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Research Article

Quality Control and Stability Studies of Some Selected Brands of Metronidazole Tablets Marketed in Daura Katsina State, Nigeria

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ABSTRACT

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Multi-source pharmaceutical products are intended to be pharmaceutically equivalent or pharmaceutical alternatives if they are bioequivalent and hence can be therapeutically equivalent and interchangeable. Thus, the need to assess different brands of the same generic to ensure the quality of these brands to achieve the same pharmacological value is necessary. Therefore, seven (7) brands of Metronidazole (200 mg) tablets marketed in Daura, Katsina State, Nigeria were selected randomly for the study. Quality control parameters and stability studies were conducted on these brands which include, identification test, weight variation test and friability test by official method. UV Spectrophotometric method was used to test for the assay of the selected brands. The presence of Metronidazole was observed in all the samples. The Assay percentages of the selected brands are in the range of 97.08 – 98.29 %. Weight variation are within acceptable limit except KK 5. The friability value of samples KK1, KK2 and KK7 showed acceptable levels of 1 % while KK 3, KK 4, KK 5 and KK 6 have values of 1.97 %, 5.30 %, 3.90 % and 100 % respectively. The stability of the samples at 0°C, 25°C, and 37.5°C showed insignificant change in the percentage content. However, at 50°C and 60°C a significant decrease in percentage content was observed. The samples of the Metronidazole 200 mg tablets analysed can be used interchangeably even though there was some variation in some of their pharmaceutical equivalences and storage temperature of Metronidazole tablets can be in the range of 25°C - 37.5°

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INTRODUCTION

Pharmaceutical products especially, tablets are the most widely used oral solid dosage form due to its advantages of compactness, stability, portability, blandness of taste and ease of administration. Hence, these dosage forms are convenient for both the manufacturer and the patient. Because of this, there is increase in the risk of being faked or counterfeited (Gu, *et al.*, 2016). Therefore, for a drug to be of good quality, it has to conform to standard requirements as prescribed in official

monographs. Therefore, it is the responsibility of the drug manufacturer to adopt and/or modify such procedures with the aim of producing drugs that are of good quality (Balat, 2006). These modifications by manufacturers bring about differences in brands. Metronidazole is of the tablet that has so many Brands. It is a nitroimidazole derivative, classified as tissue and luminal amoebicides. It is effective against protozoal infestations and bacterial infections (Naveed and Qamar, 2014).

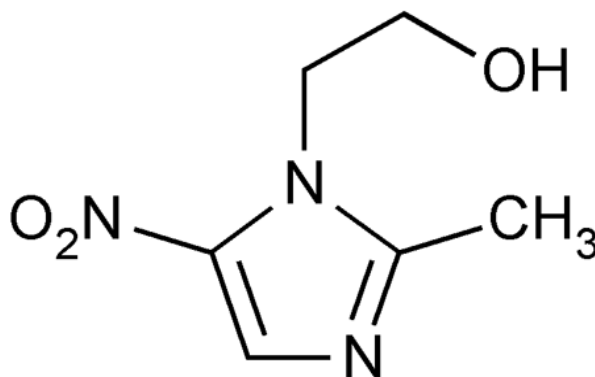


Figure 1: Metronidazole Structure

Daura, in Katsina State is a border town, which made it to be a susceptible to influx of all kind of drugs. Metronidazole, being a common antibiotic, it is likely to be misused or abused. It is also possible to have substandard drugs in area due tendency of people to have cheap pharmaceutical products. Therefore, the study intends to single out Metronidazole for quality control analysis of different brands being sold in the area. The whole town was mapped out into trapezium and samples were collected randomly.

MATERIALS AND METHODS

Equipment and Glasswares

Beakers, measuring cylinders, pipettes, volumetric flasks, Refrigerator, Analytical weighing balance by Mettler Phillip Harris., England 2011, UV spectrophotometer (Single beam 7315) by JENWAY, Bibby scientific Ltd. United Kingdom 2006, Friabilation apparatus (Type TA-3R, Euweka GmbH, Germany 2007)

Chemicals and Reagents

Distilled water, Deionised water, Sodium nitrite (0.2%), Sulphamic acid (0.5%), Hydrochloric acid (0.1M), Sodium hydroxide (5M), 2-naphthol solution (1%), Zinc powder

Samples Collection

Standard Metronidazole powder was obtained from Research Laboratory, Faculty of Pharmaceutical Sciences, University of Lagos Nigeria. Seven (7) brands of Metronidazole were purchased from different pharmacy shops and other Drug outlets located within Daura metropolis Katsina state, Nigeria.

METHODS

Physical Examination

A sachet containing 10 tablets for each of the samples was randomly taken, the tablets were removed and examined for lustre, colour, texture, nature of surface and presence of score (BP, 2009).

Weight Variation

Twenty tablets were randomly selected. The tablets were weighed individually and collectively. The individual weights were compared with the average weight. Mean weight was calculated and the deviation from the mean for each tablet was calculated (B.P. 2009).

Friability Test

Ten tablets of each sample were initially weighed and then placed in friabilator which operated at 25 revolutions per minute. After 4 minutes run, the remaining intact tablets were removed, dusted with a tissue paper and reweighed. The loss in weight was noted and the percentage lost calculated (B.P. 2009).

Identification Test

Tablets powder containing 10 mg of Metronidazole, 10 mg of Zinc power, 1 ml of deionised water and 0.25 ml of Hydrochloric acid were mix in a test tube and heated on a water bath for 5 minutes. The test tube was cooled, then 0.5 ml of Sodium nitrite solution was added and the excess nitrite was removed with sulphamic acid. Then 0.5 ml of 2-naphthol solution and 2 ml of 5 M Sodium hydroxide were added. The procedure was repeated for all the samples and the reference standard powder (B.P. 2009).

Preparation of Metronidazole Standard (20 µg/ml):

A quantity of the standard Metronidazole powder weighing 4 mg was carefully transferred into 100 ml cleaned and dried volumetric flask. 20 ml of 0.1 M HCl acid was added. The flask was vigorously shaken to dissolve the powder and the volume made up to the mark with same acid. The resulting solution was 0.04 mg/ml from which a stock solution of 0.02 mg/ml was formed through serial dilution method (USP. 2008)

Construction of Calibration Curve

A quantity of Metronidazole Standard powder weighing 4 mg was dissolved in 100 ml of 0.1 M HCl as the stock solution. Concentrations of 0.5, 1, 2.5, 5, 10, 15, 20, 25, 30, 35 and 40 µg/ml were prepared from the stock solution. A calibration graph of Absorbance against Concentration was plotted.

Procedure for Assay

Method was adopted from United States Pharmacopoeia (USP 2008) and Validated. One tablet of Metronidazole was transferred to a 250-ml volumetric flask. 100 ml of dilute hydrochloric acid (0.1 M) was added and shaken for 30 minutes. It was then diluted with same acid to volume. It was mixed and filtered. Then the first 15 ml of the filtrate was discarded. 0.2 mg/ml of Metronidazole was prepared from the filtrate with dilute hydrochloric acid (0.1 M). 10 ml of this solution was mixed with 90 ml of same acid to make a concentration of 20µg/ml. It was scanned at wavelength of 278 nm and the Absorbance of each was taken. The concentration of each of the samples was extrapolated to its Absorbance on the calibration graph (USP. 2008).

Validation of the Method

The precision of the adopted method for both intra-day and inter-day analysis was carried out by selecting three (3) prepared concentrations from serial dilution. Each concentration was run six (6) and their percentage coefficient of variation was calculated.

Stability Studies

The solutions used were prepared the same as that of Assay for all the samples and 20µg/ml of the standard. They were all treated at 0, 25, 37.5, 50 and 60°C for 24 hrs, 24 hrs, 24 hrs, 1 hr and 1 hr respectively, and then their respective absorbance was measured and percentage content was calculated (USP. 2008).

RESULTS

Calibration Curve

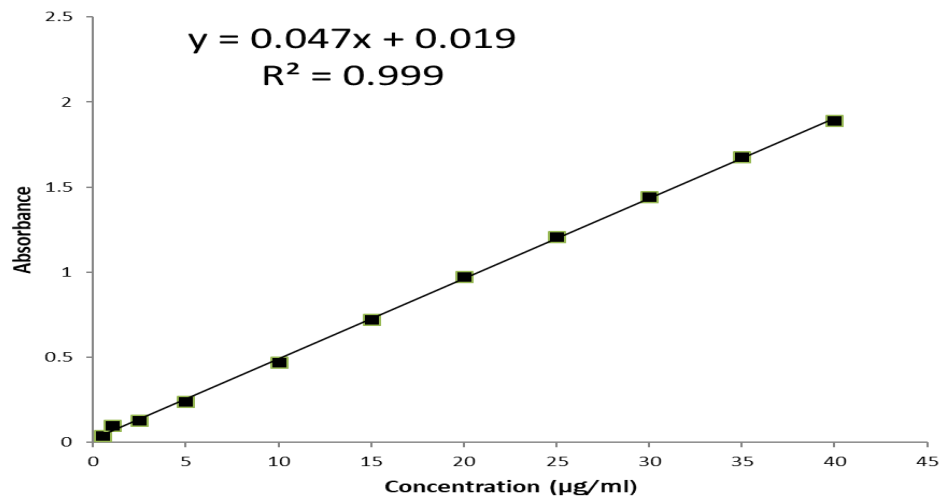


Figure 2: Calibration Curve

Table 1: Labels of Randomly Selected Samples

Brand	Country of Origin	Batch number	NAFDAC Number	Manufactured Date	Expiry Date
KK 0	Nigeria	T2416779	04-9696	June, 2023	May, 2026
KK 1	Nigeria	T2423135	04-9620	June, 2023	May, 2026
KK 2	Nigeria	MET 22/007	A4-2057	November, 2022	October, 2025
KK 3	Nigeria	008	A4-8497	September, 2023	August, 2026
KK 4	Nigeria	MEW 23108	04-5624	December, 2023	November, 2026
KK 5	Nigeria	S24023	04-0275	January, 2023	December, 2026
KK 6	Nigeria	M32005	A4-2069	October, 2023	September, 2026

Table 2: Results for Assay

Brands	Wavelength (nm)	Absorbance	Concentration (mg)	Percentage content (%)
KK 0	278	3.250	194.16	97.08
KK 1	278	2.612	194.32	97.16
KK 2	278	1.161	196.22	98.11
KK 3	278	1.062	196.58	98.29
KK 4	278	3.153	194.18	97.09
KK 5	278	3.161	194.18	97.09
KK 6	278	1.746	195.20	97.60

Table 3: Result Precision of the Method

Sample	Concentration µg/ml	CV %	N
Intraday run	0.5	3.4 ± 0.56	6
	5.0	1.8 ± 0.87	6
Inter-day run	25	0.5 ± 0.64	6
	0.5	4.2 ± 0.23	6
	25	3.5 ± 0.41	6
	25	1.2 ± 0.04	6

CV = Coefficient of Variation; N = Number of repeat test

Table 4: Results for Friability Tests

Brands	Initial weight of 10 tablets (mg)	Final weight of intact tablets (mg)	Net difference (mg)	Friability (%)
KK 0	4.990	4.952	0.038	0.76
KK 1	4.432	4.421	0.011	0.25
KK 2	4.301	4.261	0.040	0.93
KK 3	4.001	3.922	0.079	1.97
KK 4	3.791	3.590	0.201	5.30
KK 5	3.182	3.055	0.127	3.99
KK 6	6.521	0.000	6.521	100

Table 5: Results for Uniformity of Weight

Brands	Average weight of 20 tablets (mg)	Number of tablets deviated by ≥ 5%	Standard Deviation %
KK 0	498.33	None	15.81
KK 1	445.12	None	11.34
KK 2	431.24	None	11.37
KK 3	404.19	2	14.46
KK 4	378.25	1	13.12
KK 5	319.96	5	15.20
KK 6	650.7	2	24.29

Table 6: Results for Stability Studies

Brands	0°C		25°C		37.5°C		50°C		60°C		Standard Deviation
	Content (%)	Net loss (%)	Content (%)	Net loss (%)	Content (%)	Net loss (%)	Content (%)	Net loss (%)	Content (%)	Net loss (%)	
KK 0	97.08	0.00	97.08	0.00	97.08	0.00	97.06	0.02	96.03	1.05	0.467
KK 1	97.15	0.01	97.16	0.00	97.16	0.01	97.11	0.05	96.10	1.06	0.468
KK 2	98.11	0.00	98.11	0.00	98.11	0.00	98.10	0.01	97.00	1.11	0.495
KK 3	98.28	0.01	98.29	0.00	98.28	0.01	98.26	0.03	97.30	0.99	0.437
KK 4	97.08	0.01	97.09	0.00	97.08	0.01	97.00	0.09	96.00	1.09	0.477
KK 5	97.08	0.01	97.09	0.00	97.08	0.01	97.06	0.03	96.10	0.99	0.437
KK 6	97.58	0.02	97.60	0.00	97.54	0.06	96.20	1.40	95.51	2.09	0.973

DISCUSSION

All the seven samples of Metronidazole tablets examined were registered with the NAFDAC and have reasonable shelf life as shown in table 1. Similarly, the seven brands of Metronidazole tablets as well as the reference standard produced the orange-red color indicating the presence of Metronidazole in each of the samples according to the BP 2009 and USP 2008.

The assay test was conducted using UV Spectrophotometric method and the percentage content was found to be in the range of 97.08 – 98.29 % (Table 2). The values were in agreement with the United States Pharmacopoeia (USP 2008) and International Pharmacopoeia (IP 2003) specification of 90 - 110 % for tablets dosage form. While BP (2009) specification for Metronidazole tablets is 85 – 115%. This shows that all the samples of Metronidazole tablets as well as the reference standard collected were chemically equivalent to each other. This was similar to a research where the content uniformity of 12 samples of Metronidazole tablets were found to be in the range of 92.45 - 106.14 % which were all within the normal range with reference to the same BP 2009 (Aliyu, 2010).

All the samples, with the exception of KK5, complied with the BP (2009) specification for uniformity of weight which states that for tablet weighing 200 mg or more, weight of not more than two (2) tablets should differ from the

average weight by more than 5 %. Five (5) tablets deviated by 5 % for sample KK5 which was an indication of deviation from the compendia specifications (Table 3). This might be as a result of non-uniformity of active ingredient and pressure difference during the compression process (Mullaicharam, *et al.*, 2012). However, the difference in inter batches could be attributed to variations in percentage of excipients, especially diluents, or bulking agents, which is usually the decision of formulation pharmacist (Ibezim, *et al.*, 2008). Uniformity of weight does serves as a pointer for good manufacturing practice (GMP) as well as amount of the Pharmaceutical ingredient (API) in a product (Ngwuluka, *et al.*, 2009).

Tablet friability is used to evaluate tablets resistance to abrasion (B.P. 2009). The acceptable limit maximum is 1 % (B.P. 2009). This research work showed that all samples had acceptable friability values with the exception of KK3, KK4, KK5 and KK6 which have a friability value of 1.97 %, 5.3 %, 3.99 % and 100 % respectively (table 4). The high friability value for KK6 is an indication of using binder with low adhesive strength or absence of binder, as well as tableting done under low compressing force (Ibezim, *et al.*, 2008). This was similar to a research conducted where all the brands of the samples had acceptable friability values with the exception of those with 1.70 %, 1.81 %, 1.62 % and 10.25 % friability respectively (Aliyu,

2010). This is clear indication that not tabulated medicine fall within acceptable range.

The Stability Study showed there was an insignificant change in the percentage content at temperatures 0°C and 37.5°C. At 25°C there was no loss in content recorded. This was also similar to a stability research for two brands of Metronidazole stored at 25°C which gave a shelf life of 4.96 years while storage at 30°C gave 3.86 years (Oga and Ochekepe, (2009). Similarly, Stability studies were carried out for most satisfactory formulation at $30 \pm 2^\circ\text{C} / 65 \pm 5\% \text{ RH}$ and $40 \pm 2^\circ\text{C} / 75 \pm 5\% \text{ RH}$ for two months as per ICH guidelines. At various time intervals of 30 days and 60 days, those samples were evaluated and there was no major change in the various physiochemical parameters evaluated (Rajeshwar, *et al.*, 2014).

However, at 50°C a significant decrease in potency was observed in KK1, KK4 and KK6 with 0.05%, 0.09% and 1.4% loss respectively. At 60°C, a more significant loss was observed with percentage loss of all samples were found to be significant, ranging from 0.99 – 2.09%. This is possibly because the increase in temperature condition accelerates the chemical reactions within the tablets, leading to the breakdown of the active ingredient. This can reduce the efficacy of the drug or even render it ineffective (Ogah, *et al.*, 2002).

CONCLUSION

All the seven samples of Metronidazole tablets as well as the Reference Standard passed the identification test for Metronidazole. The samples also passed percentage content test as they show an acceptable level of percentage active ingredient present and thus can be used interchangeably. This shows that there is no difference in the pharmaceutical, physical and chemical equivalences between the selected brands of Metronidazole marketed in Daura metropolis as shown by this research. However, there was variation in the Pharmaceutical parameters of the samples. Sample KK5 failed weight variation test. KK3, KK4, KK5 and KK6 failed friability test; with KK6 recording 100% friability index. Stability studies revealed 25°C - 37.5°C as recommended temperature storage for the tablets studied.

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