract infection (UTI)[2]. The use of sulfonamides has increased greatly with the introduction of trimethoprim - sulfamethoxazole mixtures which represent a synergistic combination of antibacterial agents[3].

There is need to ascertain the chemical and biological equivalence of antibiotics due to global health problem posed by antibiotic and multi-drug resistance [4]. The multi- drug resistance by infective agents might be due to chemical in equivalence and bioinequivalence. Though the problem is worldwide, Southeast Asia and Africa seem to be particularly plagued by counterfeited pharmaceuticals[5]. For example, a study done in Southeast Asia in 2001 showed that 38% of antimalarial on sale in pharmacies did not have any active ingredients[6]. In a WHO survey, 20-90% of antimalarial[7] and 28% of antibiotic[5]drugs failed quality specifications.

There are more than ten brands of Co-trimoxazole tablets registered in Yemen, produced by various manufacture. Due to possible difference in the quality of raw material it was necessary to conduct this in

vitro evaluation for effective agent in these products. This study will be conducted in comparison with the original product.

Materials

Sulphamethoxazole RS and Trimethoprim RS were obtained as a gift sample from Modern pharmaceutical company, Potassium dihydrogen phosphate and Hydrochlorid Acid, Scharliu, Europian; Acetonitrile, Sigma, Germany; and Phosphoric acid from Acrouzr, USA.

METHODOLOGY

All the analytical Methods were done in the quality control laboratory of Modern pharma company.

The project of the method as the following:

Table (1) shows the Co-trimoxazole brands which used in this study.

No.	Name of drug		Batch Number	Production date	Expiration date
1	Reference	Septrim	B0000J	10 / 2010	10 / 2013
2	Local products	Cotrix	10214	4 / 2010	4 / 2014
3		Septram	11057	4 / 2011	4 / 2014
4		Shatrim	5429	10 / 2010	10 / 2013
5		Batrim	11326	9 / 2011	9 / 2014
6	Imported Products	Balkatrin	256025	1 / 2012	1 / 2017
7		Omtran	1210	10 / 2010	10 / 2015
8		Farcotrim	342	9 / 2011	9 / 2014
9		Sinotrim	LoTS10002	10 / 2011	10 / 2014
10		Amirtrim	175	10 / 2011	10 / 2014

All products were evaluated according to the pharmacopeias USP and BP, then the results were analyzed statically.

i. Verification of analytical method:

Calibration for Co-trimoxazole

500mg of Sulfamethoxazole reference standard and 100mg of Trimethoprim reference standard were weighed accurately then added to 100ml volumetric flask and diluted with methanol to volume then sonicate for 10 minutes, cool at room temperature. The concentrations were prepared by transferring 2ml of stock solution into 100ml mobile phase, 4ml of stock solution to 100ml mobile phase, 3ml of stock solution to 50ml mobile phase, 4ml of stock solution to 50ml of mobile phase, and 5ml of stock solution to50ml of mobile phase. Then injected and measured by HPLC and the measuring was repeated more than one at different time.

Assay test for Co-trimoxazole reference:

HPLC conditions: calibrated HPLC instrument was used as the following:

Column: C18-30cm, Sensitivity:1, Pressure:518 Mpa, Wavelength 254nm, Flow = 1ml/min, End time: 4.5min.

The mobile phase(Buffer pH=4 : Acetonitrile) (300:700) i.e. Buffer (pH=4) was prepared by dissolving1.5g of KH_2PO_4 in 300ml of water, and 700ml of Acetonitrile was added, after that the pH was adjusted to 4 with H_3PO_3,then mixed and filtered.

Preparation of stock standard solution:

32 mg of Trimethoprim RS and 160mg of Sulfamethoxazole RS were weighed into 100ml volumetric flask, then dissolved and diluted with methanol to volume and mixed well. 5ml of this solution was added to 50ml volumetric flask, and the volume was completed with mobile phase (0.023mg/ml and 0.16 mg/ml)[8].

ii. Evaluation tests of Co-trimoxazole brands

1. Assay test

Preparation of test solution

Powdered tablets equivalent to 160mg of Sulfamethoxazole and 32mg of Trimethoprim were weighed and transferred into 100ml volumetric flask. After that the mixture was diluted with methanol to volume then sonicate for 10 minutes, cool at room temperature. 5ml of this mixture was transferred to volumetric flask and the volume was completed with mobile phase then mixed and filtered (0.16mg/ml Sulfamethoxazole and 0.032mg/ml Trimethoprim) [8].

2. Dissolution test for Co-trimoxazole[9]:

Method of dissolution test

Dissolution test conditions:

Medium: 900ml of 0.1MHCl, rotate per minute: 75R.P.M, Time: 60 min, Tolerance: Not less than 70%, Apparatus paddle II.

Preparation of standard solution:

Powder equivalent to 25mg of Trimethoprim RS and 100mg of Sulfamethoxazole RS were weighed accurately and added to 500ml volumetric flask then dissolved and diluted with 0.1M HCl to volume and mixed well. Then 5ml of this solution was transferred into 50ml volumetric flask, the volume was completed with 0.1M HCl and mixed well (0.025mg/ml and 0.1 mg/ml).

Preparation of test solution:

5ml of filtrate solution was taken into 25ml volumetric flask and the volume was completed with 0.1M HCl and mixed well.

HPLC conditions:

Column: C18-30cm, sensitivity:1, Pressure 565, Wavelength 254nm, End time 5min, Flow rate: 1 ml\min.

3. Disintegration test for Co-trimoxazole[10,11] :

The procedure for disintegration apparatus was prepared as the following:

Medium: purified water 700ml, Temperature: 37°C, Limit: 15mins.Then the disintegration time was recorded when the tablet disintegrated.

4. 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 oblong tablet was measured using Digital Caliper [8].

5. 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) [11]. There after they were removed; weighed again and the percent friability was determined [12]. The result was calculated as the following:

$$\% = \frac{wt.before - wt.after\ test}{wt\ before\ test} * 100$$

RESULTS AND DISCUSSION:

Calibration of Co-trimoxazole

Calibration curve for Sulfamethoxazole RS and Trimethoprim RS and the concentrations which used was illustrated in table (2).

From the above results of calibration curve in figure (1) for Sulfamethoxazole illustrate linearity was demonstrated by plotting peak area vs. concentrations of Sulfamethoxazole with regression equation (R^2= 0.997), and curve in figure(2) for Trimethoprim illustrates the linearity with regression equation(R^2=0.999) this indicate the validity of HPLC in this study.

Table (2): illustrates the concentration of Sulfamethoxazole and Trimethoprim which used for calibration

Sulfamethoxazole		Trimethoprim	
Conc. of mg/ml	**Peak Area**	**Conc. of mg/ml**	**Peak Area**
0.1	**3991173**	**0.02**	**428065**
0.2	**7773218**	**0.04**	**855460**
0.3	**11414790**	**0.06**	**1294832**
0.4	**14451881**	**0.08**	**1702199**

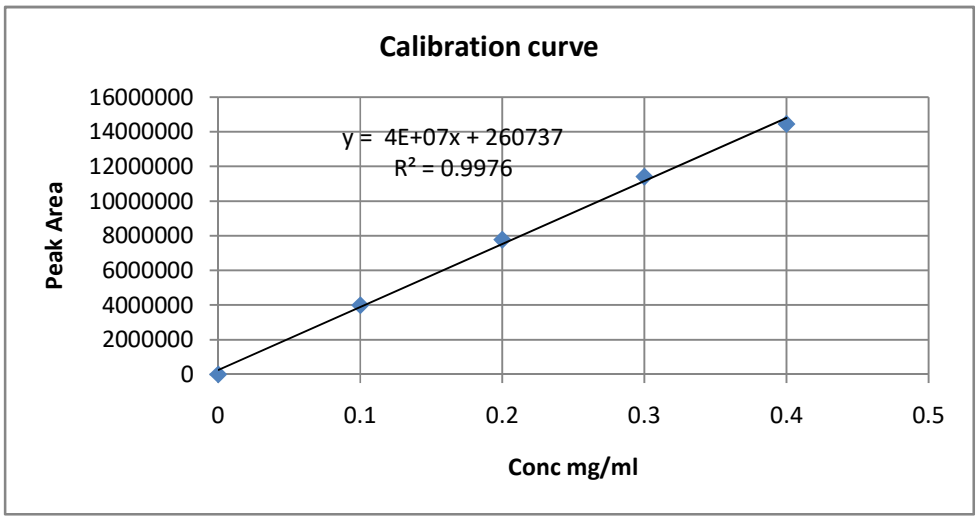

Figure (1): illustrates the linearity of calibration curve of Sulfamethoxazole

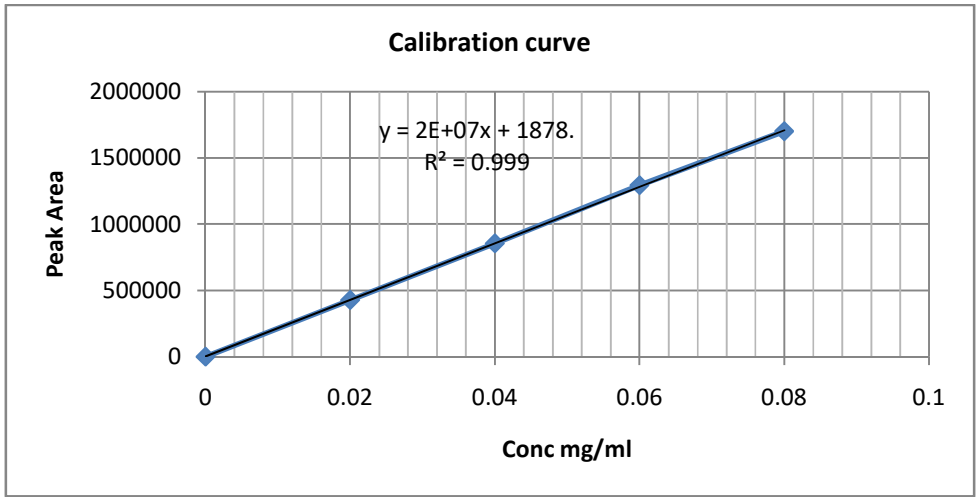

Figure (2) illustrates the linearity of calibration curve of Trimethoprim

Results of assay for all products of Co–trimoxazole

Table (3) shows the result HPLC assay test for ten brands of Co-trimoxazole

Products		Batch number	Sulfamethoxazole		Trimethoprim	
			Assay	RSD	Assay	RSD
Reference product	Septrim	B0000J	101.3 %	0.23%	99.5 %	0.02%
Local brands	Cotrix	10214	102.7 %	0.1%	103.6 %	0.19%
	Septram	11057	105 %	0.17%	103.8%	0.19%
	Shatrim	5429	101.7 %	0.05%	100.7 %	0.12%
	Batrim	11326	98.2 %	0.22%	99.3 %	0.14%
Imported brands	Balkatrin	256025	100.2 %	0.16%	100.3 %	0.05%
	Omtran	1210	101.3 %	0.23%	101.9 %	0.04%
	Farcotrim	342	102.5 %	0.56%	102.9 %	0.118%
	Sinotrim	LoTS10002	101.1 %	0.05%	103.6 %	0.06%

	Amirtrim	**175**	**103.8 %**	**0.37%**	**100.0 %**	**0.37%**
The limit	**90.0% to 110.0%**					

Table (3) reveals the results of assay for all brands were conformed to the pharmacopeial requirements for each Sulfamethoxazole and Trimethoprim, the result of assay for reference (original) product Septrim (batch no. B0000J) after calculating the mean of results of assay for one sample was for Sulfamethoxazole 101.3% with RSD 0.23%, but for Trimethoprim was 99.5% with RSD 0.02%. Also the results of assay for local brand product Cotrix (batch no. 10214) for Sulfamethoxazole was 102.7% with RSD 0.1% and for Trimethoprim was 103.6% with RSD 0.19%. Similarly for local brand product Septram (batch no. 11057) after taking the mean of results of assay for sample for Sulfamethoxazole was 105% with RSD 0.17% and for Trimethoprim was 103.8% with RSD 0.19%. Also the results of assay for local brand product Shatrim (batch no. 5429) the result of assay for Sulfamethoxazole was 101.7% with RSD 0.05% and for Trimethoprim was 100.7% with RSD 0.12%. And the result of assay for local brand Batrim (batch no. 11326) for Sulfamethoxazol was 98.2% with RSD 0.22% and for Trimethoprim was 99.3% with RSD 0.14%. The result of assay for imported brand Balkatrin (batch no. 256025) for Sulfamethoxazole was 100.2% with RSD 0.16% but for Trimethoprim was 100.3% with RSD 0.05%. The result of assay for imported brand product Omtran (batch no. 1210) for Sulfamethoxazole was 101.3%with RSD 0.23% and for Trimethoprim was 101.9% with RSD 0.04%. Also the result of assay for imported brand product Farcotrim (342) for Sulfamethoxazole was 102.5% with RSD 0.56% and for Trimethoprim was 102.9% with RSD0.18%. Similarly the result of assay for imported brand product Sinotrim (batch no. LoTs10002) for Sulfamethoxazole was 101.1% with RSD 0.05% and for Trimethoprim was 103.6% with RSD 0.06%. Finally the result of assay for imported brand product Amirtrim (175) for Sulfamethoxazole was 103.8 % with RSD 0.37% and for Trimethoprim was 100.0% with RSD 0.37%.

Table (4) illustrates the results of dissolution test, disintegration test, friability and hardness for all brands of Co–trimoxazole.

Products	**Sulfamethoxazole**	**Trimethoprim**	**DisintegrationTime (min)**	**Friability%**	**Hardness Kg/cm^2**
	Dissolution test	**Dissolution test**			

		Release%	RSD%	Release%	RSD%			
Reference	**Septrim**	**100.4**	**0.02**	**100.55**	**0.19**	**5:07 min.**	**0.735**	**18.1**
Local brands	**Cotrix**	**100.3**	**0.02**	**103.65**	**0.19**	**1:25 min.**	**0.322**	**13.6**
	Septram	**99.65**	**0.06**	**102.3**	**0.13**	**2:18 min.**	**0.234**	**15.9**
	Shatrim	**101.85**	**0.025**	**100.55**	**0.03**	**5:35 min.**	**0.896**	**18.4**
	Batrim	**76.5**	**0.015**	**98.5**	**0.04**	**2:05 min.**	**0.385**	**9.03**
Imported brands	**Balkatrin**	**99.4**	**0.02**	**98.45**	**0.08**	**4:08 min.**	**1.3**	**10.4**
	Omtran	**96.8**	**0.075**	**99.5**	**0.02**	**1:20 min.**	**0.565**	**13.7**
	Farcotrim	**99.45**	**0.6**	**101.1**	**0.12**	**1:00 min.**	**0.296**	**23.6**
	Sinotrim	**100.05**	**0.34**	**101.55**	**0.3**	**1:10 min.**	**0.24**	**18.6**
	Amirtrim	**97.95**	**0.02**	**98.6**	**0.03**	**7:51 min.**	**0.776**	**17.2**
The limit		**≥80%**				**≤15minutes**	**≤1%**	**>5 kg/cm^2**

About the reference product Septrim (B0000J) the above table (4) shows that the mean value of dissolution test for six samples of Sulfamethoxazole was 100.4%with RSD 0.02% but for Trimethoprim was 100.55% with RSD 0.19%. This result within the limit (not less than 80%) according to British pharmacopoeia. For the local brands all the results of dissolution test were conformed except Batrim. Firstly the local brand Cotrix (10214) the mean value of dissolution for six sample of Sulfamethoxazole was 100.4% with RSD 0.02% and for Trimethoprim was 100.55% with RSD 0.19%. Also for the local brand Septram (11057) for six sample of Sulfamethoxazole was 99.65% with RSD 0.06% and for Trimethoprim was 102.3% with RSD 0.13%. And result of dissolution test for local brand Shatrim (5429) the above table (4) shows the mean value of result of dissolution test for six sample of Sulfamethoxazole was 101.85% with RSD 0.025% and for Trimethoprim was 100.55% with RSD 0.03%. Whereas the result of dissolution test for local brand product Batrim (11326) was not conformed to pharmacopeial requirements, the result of dissolution for six sample of Sulfamethoxazole was 76.5% with RSD 0.015% and for Trimethoprim was 98.5% with RSD 0.14%.

The results of dissolution test for imported brands products Balkatrin (256025), Omtran (1210), Farcotrim (342), Sinotrim (LoTS0002), and Amirtrim (175) were within the limits and conformed the pharmacopeial assay test. The dissolusion test results for six sample of Sulfamethoxazole were 99.4%, 96.8%, 99.45%, 100.05%, and 97.95% respectively with RSD not more than 0.34% and about Trimethoprim for five imported brands were

98.45%, 99.5%, 101.1%, 101.55%, and 98.6% respectively with RSD not more than 0.3.

Disintegration is a crucial step for immediate release dosage forms because the rate of disintegration affects dissolution and subsequently therapeutic efficacy of medicine[13]. All brands included in the study were conformed the disintegration test pharmacopeia requirements. The mean disintegration times of different brands of co-trimoxazole tablets included in the study are shown in table (4).

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 above (4). Similarly, the mean values of hardness in tablets of Co-trimoxazole in this study are shown in table (4). A force of about 5 kg/cm^2 is the minimum requirement for a satisfactory hardness of tablets[14]. Generally, all the studied tablets passed hardness and the friability test all brands were conformed except Balkatrin 1.3% out of the limit.

In summary, the is no significant difference between all studied Co-trimoxazole brands (original , imported and local brands)in any test performed that indicate the maintaining cGMP and high quality of national manufacturing in Yemeni Companies.

CONCLUSION

Ten brands of Co-trimoxazole tablets have been subjected to analysis according to the monograph of BP and USP. The results indicated that most brands of co-trimoxazole tablets (imported and local brands) included in this study were chemically equivalent and the mean valuesof dissolution test for samples of Sulfamethoxazole and for Trimethoprim were within the limit of pharmacopeia. For the local brands all the results of dissolution test were conformed except Batrim. However the results of dissolution test for imported brands products Balkatrin, Omtran, Farcotrim, Sinotrim, and Amirtrim were within the limits and conformed the pharmacopeial assay test. Moreover all brands included in this study were conformed the disintegration test pharmacopeial requirements and about hardness and the friability tests all brands were conformed except Balkatrin out of the pharmacopeial limit in friability test.

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