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EVALUATION OF DIFFERENT BRANDS OF METRONIDAZOLE TABLETS MARKETED IN SAUDI ARABIA: A COMPARATIVE STUDY

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ABSTRACT

Metronidazole (MTZ) is an antiprotozoal medication that kills bacteria and is commonly used to treat amebiasis infection, bacterial infection, bacterial vaginosis and trichomoniasis infection. An array of varied brands of MTZ is available in Kingdom of Saudi Arabia. The aim of present study was to evaluate the selected four brands of MTZ 500 mg tablets (A, B, C and D) purchased from the retail pharmacy outlet in Abha province, Saudi Arabia with a view to ascertain their interchange ability in clinical practice. The study was done by quality control tests on branded tablets like; weight variation, hardness, friability, disintegration and dissolution, to list a few. Results of all the selected marketed products were complied and compared with the official specifications. The results showed that all parameters recorded for MTZ tablets were in accordance with the USP limits. The tested four brands were bioequivalent and have complied with the official tests specifications for weight variation, friability, disintegration and dissolution test. The percentage release of MTZ from tablets was in the range of 89.6% to 99.1% and drug content was in range 94.93% to 100%. Tablet C took 5.2 min to disintegrate, whereas the highest disintegration time of 14 min was exhibited by tablet D. All the tested brands of MTZ 500mg tablets (A, B, C and D) have complied with the official critical quality specifications. The four selected brands assessed in the present study could be considered bio pharmaceutically equivalent and therefore, when there is inaccessibility of a particular brand; patients can safely switch from one brand to another.

KEYWORDS

Tablets, Metronidazole, Bacterial infection, Quality control, Bioequivalence and Safety.

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INTRODUCTION

Metronidazole is an antibiotic and antiprotozoal medication that kills the bacteria and it is commonly used to treat amebiasis infection, bacterial infection, bacterial vaginosis and trichomoniasis infections. Unionized metronidazole is selective for anaerobic bacteria due to their ability to intracellularly reduce metronidazole to its active form. This reduced metronidazole then covalently binds to DNA,

disrupt its helical structure, thereby inhibiting bacterial nucleic acid synthesis and ultimately resulting in bacterial cell death. Adverse drug reactions associated with systemic metronidazole therapy include nausea, headache, diarrhea, taste of metal, dry mouth, appetite disorder, abdominal pain, itch, dizziness and dark coloration of urine[1]. Candidiasis or thrush is a fungal infection (presence of parasitic infection in or on any part of the body i.e., mycosis) caused by any of the species from the genera *Candida*, amongst which *C. albicans* is the most common causative species. A number of antifungal drugs are found to be efficient and are available for the treatment of candidiasis[2,3]. Metronidazole and Clotrimazole are most used antifungal drugs for the treatment of candidiasis. Metronidazole also has an antibacterial, antiprotozoal, antiamoebic effect[4]. Drug products that are biopharmaceutical and chemically equivalent must be identical for their quality, strength, purity and active ingredient release profile[5,2]. Manufacturing methods and the excipients used in the production processes could contribute to the quality and release skillfulness of medicament. Therefore, to ensure the requisite quality, drug manufacturers are required to examine their products during and after manufacturing and at various intervals during the shelf life of the product[6,7]. Many different brands of an antiprotozoal drug metronidazole tablets are available in Saudi Arabia. The aim of present study was to evaluate the four selected brands of MTZ 500mg tablets (A, B, C and D) purchased from the retail pharmacy outlet in Abha, Saudi Arabia, with a view to ascertain their interchange ability in clinical practice; when there is unavailability of a particular brand.

MATERIAL AND METHODS

Collection of samples

Marketed samples of four brands (60 tablets of each brand) of metronidazole (500mg) tablet were procured at MRP from 'Nahdi Pharmacy' outlet of Abha, Saudi Arabia. The samples were randomly coded as A, B, C and D. The samples were properly assessed at the time of purchase for their physical appearance, brand name, name of manufacturer, manufacturing date and expiry date as listed in Table No.1.

Chemical reagents

0.1N Hydrochloric acid and distilled water. Distilled water was collected from the Department of Pharmaceutical Chemistry, King Khalid University (KKU), Abha, Saudi Arabia.

Analytical methods

Determination of λ_{max} of Metronidazole in 0.1 N HCl

Working Standard solution

100mg of metronidazole was accurately weighed and transferred to a 100ml volumetric flask. It was dissolved in about 40ml of 0.1 N HCl and then volume was made up to the mark with 0.1 N HCl (1000µg/ml). 10ml of the stock solution was transferred to 100ml volumetric flask and was diluted to 100ml with 0.1 N HCl solution. This solution was used as metronidazole working standard (100µg/ml)[8].

Scanning

From the working standard solution, 6µg/ml solution of metronidazole was prepared and scanned between the wavelengths of 200-400 nm to get λ_{max}. Three replicates were scanned for obtaining and confirming the λ_{max}.

Calibration curve of Metronidazole in 0.1 N HCl

Into a series of 10ml volumetric flasks different aliquots of 0.3, 0.6, 0.9, 1.2 and 1.5ml were transferred from 100µg/ml strength stock solution, and diluted up to the mark with 0.1 N HCl to obtain concentrations 3, 6, 9, 12 and 15µg/ml, respectively. The absorbance of these solutions was measured and a graph of concentration versus absorbance was plotted. The absorbance's were recorded for three replicate samples for assuring and confirming robustness of method and the analytical method was thoroughly validated.

Visual examination

In order to know the size, shape and color of the tablets visual examination was carried out at the beginning of the study itself.

Weight variation test

Non-uniformity of the tablet weight may result in variation of dose. Hence weight variation of tablets was measured using electronic digital balance (DJ300S, Shinko Sansui, Japan). 20 tablets were selected from each brand and weighed using electronic digital balance. The following formulas were used to calculate average tablets weight and ± % deviations.

Average weight = Total weight of all tablet/ No. of tablets ……..Eq. (1)

% Deviation = [(maximum weight - average weight)/average weight] X 100 …….Eq. (2)

Hardness test

Hardness of tablet has effect on disintegration time of tablet. A variety of factors determines the hardness of the tablets like amount of binder used, the space between the lower punches and upper punches during compression and pressure utilized during compression[9]. To quantify the hardness of tablets 10 tablets were randomly selected from each brand and their hardness were determined (n=10) using Hardness Tester (PTB311E, SN: 14301 Pharma Test, Germany). Hardness of the tablet has impact on tablet disintegration time. Very hard tablet may not disintegrate in the required time and very soft tablet fails to handle pressure and attrition during the coating, packaging and transport. The following formula was used to determine the average hardness of the tablets:

Average Hardness = Total hardness of all tablets/No. of tablets ----------Eq. (3)

Thickness and diameter of tablet

Micrometer screw gauge was used to measure the thickness and diameter of the tablets. 10 tablets were selected from each brand and thickness and diameter of the tablets was assessed using micrometer screw gauge. The average thickness and diameter of tablets from each brand were determined in mm.

Friability test

Friability test was carried out using Roche Friabilator (PTE 10E, SN: 14343 Pharma Test, Germany). The test was performed to find out the ability of tablets to with stand abrasion at the time of packaging, handling and transportation. The acceptable limit as per the Pharmacopeia is maximum weight loss of not more than 1%[10]. 10 tablets of each brand of metronidazole were randomly chosen and placed in a friabilator to achieve uniform tumbling motion for specified period of time i.e. 25 rotation/minute for 4 minutes. Then tablets were collected, de-dusted and weighed. Test was repeated thrice for each brand and percentage friability was calculated using the following equation:

% Friability = [(Weight before test - Weight after test) / Weight before test] X 100 …….Eq. (4)

Disintegration test

Disintegration of the dosage form is an important property of the tablet which is related to the dissolution rate of the drug. If tablet takes more time to disintegrate it will reduce the dissolution rate thereby reducing the rate of absorption which affect bioavailability of the drug.

Disintegration test was performed for all tablets[11]. 1000ml beaker was filled with 0.1N HCl pH 1.2 (in order to mimic gastric environment) and temperature was maintained at 37±0.5ºC. Six tablets were chosen randomly from each brand of metronidazole and placed in the disintegration tester along with discs in the tubes of disintegration test apparatus (ZT41, Erwika, Germany). Time taken by each tablet to disintegrate entirely with no mass left over in the apparatus was recorded.

***In vitro* dissolution study**

The *in-vitro* release study was performed using USP Type-II dissolution apparatus (paddle assembled) (PT-DT70, Pharma Test, Germany) at 100rpm using 900ml of 0.1N HCl as dissolution medium having a pH 1.2 and temperature was maintained at 37±0.5ºC. Aliquots (5ml) were withdrawn at predetermined time intervals, followed by filtration, appropriate dilution and spectrophotometric analysis. Equal volumes of pre-warmed media were added to the dissolution baskets so as to maintain the sink condition. Absorbance was measured at 276nm by UV-Spectrophotometer (Shimadzu UVmini 1240, Japan)[12,13].

Drug content

Ten tablets were accurately weighed and pulverized into a fine powder. Tablet powder equivalent to 100mg metronidazole was weighed and transferred to 100ml volumetric flask and dissolved in 0.1N HCl by frequent shaking, and volume was made up to the mark with 0.1N HCl. It was then filtered in to 50ml conical flask, 10ml of the filtrate was diluted to 100ml with 0.1N HCl. 0.5ml of the above solution was transferred to 10 ml volumetric flask and made up to the mark with 0.1N HCl to get the solution of concentration 5µg/ml. Absorbance of the above solution was recorded at 276nm using Shimadzu UV-VIS Spectrophotometer with matched quartz cells. Total content of metronidazole per tablet was calculated from the calibration curve or computed from the regression equation derived using the Beer's law data. The readings were taken in triplicate[14,15].

RESULTS AND DISCUSSION

The aim of present study was to evaluate the four brands of metronidazole 500mg tablets (A, B, C and D) purchased from the retail pharmacy outlet in Abha, Saudi Arabia with a view to ascertain their interchange ability in clinical practice. All the brands of metronidazole tablets used were within their self-life when study was carried as shown in Table No.1. The quality control metronidazole 500mg tablets of the selected brands were tested by analysing the following parameters; uniformity of weight, thickness and diameter, hardness, friability, disintegration time, dissolution tests and drug content. Prior to these evaluations analytical method was developed and validated, and absorption maxima of metronidazole was determined. The absorption spectrum of 6µg/ml solution of metronidazole in 0.1N HCl was recorded between 200-400nm. It exhibits λ_{max} at 276nm and the same is shown in Figure No.1. All the absorbance measurements were done at this wavelength. Absorbance of five standard solutions of concentrations 3, 6, 9, 12, 15µg/ml was measured at 276nm to construct calibration curve as depicted in Figure No.2. Following equation was used to determine pure drug content of MTZ in different tablets.

$y = 0.0353x + 0.0283$ ($R^2 = 0.9993$). Eq. (5)

The weight variations for 20 tablets from each brand are depicted in Figure No.3 and percentage weigh variation observed is shown in Table No.2. According to US Pharmacopeia, (not more than 2 tablets should deviate from the average weight by more than the 7.5% deviation). From the tabulated results, it was obvious that the deviations from the average weight were within limits in all branded tablets and all brands showed different mean weight; which indicates the use of different excipients in the different brands.

Results of thickness and diameter of the tablets quantified using micrometer screw gauge are depicted in Figure No.4 and Figure No.5. The results obtained for thickness and diameter of the tablets were well within the range and and complied with USP specifications with a deviation less than 5% from the mean value.

In order to judge the ability of tablets to resist chipping, abrasion or breakage during transportation, handling and storage hardness of the tablet is an important parameter. The hardness of the branded tablets was found to be in range 4.6-5.8kg/cm^2 (Table No.2). Figure No.6 depicts the bar graph of hardness of different selected brands of metronidazole tablets. Among all tablets Brand C required more pressure to break the tablet, where as Brand A required least pressure to break the tablet. Results of hardness for the all the brands were in the allowable Results obtained for friability test for 20 tablets from each brand is depicted in Figure No.7 and percentage friability noted is quoted in Table No.2. As per USP, conventional compressed tablets showing percentage friability less than 1% are acceptable. The % friability for the all the selected brands of Metronidazole tablets were within 1%; which is within the given limit as per the standards.

Disintegration of the dosage form is an important property of the tablet which is related to the dissolution rate of the drug. If tablet takes more time to disintegrate it will reduce the dissolution rate thereby reducing the rate of absorption; which

affect bioavailability of the drug. Disintegration time of the tablets also depends on type and quantity of excipients utilized in the formulation and manufacturing process as well. The disintegration time of branded tablets of metronidazole was analyzed as per USP. The branded tablets pass the disintegration test if each of the six tablets disintegrates in not more than 60 minutes. The results of the disintegration test of all brands (A, B, C and D) are presented in Table No.2. Tablet B disintegrated in less than 5.25±0.05 min whereas tablet D took long time of 14.02±0.03 min for entire tablet disintegration. The results showed that all the brands of metronidazole tablets used for the study have passed the disintegration test.

Amount of drug released with respect to time was measured by carrying out *in-vitro* drug release study. This study gives an idea of amount of drug available for absorption post oral administration. Drugs with poor dissolution profile would not be available in the GI for absorption and thus consequently wouldn't attain minimum therapeutic concentration in the system circulation to elicit the therapeutic effect.

The results of the *in-vitro* release of four branded tablets of metronidazole are shown in Figure No.8. At the end of 90 minutes of the *in-vitro* release test, the percentage drug release for brands A, B, C and D was found to 91.1%, 99.1%, 94.4% and 89.6%, respectively. More than 90% of the drug was released within 2 hr. The fit factor was expressed employing the similarity factor (f_2) approach in order to define the closeness between the *in-vitro* drug release profiles of branded tablets of metronidazole. The *f*2 values found for the product profiles A-B, B-C and C-D were 56.34, 67.33 and 58.72, respectively. Results of *f*2 values observed for all the dissolution profiles were in the range between 50-100 hence selected branded products profiles were considered as similar and bioequivalent.

According to US Pharmacopoeia, for each of the tablets tested for dissolution, the amount of active ingredient in solution should not be less than 70% of the prescribed or stated amount. Tablet C has highest release of drug in 15 min, whereas, tablet B show slower and gradual increase of drug and has depicted the better dissolution than other tablets. The results obtained from the present study have revealed that all the selected four brands of metronidazole tablets passes the USP general specifications for dissolution. Moreover, according to the Pharmacopoeia, metronidazole tablets should contain not less than 95% and not more than 105% of the stated amount of metronidazole. Amount of metronidazole in all the selected four brands have ranged from 94.93%-100%; which lies within the Pharmacopeia specified range. Compiled results of diverse quality control parameters and tests, for which the four brands of metronidazole tablets were subjected are presented in Table No.2.

Table No.1: Selected metronidazole tablets of different brands available in Saudi Arabia

S.No	Brand Code	Mfg. Date	Exp. Date	Labelled Strength
1	A	06/2016	06/2019	500mg
2	B	05/2017	04/2020	500mg
3	C	02/2017	02/2020	500mg
4	D	11/2016	11/2019	500mg

Table No.2: Results of quality control tests of selected four different brands of metronidazole tablet

S.No	Tablets	Thicknes (mm±SD)	Diameter (mm±S)	Hardness (kg/cm^2 ±SD)	Friability (%±SD)	Weight variation (%±SD)	Disintegration (min±SD)	Drug content (%±SD)
1	A	4.86±0.35	13.1±0.05	4.6±0.1	0.268±0.04	2.82± 0.42	8.2 ±0.014	94.93±1.12
2	B	4.8±0.41	12.9±0.01	5.3±0.2	0.287±0.05	0.57± 0.56	5.25 ±0.05	96.17±1.53
3	C	5.1±0.33	12.8±0.03	5.8±0.15	0.613±0.06	2.4 ± 0.12	6.19±0.08	96.86±2.39
4	D	5.3±0.37	12.9±0.04	5.7±0.21	0±0.05	4.41± 0.73	14.02±0.03	100.12±1.81

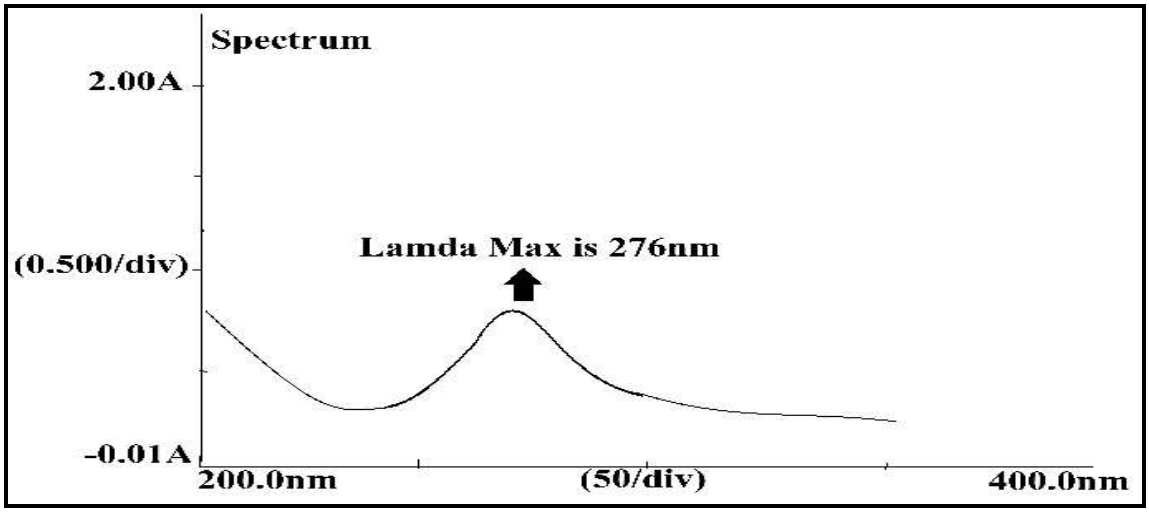

Figure No.1: Absorption spectrum of metronidazole

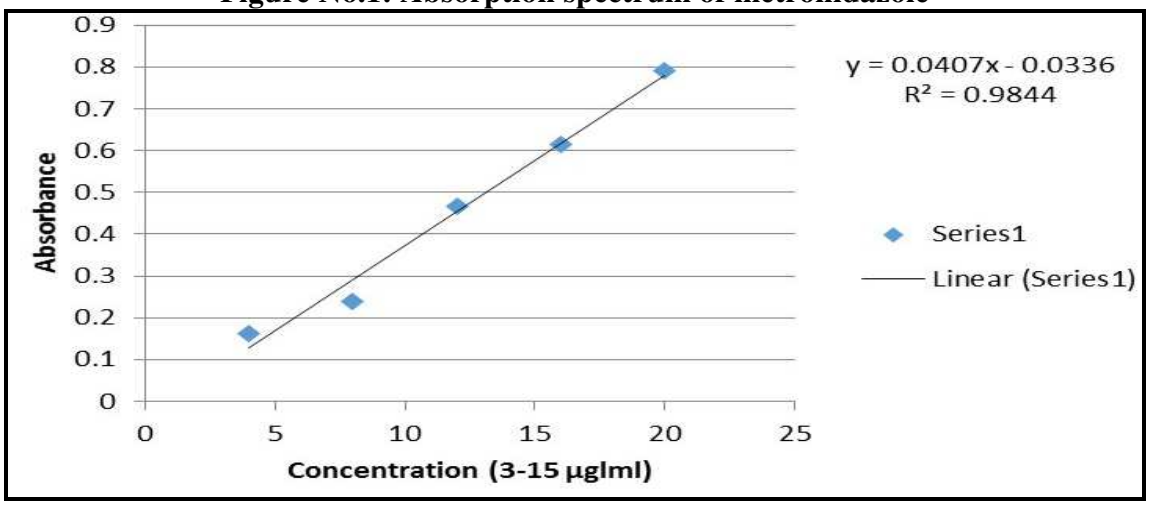

Figure No.2: Calibration curve of metronidazole

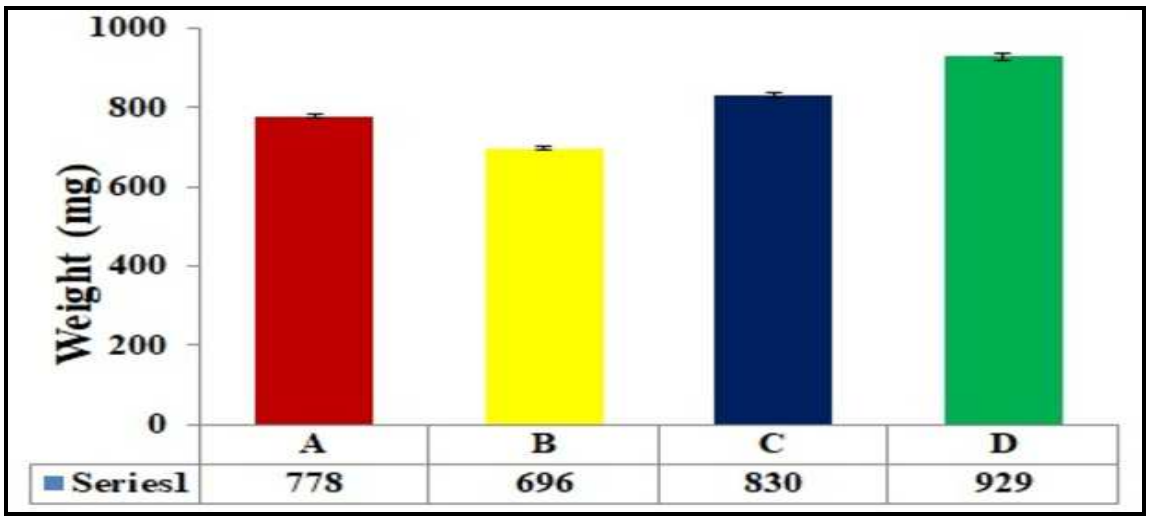

Figure No.3: Weight variations bar graph

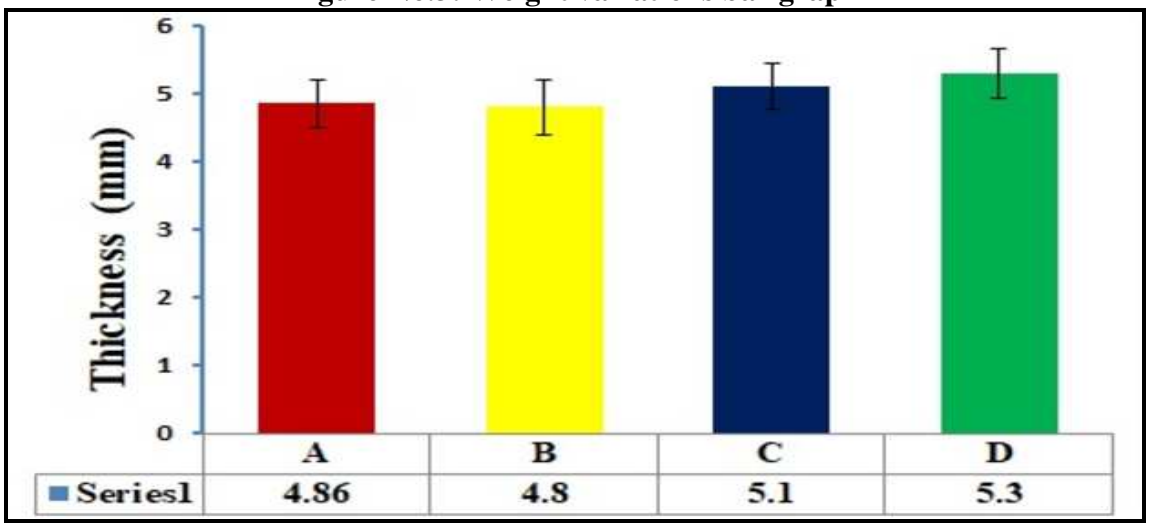

Figure No.4: Thickness determination bar graph

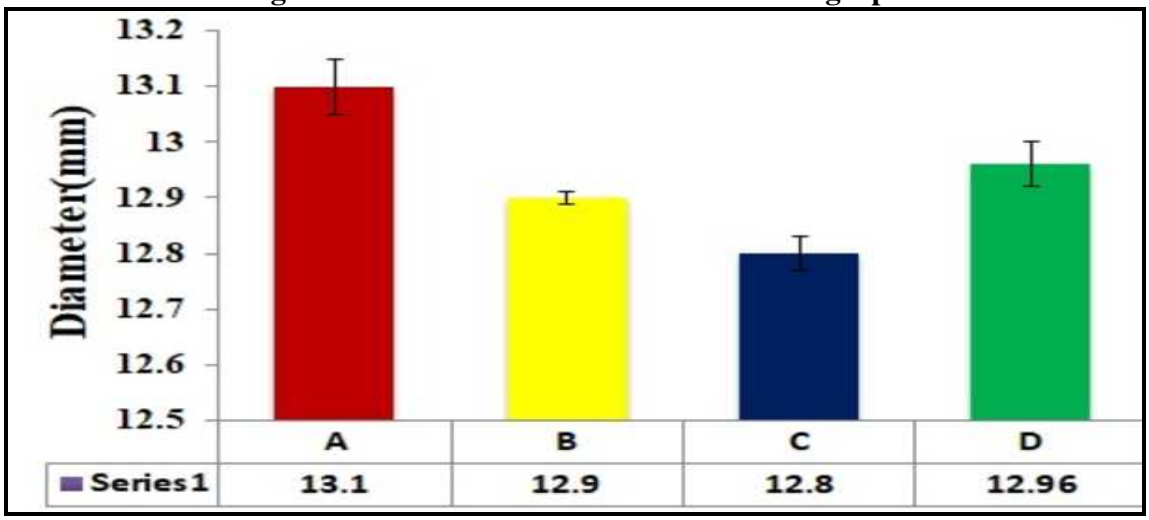

Figure No.5: Diameter determination bar graph

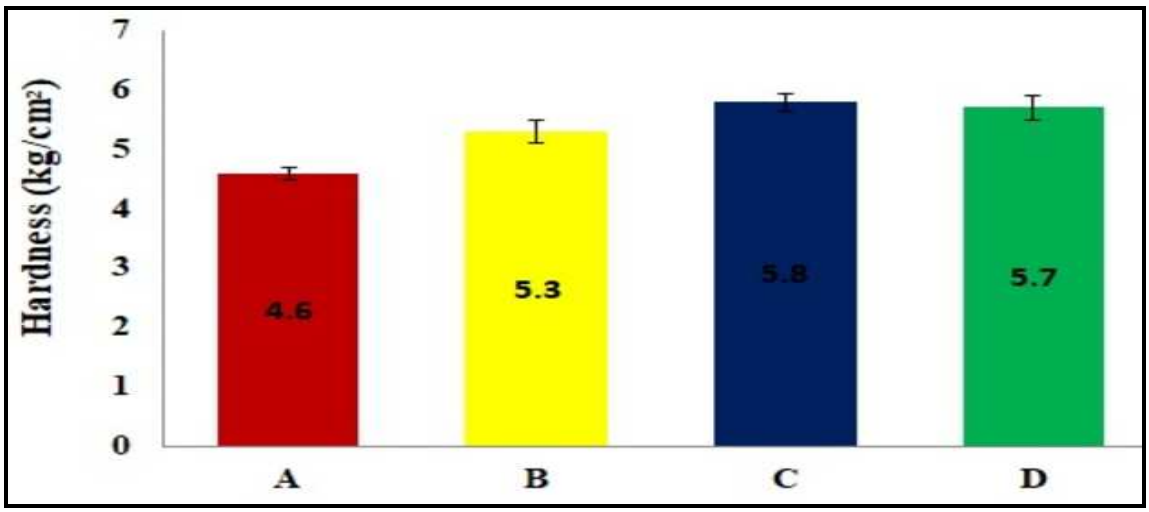

Figure No.6: Hardness determination bar graph

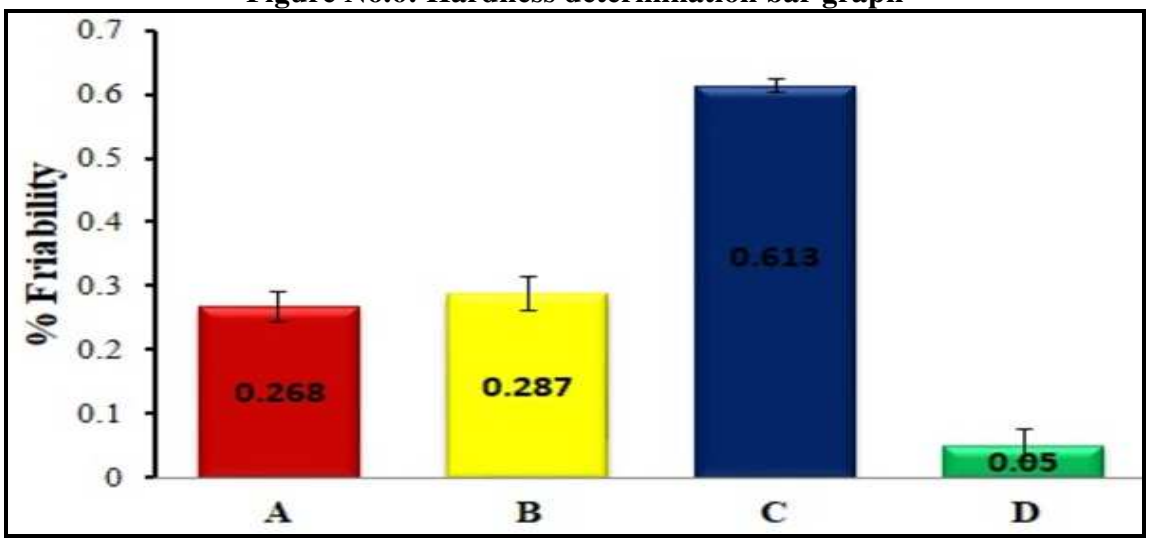

Figure No.7: Friability test bar graph

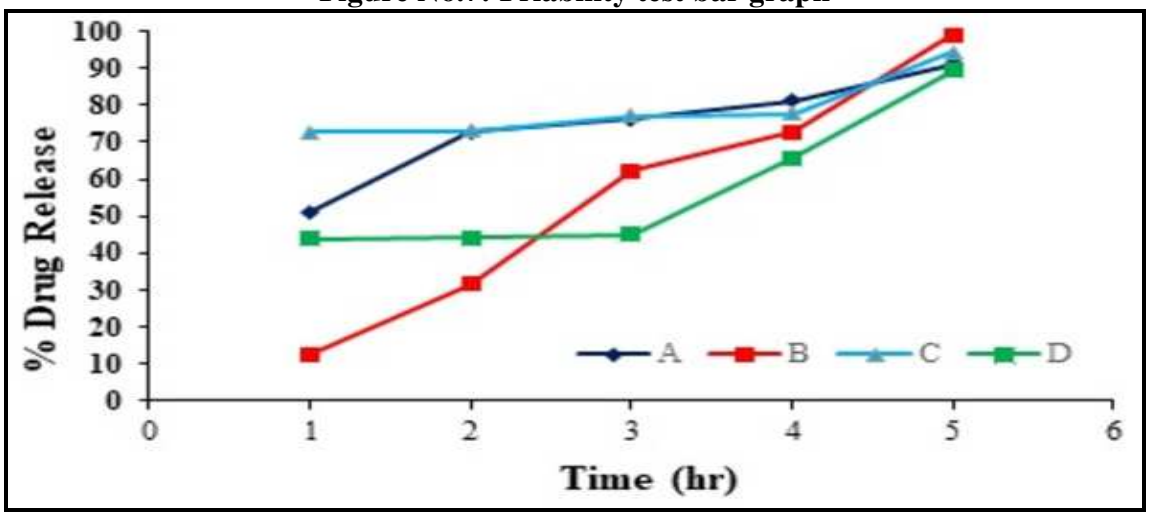

Figure No.8: *In vitro* drug release

CONCLUSION

Metronidazole is a commonly prescribed antiprotozoal drug for amoebiasis and other anaerobic infections. Currently many generic and multinational brands of this drug are available in the market in Saudi Arabia. The present study was carried out in order to evaluate various available brands of metronidazole tablets in Saudi Arabia for their performance to determine interchangeability of the brands by pharmacist and health care professional; when there is unavailability of any brand. Four different brands of Metronidazole 500mg were selected and coded as A, B, C and D. Small differences in the manufacturing process, different formulation factors such as type and amount of excipients, packaging or storage factors and substandard as well as counterfeit products could alter the disintegration, dissolution and other parameters that consequently lead to variation in therapeutic response. Physicochemical evaluation of pharmaceutical products is of great importance in ensuring the quality of drug products .The results of evaluation parameters for all chosen brands of metronidazole tablets have complied with specifications and limits of US Pharmacopoeia. All the selected brands were noted to be bioequivalent and all evaluations parameters such as weight variation, friability, hardness, disintegration and dissolution tests were well within the specified limits. The percentage friability was less than 1%. The percentage release of metronidazole from tablets was in the range between 89.6%-99.1% and drug content was in range between 94.93%-100%. Tablet C took 5.2 min to disintegrate, whereas the highest disintegration time of 14 min was shown by tablet D. *In-vitro* drug release was also noted to be good enough for optimum oral absorption and attainment of therapeutic blood concentration. The percentage content of active ingredient of four brands of metronidazole tablets showed values within the monograph specifications (95-105%). Thus, all the four brands evaluated in the present study could be considered as biopharmaceutically equivalent and hence, patients can safely switch from one brand to another when there is un availability of a particular brand or any other such circumstances occur.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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