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Evaluation of the Quality and *In Vitro* Pharmaceutical Equivalence of Generic Metronidazole Tablet Brands Marketed in Kenya

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Metronidazole is one of the most affordable, accessible and prescribed antimicrobials. It is included in the Essential Medicines List by the World Health Organization due to its pivotal role in public health. This study sought to evaluate the quality and pharmaceutical equivalence of generic metronidazole tablet brands marketed in Kenya. Nine metronidazole tablet brands were subjected to standard physicochemical tests for identity, uniformity of weight, friability, hardness, disintegration, assay, and dissolution as specified by the British Pharmacopoeia and the United States Pharmacopeia. The dissolution data of the eight generic brands were compared to that of the innovator brand using fit factors f_1 and f_2, and dissolution efficiency. All the nine metronidazole tablet brands complied with the tests for identity, friability, hardness, disintegration, and dissolution. One brand (11.1%) failed the test for uniformity of weight, while four brands (44.4%) did not meet the compendial limits for assay with values less than 95.0% label claim. The analyzed metronidazole tablet brands had similar drug release profiles and may therefore be considered pharmaceutical equivalents. Although most of the generic metronidazole tablet brands analyzed in this study are of the required quality, regular post-marketing surveillance is recommended to ensure that non-compliant pharmaceutical products are flagged and corrective actions instituted.

Keywords: Metronidazole tablets, quality parameters, pharmaceutical equivalence.

INTRODUCTION

Medicines for humans and animals must comply with defined quality, safety, and efficacy (QSE) attributes to achieve the desired pharmacological response and preclude avoidable side effects. The QSE attributes for medicinal products for human use are stipulated in the International Council for Harmonization (ICH) of Technical Requirements of Pharmaceuticals for Human Use guidelines.[1] The third sustainable development goal of the United Nations, that advocates for universal health coverage (UHC), targets the achievement of "access to safe, effective, quality, and affordable medicines and vaccines for all".[2] Therefore, quality medicines are necessary for the attainment of UHC.[3] Unfortunately, the variability of QSE attributes of medicines in the clinical market is one element that contributes to inefficiency in the healthcare systems. The World Health Organization (WHO) estimates that in low- and middle-income countries (LMICs), there is one substandard or falsified medicinal product in every ten. A meta-analysis carried out by Ozawa *et al.* in 2018 indicates that 13.6% of essential medicines in LMICs were substandard or falsified, with a higher percentage being antimalarials (19.1%) and antibacterials (12.4%). The highest prevalence of these substandard and counterfeits was reported in Africa (18.9%), followed by Asia (13.7%).[4]

After the introduction of the innovator brand to the market, it takes time before generic products containing the same active pharmaceutical ingredient (API) are approved.[5] The WHO recommends use of generic brands in developing countries to reduce the cost of medication and treatment[6] because the price difference between generic and innovator brands can be as high as over 90%. For a generic product to be a proper substitute for the innovator brand, it must contain the same amount of the API in the same dosage form and for similar routes of administration. In

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addition, there should be no significant difference in the availability of the drug at the site of action between the innovator and generic brands when administered at the same molar dose under similar conditions in an appropriate study.[7,8]

Metronidazole is a synthetic 5-nitroimidazole antimicrobial with antibacterial and antiprotozoal activities.[9,10] It is used singly or in combination to treat endocarditis, pelvic inflammatory disease, meningitis and brain abscess, bacterial vaginosis, and mild to moderate *Clostridium difficile* colitis as an alternative to vancomycin.[11] The drug is also effective for intestinal and liver amoebiasis, trichomoniasis, giardiasis, and dracunculiasis. Metronidazole was first marketed for clinical use in 1959 by Sanofi-Aventis under the brand name Flagyl®.[12] Several generic brands have since been introduced in the global market. The price for metronidazole tablet brands available in Kenya is in the range of USD 0.0068-0.1 per tablet, which gives a 93.3% price differential.

Metronidazole is also among the most prescribed antimicrobials in Kenya. A study conducted in public hospitals in Kenya in 2020 showed that 20% of the total prescriptions contained 5-nitroimidazole derivatives (mainly metronidazole), second only to cephalosporins, which was the most prescribed therapeutic class at 26.0%.[13] Another study at Kenyatta National Hospital, Kenya, showed that 20% of the prescriptions contained metronidazole, as the third most single-prescribed antibiotic after benzylpenicillin (25.1%) and ceftriaxone (39.7%).[14] The high demand has resulted in enhanced local manufacture and importation of metronidazole multisource drug products (MSDPs), hence the compelling need for continuous post-market surveillance (PMS) of the drug product to ascertain the quality of various generic brands in the Kenyan market and their clinical interchangeability.

EXPERIMENTAL

Materials and reagents

Eight generic formulations of metronidazole tablets with marketing authorization in Kenya and Flagyl® were purchased from different retail pharmacies in Nairobi Central Business District in their original packaging. All the pharmaceutical tests were performed within the expiry dates of the products. Metronidazole BP (99.68% w/w, Hubel Hongyuan) chemical reference substance (CRS) was purchased from Hubel Hongyuan Pharmaceutical Technology Co. Ltd (Cairo, Egypt). Concentrated HCl was from Finar Limited Chemicals Co. (Telangana, India).

Equipment

An SP-UV 500 DB Spectrophotometer (Shanghai Spectrum Instruments Co., Shanghai, China) was used to obtain ultra-violet (UV) light spectra and absorbances of all test solutions. The weight measurements were taken on a Shimadzu AUW220D electronic semi-micro analytical weighing balance (Shimadzu Corporation, Kyoto, Japan). A Wise Clean® ultrasonic bath (DAIHAN Scientific Co., Ltd Seoul, Korea) sonicator was used to hasten the dissolution of metronidazole tablet powders.

Dissolution testing was conducted using an Electrolab dissolution tester (Electrolab India Pvt. Ltd, Mumbai, India) fitted with type 1 apparatus, while disintegration was conducted on an Erweka-Apparatebau-G.m.b.H. disintegration tester (Heusenstamn Kr. Offenbach/Main, Western Germany). Friability was performed using a TA3R Erweka-Apparatebau-G.m.b.H. friabilator (Heusenstamn Kr. Offenbach/Main, Western Germany) while a Schleuniger-2E Electronic hardness tester (Dr. K.Schleuniger and Co, Switzerland) was employed in determining the mechanical strength of the tablets.

Test for identity

The test for identity was performed according to the United States Pharmacopeia (USP) 2018 specifications. For each brand, a 15 mg/ml metronidazole test solution was prepared in 0.1N HCl from powdered tablets. The solutions were shaken and sonicated to dissolve and filtered. A standard solution of metronidazole CRS was similarly prepared. The UV absorption spectra of the test and standard solutions were obtained in the UV (200-400 nm) region. The absorption maxima and minima wavelengths of test solutions were compared to the metronidazole CRS.

Assay

The API content of each metronidazole tablet brand was determined by UV spectrophotometry according to the procedure described by Noor et al.[15] with slight modifications.

Preparation of the standard curve

A 10 mg aliquot of metronidazole CRS was dissolved in 0.1N HCl in a 100 ml volumetric flask and made to volume. A 40 ml aliquot was pipetted into a 100 ml volumetric flask and made to volume using 0.1N HCl, giving a 40 µg/ml stock solution. From the stock solution, 10 ml dilutions of 4, 8, 12, 16, 20, 24, and 28 µg/ml of metronidazole were made and their UV absorbances measured in triplicate at 275 nm against 0.1N HCl blank. A calibration curve was prepared by plotting a chart of mean absorbance versus metronidazole concentration.

Preparation of metronidazole test solutions

Twenty metronidazole tablets for each brand were weighed and ground to a fine powder using mortar and pestle. Quantity of powder equivalent to 30 mg metronidazole was dissolved in 0.1N HCl to 100 ml solution with sonication and filtered. A 5.0 ml aliquot was diluted to 100 ml using 0.1N HCl. The UV absorbance of the resulting solution was measured in triplicate at 275 nm against 0.1N HCl blank. The metronidazole content was calculated against the metronidazole CRS and evaluated for compliance with the British Pharmacopoeia (BP) 2017 specifications.

Disintegration

Six tablets of each brand were placed in six baskets of the disintegration tester independently and lowered into a one litre vessel containing 900 ml distilled water maintained at 37±1°C. The time taken for complete disintegration of each tablet was recorded, and the average thereof compared to BP (2017) specifications.

Uniformity of weight

Twenty tablets were dusted and weighed individually, and the average weight determined. The percentage weight deviation of each tablet from the mean weight was calculated and compared to the acceptance criteria for weight variation in the BP (2017).

Friability

Twenty tablets were weighed, placed in the friabilator, and tumbled at 25 revolutions per minute (rpm) for four minutes. The friabilated tablets were dusted, re-weighed, the weight loss calculated, and the percent friability compared to the USP (2018) acceptance criteria.

Test for mechanical strength

Six tablets were each placed between the jaws of an electronic hardness tester, oriented similarly relative to the direction in which the force was applied, and the load scale set to zero. The force that initiated the tablet fracture was recorded, and the average mechanical strength calculated.

Dissolution testing and in vitro pharmaceutical equivalence

Dissolution testing was carried out according to the USP (2018) method using 900 ml 0.1N HCl maintained at 37±0.5°C. Six tablets of each brand were placed individually in separate baskets, and dissolution carried out at 100 rpm for 60 min. At 5, 15, 30, 45 and 60 min, 5.0 ml aliquots were sampled and replaced with an equal amount of fresh dissolution medium to maintain sink conditions. The solutions were filtered, and metronidazole concentration determined by UV spectrophotometry at 278 nm. The percentage amount of metronidazole dissolved was computed and compared to the USP (2018) specifications. The dissolution profile of each brand was determined from the graph of the percentage amount of metronidazole released relative to time. The difference factor (f_1), similarity factor (f_2), and dissolution efficiency (DE) were determined from the dissolution data.

Data analysis

The data for uniformity of weight, friability, hardness, disintegration, and assay were tabulated, while the dissolution profiles were represented graphically. Fit factors f_1 and f_2, and the DE, calculated according to Equations 1, 2, and 3, respectively, were used for the comparative *in vitro* pharmaceutical equivalence. The area under the curve (AUC), represented by the integral of the numerator, was calculated using the trapezoidal rule (Equation 4).

$$f_1 = ([\sum_{t=1}^{n}|Rt - Tt|]/[\sum_{t=1}^{n} Rt])x\ 100 \quad \textit{Equation 1}$$

$$f_2 = 50.log\left(\left[1 + \frac{1}{n}\sum_{t=1}^{n}(Rt - Tt)^2\right]^{-0.5} x100\right) \quad \textit{Equation 2}$$

$$DE = \frac{\int_{t1}^{t2} y.dt}{y_{100}\, x\, (t_2 - t_1)} x100 \quad \textit{Equation 3}$$

$$AUC = \sum_{i=1}^{i=n} \frac{(t_1 - t_{i-1})(y_{i-1} + y_i)}{2} \quad \textit{Equation 4}$$

Where:
y is the percentage of the product that is dissolved.
DE is the area under the dissolution-time curve between the time points t_1 and t_2 expressed as a percentage of the curve at maximum dissolution ($y100$) over the same period.

RESULTS

Quality parameters

Table 1 summarizes the test results for uniformity of weight, hardness, friability, assay, and disintegration. The metronidazole tablet brands were coded using numerals and the prefix MTZ (MTZ-01–MTZ-09), with MTZ-01 being the innovator brand. Out of the nine brands analyzed, four (44.44%) complied with all the quality specifications tested. Conversely, one brand (11.11%) did not comply with the test for uniformity of weight, while four (44.44%) did not comply with the assay specification.

The test for identity confirms the presence of API in drug products. All nine metronidazole brands complied with the USP (2018) test for identity by UV spectroscopy compared to the standard solution maxima (276.8 nm) and minima (241 nm). The test for uniformity of weight is an indicator of Good Manufacturing Practices (GMP) with respect to process optimization.[16] Brand MTZ-01 failed the test for uniformity of weight with three tablets having more than 5% weight deviation.

The hardness test is a non-compendial quality parameter that evaluates the ability of a tablet to withstand forces encountered during handling, packaging, and transit without fracturing, crumping, or chipping.[17] Additionally, it influences other parameters, such as disintegration and friability. Tablet hardness depends on the geometry of the tablets. MTZ-09 needed the least force (47.6 N ±8.63), while MTZ-03 needed the highest force to initiate fracture (148.2±11.97 N). All nine brands met the acceptance criteria for mechanical strength (minimum force of 40 N).[18] The friability test evaluates the ability of tablets to withstand forces of abrasion and attrition.[19] All the nine brands analyzed complied with the USP (2018) specification for friability. When placed in an aqueous medium, the disintegration test measures the time a tablet takes to break into smaller particles.[20] All nine brands were film-coated and met the BP (2017) specification for disintegration (30 min).

Assay determines whether the drug formulation contains the API at the requisite content.[21] The quantitation of metronidazole in the test samples was based on a linear calibration curve of equation; $y = 0.0375x + 0.0027$ ($r^2 = 0.9992$), in the 0–28 µg/ml range. When compared against the BP (2017) specifications, four (4) brands failed to meet the limits for metronidazole content (95.0%–105.0% of the label claim). These were MTZ-04 (90.6 %), MTZ-05 (90.1%), MTZ-06 (89.5%), and MTZ-07 (94.9 %).

Dissolution profiles

Similar drug products containing the same API but formulated differently may differ in their drug release characteristics.[22] All nine brands complied with the USP (2018) specification of at least 85% metronidazole released within 60 min. The results of the dissolution study are summarized in Table 2, while the dissolution profiles are graphically represented in Figure 1. In this study, the dissolution profiles were compared using two methods, the fit factors f_1 and f_2, and the DE as summarized in Table 2. The DE was calculated by comparing the dissolution profiles of the generic brands to that of the innovator brand expressed as percent deviation.

Table 1: Quality control test results of the analyzed metronidazole tablet brands

Brand code	Average weight ± SD	Deviation from average weight (%)	Hardness (N) average (± SD)	Friability (%)	Assay (%) (SD)	Disintegration time in min (SD)
MTZ-01	0.430 (0.0100)	-8.45-5.63	91.1 (5.28)	0.95	97.0 (0.0011)	1.41 (0.23)
MTZ-02	0.604 (0.0075)	-2.32-2.65	132.2 (13.75)	0.15	103.0 (0.0044)	0.94 (0.16)
MTZ-03	0.579 (0.0044)	-1.55-1.90	148.2 (11.97)	0.16	103.5 (0.0095)	0.78 (0.17)
MTZ-04	0.519 (0.0112)	-5.59-4.05	112.3 (16.41)	0.18	90.6 (0.0056)	15.52 (7.59)
MTZ-05	0.492 (0.0158)	-6.50-3.66	80.7 (12.32)	0.73	90.1 (0.0179)	0.47 (0.11)
MTZ-06	0.548 (0.0133)	-5.02-4.11	121.9 (10.91)	0.48	89.5 (0.0125)	1.32 (0.23)
MTZ-07	0.448 (0.0072)	-3.91-2.79	70.0 (2.62)	0.59	94.9 (0.0064)	0.67 (0.14)
MTZ-08	0.242 (0.0059)	-4.76-3.52	114.0 (11.09)	0.36	101.0 (0.0061)	9.44 (1.74)
MTZ-09	0.273 (0.0072)	-4.59-2.75	47.6 (8.63)	0.32	99.6 (0.0159)	2.59 (0.48)

Key: MTZ-01= Innovator brand; SD= Standard deviation

Table 2: Dissolution data, calculated fit factors f_1 and f_2, and dissolution efficiencies of metronidazole tablet brands

	Percentage metronidazole released (average, n=6)					Fit factors		Dissolution efficiency	
Brand code	5 min	15 min	30 min	45 min	60 min	f_1	f_2	Area under the curve	Deviation (%)
MTZ-01	95.2	96.8	97.5	97.6	101.2	-	-	56.10275	0.00
MTZ-02	64.9	95.1	100.8	103.0	103.8	9	43*	55.11725	1.76
MTZ-03	99.5	99.8	100.8	101.1	101.7	3	73	58.00075	3.38
MTZ-04	91.7	99.9	100.5	100.5	101.1	3	73	57.47375	2.44
MTZ-05	92.8	95.1	100.7	101.5	101.7	3	71	57.33000	2.19
MTZ-06	95	99.1	99.7	100.3	100.8	2	84	57.05825	1.70
MTZ-07	89.2	95.8	96.8	97.9	99.4	2	76	55.31175	1.41
MTZ-08	60.1	94.7	96.6	97.6	98.1	14	38*	57.82600	3.07
MTZ-09	94.9	97.5	98.1	98.5	99.1	1	91	56.22150	0.21

MTZ-01= Innovator brand; *= Failed to meet the specification for f_2.

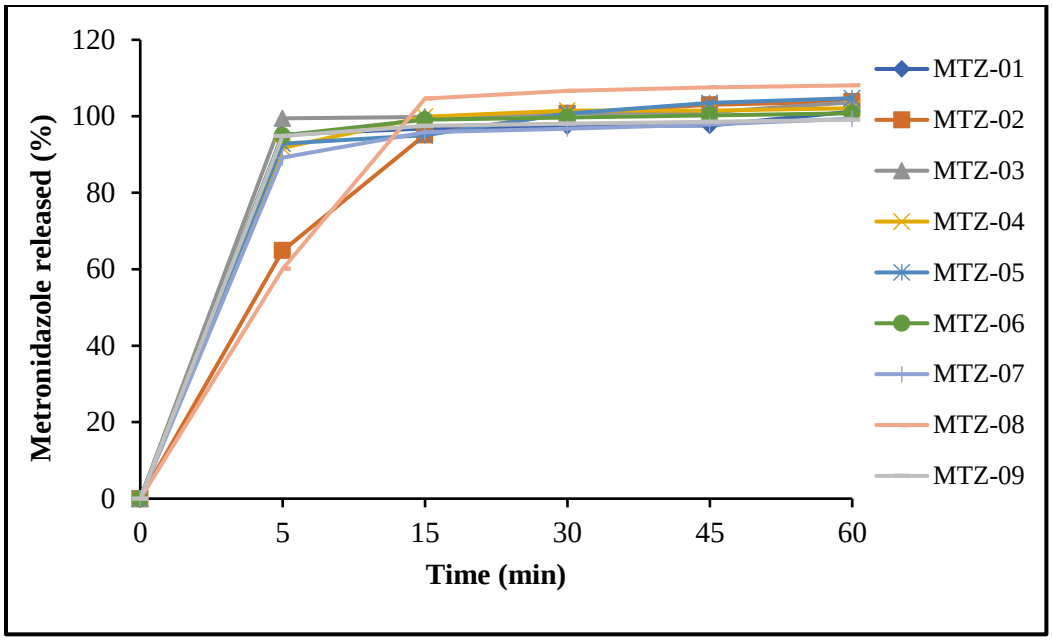

Figure 1. Dissolution profiles of the analyzed metronidazole tablet brands.

The dissolution profiles of the generic brands were all within the acceptable limits of 0–15 to that of the innovator brand with respect to f_1 values. However, with respect to f_2, two brands, MTZ-02 (f_2=43) and MTZ-08 (f_2=38), failed to meet the acceptable limits of 50-100.[22] Hence, all the eight MSDPs may be considered pharmaceutically equivalent to the innovator brand based on the difference factor f_1, but according to similarity factor f_2, MTZ-02 and MTZ-08 are non-equivalent. On the other hand, based on the DE parameter, the percentage deviations of the metronidazole MSDPs were less than 10%, indicating that at any one point in the dissolution-time curve, the amount of metronidazole released from each of the eight MSDPs did not deviate from the innovator brand by more than 10%. This implies that the MSDPs and the innovator brand would likely have similar bioavailability and may therefore be considered pharmaceutically equivalent.

DISCUSSION

The dissolution testing and the derivatives thereof comprising the fit factors f_1 and f_2, and dissolution efficiency (DE), are acceptable approaches for assessing the similarity of drug products QSE parameters, and predicting in vivo performance characteristics.[23] Studies have shown that, among the three parameters, the similarity factor f_2 is more predictive and has been adopted by the United States Food and Drug Administration (US-FDA) and the European Medicines Agency (EMA) as a criterion for estimating pharmaceutical equivalence.[8] When two products are ideally equivalent, their dissolution profiles would be identical with $f_2 = 100$, while an average variation of 10% at all determined time points contribute to an f_2 value of 50. Hence, the US-FDA and EMA have established a public standard for f_2 value between 50 and 100 to ensure the sameness of two dissolution profiles. In practice, drug dissolution profiles are deemed similar if the $f_2 \geq 50$, which occurs when a 10% maximum difference in the mean percentage of the dissolved drug at each time point between the test and reference formulations is obtained.[24] This shows that the f_2 is intrinsically related to the DE parameter and share the statistical interpretations for bioavailability.

The EMA guideline on the investigation of bioequivalence[25] stipulates that if on average more than 85% of a drug is dissolved in less than 15 min in both the test and reference products, then the dissolution profiles of the two formulations are deemed equivalent. In this study, all the eight metronidazole MSDPs released more than 85% metronidazole at 15 min, preliminarily

indicating their pharmaceutical equivalence to the innovator brand. The two metronidazole MSDPs, MTZ-02 and MTZ-08, that were non-compliant with the requirement for f_2 ≥50 had very low dissolution at 5 min, which may have affected their overall f_2 score.

Although this study focused on *in vitro* pharmaceutical equivalence, comparative pharmacokinetics studies are regarded as the "gold standard" in bioequivalence testing.[26,27] *In vivo* bioequivalence study is a more objective method that involves measuring the drug concentration in biological fluids such as blood, plasma, or serum.[28] The concentration-time curve is used to determine the rate and extent to which a drug is absorbed after administration. In these studies, preset acceptance limits for selected pharmacokinetic parameters allow for the determination of bioequivalence between the innovator brand and the corresponding generic products.[29]

In vitro pharmaceutical equivalence testing is preferred in routine PMS[30] due to reduced costs and time compared to bioequivalence studies. Furthermore, it offers advantages regarding ethical considerations and inter-subject variability since no human subjects are involved.[31] This study assessed only eight generic metronidazole brands, which may not be exhaustive of the products marketed in Kenya. However, the external validity of the study findings may be assumed since the eight generic metronidazole tablet brands analyzed are commonly used in Kenya hence representative of the countrywide market profile for metronidazole tablets. The results obtained underscore the need for drug regulatory authorities to reinforce PMS for essential medicines such as antimicrobials including metronidazole to ensure QSE parameters are adhered to.

CONCLUSION

All the nine metronidazole tablet brands evaluated in this study complied with the tests for identity, friability, hardness, disintegration, and dissolution. One brand failed to meet the acceptance criteria for uniformity of weight, while four brands were non-compliant with the compendial specifications for the assay of metronidazole tablets. All the brands analyzed showed similarities in their drug release profile. Based on f_1 and DE, all eight generic metronidazole tablet brands evaluated in this study may be considered pharmaceutically equivalent to the innovator brand and therefore likely interchangeable in clinical settings. Nevertheless, *in vitro* pharmaceutical equivalence testing is only predictive of *in vivo* bioavailability of oral solid dosage forms and does not necessarily confirm *in vivo* drug performance. For unequivocal therapeutic equivalence, *in vivo* BE studies should be considered for the metronidazole MSDPs.

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