British Journal of Pharmaceutical Research
7(3): 196-205, 2015, Article no.BJPR.2015.102
ISSN: 2231-2919

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In vitro Equivalence Studies/Comparative Assessment of Generic Metronidazole Tablets Commercially Available in Lagos, Nigeria

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MOI, NAM, OOO and KO designed the study, wrote the study protocol. Authors MOI, NAM and OOO wrote the first draft of the manuscript. Authors MOI, NAM, OOO and KO managed the literature searches, managing the experimental process and statistical analysis involved in this research. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJPR/2015/18572
Editor(s):
(1) Dongdong Wang, Department of Pharmacogonosy, West China College of Pharmacy, Sichuan University, China.
Reviewers:
(1) Anonymous, Sweden.
(2) Anonymous, Kaziranga University, India.
Complete Peer review History: http://www.sciencedomain.org/review-history.php?iid=1178&id=14&aid=9682

Original Research Article

Received 29th April 2015
Accepted 25th May 2015
Published 9th June 2015

ABSTRACT

Purpose: For drug products to be interchangeably used by healthcare providers, formulation characteristics, which reflect variation within brands, batches and lots examined via dissolution profile analysis, must not show high statistical discrepancies. The objective of this study is to investigate the physicochemical and *in vitro* equivalence of thirteen brands of metronidazole tablets obtained from pharmacy retail outlets in Lagos, Nigeria.
Methods: Physicochemical characteristics comprising hardness, friability, drug content were evaluated in comparison with the innovator brand MZ-1. Dissolution data was analyzed using model dependent approach of dissolution efficiency and model independent approaches.

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Results: The twelve generics brands were within compendial specified limits for hardness, friability, drug content and disintegration. Four of the brands MZ-3, 4, 10 and 13 were not pharmaceutically equivalent to the innovator brand MZ-1, Based on the results obtained from model-dependent method via dissolution efficiency where the release profile as a function of time was compared, the f_1 and f_2 deciding the difference or similarity between dissolution profiles were used adequately utilized to decide pharmaceutical equivalence.
Conclusion: The extent to which these differences affected the amount of active constituent released over time in comparison with the innovator product was evident as only 8 of the brands MZ-2, 5, 6, 7, 8, 9, 11, 12 could be considered to be bioequivalent and thus interchangeably used with the innovator product.

Keywords: Metronidazole tablets; dissolution; in vitro equivalence studies; pharmaco-vigilance.

1. INTRODUCTION

The National agency for food and drug administration and control (NAFDAC) has laws governing the registration of pharmaceutical products, subject to the ability of these products to release the active pharmaceutical ingredient at the required time in accordance with provision of Decree 19 of 1993, amended into Decree 20, of the 1999 constitution of the Federal republic of Nigeria [1]. Thus generics of antibiotics to be marketed must have a recommendation governing their drug application, components and composition i.e. excipients composition, their manufacturing site, processes and equipment to ensure their *in vitro* equivalence with innovator products. The FDA in 1995 also issued a specific guidance on immediate release solid oral dosage forms to include scale up and post approval changes involving manufacturing and controls involving *in vitro* dissolution testing accompanied by *in vivo* bioequivalence documentation [2,3].

For drugs marketed with the same active constituent as an innovator drug product, dissolution profile similarity should be obtained in comparison with the innovator product. Different methods of assessing these similarities exist and because of the varying characteristics of excipients utilized by different manufacturers causing physicochemical and dissolution properties of these drugs to vary [4]. However if similarity or dissimilarity of the generic product is within specified limits *in vivo* bioequivalence testing which is usually expensive and time consuming can be waived. Statistical evaluation of dissolution profiles can be assessed via varying methods which include model independent methods which are characterized by pair wise approach procedures [5]. These include the difference and similarity factors (*f*1and *f*2 as shown in equation 1 and 2) and Rescigno indices.

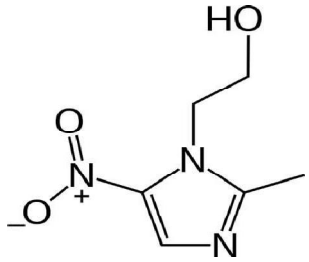
$$f_2 = 50 \log \{[1 + (^1/m) \sum_{j=1}^{m} Wj(Rj - Tj)(Rj - Tj)\ ]^{-0.5} \times 100\} \quad \text{Equation 1}$$

$$f_1 = \{[[Rj - Tj] / \sum_{j=1}^{m} Rj\ ] \times 100\} \quad \text{Equation 2}$$

Where m reflects the number of time points utilized, Rj, the cumulative percent of the reference product dissolved at specifically selected time points, Tj, the cumulative percent of the generic brand dissolved at specifically selected time points [6,7,8].

They provide a remarkably easy descriptive and comparative analysis of dissolution data where the percent error between two respective curves across determining point is measured by the *f*1 factor. Model dependent methods have been utilized extensively to define drug release from varying polymeric matrices where the value of the release constant characterizes specific release properties synonymous with the incorporated excipients and other process variables utilized in drug formulation [9,10,5]. These data provide regulatory authorities with information regarding product performance via equivalence dissolution profile testing, ensuring that large differences at any time point doesn't affect the sensitivity of the model used [9,10,11].

Metronidazole (1 β -hydroxyethyl-2- methyl 5 nitro imidazole) an antiprotozoal, antibacterial and amebicide [12] is a BCS class I drug (Fig. 1), being highly permeable and highly soluble across biological membrane, thus drug absorption depends on the ability of the drug to go into solvation/dissolution after oral administration, and then be able to permeate the biological membrane of the gastrointestinal tract [13]. Thus the dissolution process is critical in prediction of in vivo events of a drug [14,15].



$C_6H_{10}N_3O_3$ mw = 172.0717

Fig. 1. Chemical structures, molecular formulae and molecular weight (mw) of Metronidazole

In vitro equivalence studies involving dissolution comparison between the innovator brand and twelve generic brand of metronidazole were evaluated in varying simulated dissolution media over time and mathematical models comprising model dependent and independent parameters were utilized to analyze differences in the profiles and the extent to which these differences affect the amount of active constituent released over time in comparison with the innovator product.

2. MATERIALS AND METHODS

2.1 Materials

Metronidazole (≥ 98.0% purity) was purchased from Fluka Analytical (Sigma Aldrich Chemical Corps, St Louis, MO, USA, batch number M3761-5G, Lot# SLBD5470V, Flagyl® the innovator brand code named MZ1, and twelve generic brands of metronidazole tablets (Table 1) purchased from public pharmacies in Lagos Nigeria were assessed and studied. All solvents and reagents used were of analytical grade and the simulated dissolution media utilized was always freshly prepared with pH adequately adjusted prior to use.

Table 1. Brands of metronidazole used

Brand code	Brand names®	Strength	Manufac. date	Expiry date	Batch number	NAFDAC number	Company/Country of origin
MZ-1	Flagyl	400 mg	06/13	06/15	1093	04-5566	Sanofi Aventis Nigeria.
MZ -2	Loxagyl	400 mg	09/13	08/18	A130084	04-5566	May & Baker Nigeria.
MZ -3	Metrozol	400 mg	02/13	01/18	50213B	A4-6028	Vitabiotics Nigeria.
MZ -4	Metrotab	400 mg	08/13	08/18	4013	04-9101	SKG Nigeria.
MZ -5	Chimet	400 mg	10/13	09/18	237A	A4-7350	CHI Pharma Nigeria.
MZ -6	Avrogyl	400 mg	01/14	01/19	0714	A4-4689	AVRO Pharma Nigeria.
MZ -7	Vincogyl	200 mg	02/13	01/16	MET.007	A4-0944	VINCO Pharma Nigeria.
MZ -8	Unigyl	200 mg	07/13	06/16	0714	A4-4689	AVRO Pharma Nigeria.
MZ -9	Metrokris	200 mg	02/14	01/17	KP1441	A4-5659	KRISHAT Pharma. Ltd. Nigeria.
MZ -10	Metrosam	200 mg	02/14	08/16	S2479	04-0275	Sam Pharma. Ltd Nigeria.
MZ-11	Nemegyl	200 mg	02/14	02/18	02/14	04-5326	Nemel Pharma. Ltd Nigeria.
MZ -12	Garymet	200 mg	12/13	11/17	1331220	A4-3547	AGARY Pharma. Ltd Nigeria.
MZ -13	Jugyl	200 mg	11/13	10/16	B068	04-0952	JUHEL Nigeria Ltd. Nigeria.

2.2 Method

2.2.1 Uniformity of weight

For each of the metronidazole generic brands as well as the innovator brand, twenty tablets were obtained and individually weighed using a Mettler New classic ML 204/01 analytical balance. The mean and standard deviation were calculated and the percentage deviation was determined.

2.2.2 Hardness

The tablet hardness was obtained using twenty tablets obtained from each brand. The Tablet Hardness Tester HT-05P with accuracy for hardness ranging from 5-500N/0.5kp+/-0.1N manufactured by Campbell Electronics, Mumbai, India was utilized. The reading indicates the hardness of the tablet in selectable units of kg/cm^2 and Newton (N).

2.2.3 Friability

Veego® Type;VFT-2 automated friabilator, VEEGO Instrument Corporation, Mumbai India was utilized to assess the friability of twenty tablets of each brand of metronidazole tablets. At a rotation speed of 25 revolutions per minute, the test was run for 6 minutes, after which the tablets were re-weighed, recorded and the friability calculated.

2.2.4 Disintegration test

Utilizing a tablet disintegration test apparatus Veego® Type; VTD-2/20/1208 fitted with a vertical oscillatory lifting synchronous AC Motor. Twenty randomly selected tablets was taken from each of the brands and placed on the mesh in the disintegration tester operated with 0.1N HCL at 37ºC±1ºC used as the media for disintegration. The time required for absence of tablet residue from the surface of the mesh to occur was recorded as the disintegration time [16].

2.2.5 Preparation of standard curve and drug content determination

Preparation of standard curve: a series of standard solutions with different concentration of standard metronidazole 2.5, 5, 10, 20, 30, 50, 100 mg/ml were prepared by dissolving 100 mg of standard metronidazole in a 100 ml volumetric flask volume was adjusted by SIF adjusted to pH 6.8 stock solution and the average was calculated. The measured absorbance was plotted against the respective concentration of the standard solutions which gives a straight line in the concentration of 2.5 µg/ml to 50 µg/ml. The drug content of each sample was then estimated from the standard curve (Figs. 2 & 3) obtained and percentage purity calculated according to USP specification.

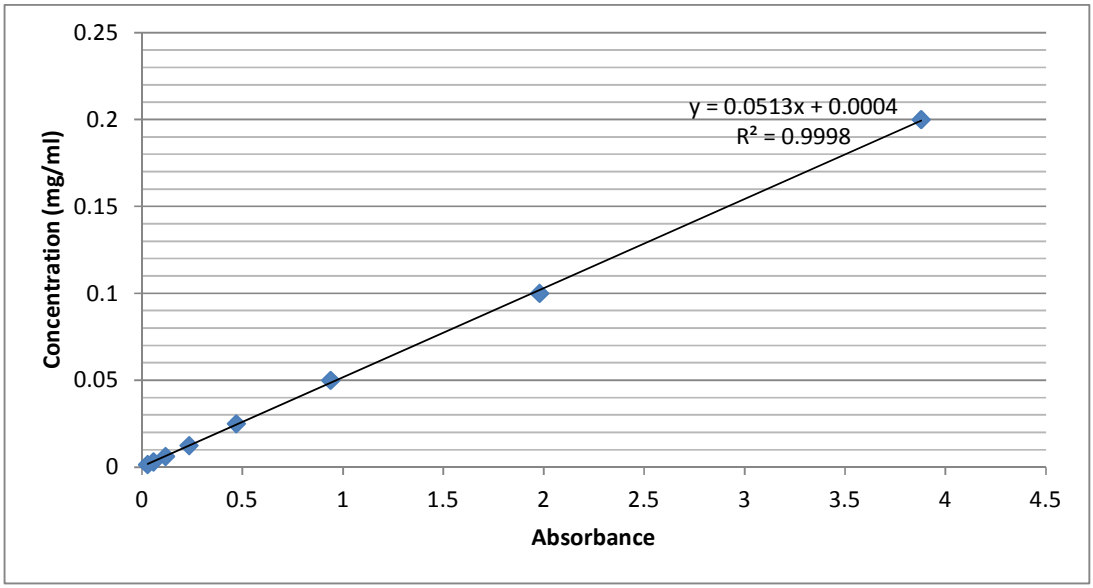


Fig. 2. Calibration curve of pure metronidazole in 0.1N HCL at 277 nm

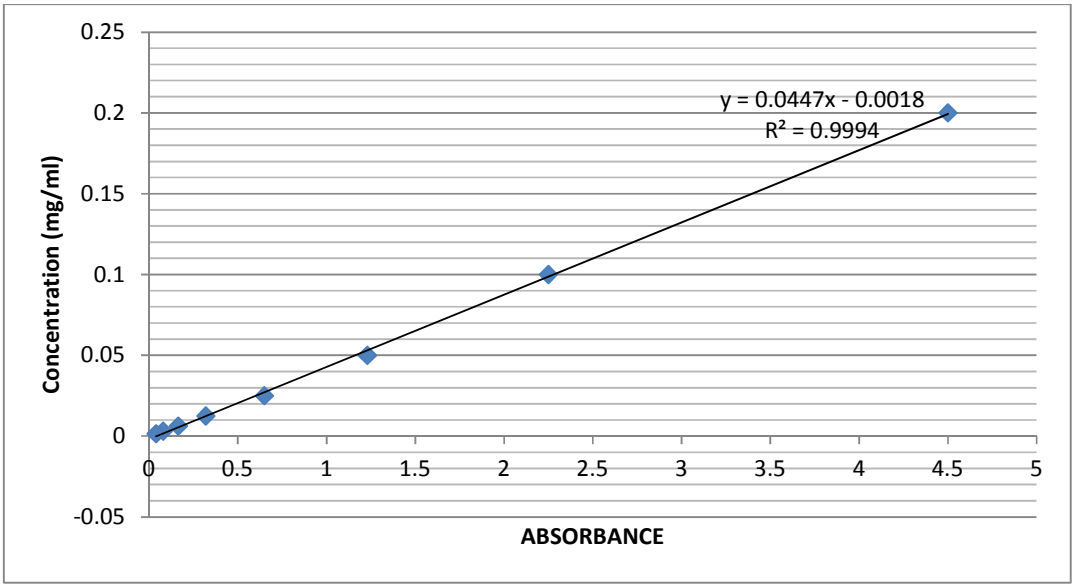


Fig. 3. Calibration curve of pure metronidazole in 6.8 simulated intestinal fluid at 322 nm

2.2.6 Assay of metronidazole tablets

A portion of powdered tablets equivalent to 300mg of metronidazole was weighed, 20 mls dilute hydrochloric acid (1 in 100) added, shaken for several minutes and filtered. Suitable aliquots of the filtrate responded to the USP identification test [17].

2.2.7 *In vitro* dissolution study

The innovator brand of metronidazole Flagyl® coded MZ-1 and twelve generic brands of metronidazole MZ-2 to MZ-13 (Table 1) were studied. Using an Instron® dissolution tester, USP apparatus-II (Paddle) at 37±0.5ºC at a speed of 50 rpm in 900 ml of dissolution media (0.1N HCL and simulated intestinal fluid phosphate buffer pH 6.8.), and dissolution was carried out on 12 units of each formulation according to FDA / USP specification to enable statistical analysis. 5mls of sample was withdrawn and filtered using a millipore filter 0.45µm at specific time intervals, after which fresh dissolution medium replacement constituting the exact volume at the same temperature withdrawn took place. Samples were analyzed utilizing UV spectrophotometer-2600/2700 series at 275 nm after the calibration curve (Figs. 2 & 3) has been established.

2.3 Statistical Evaluation of Dissolution Data

One-way ANOVA testing of percentage dissolved data was utilized using Microsoft excel 2010. Similarity and difference factors as well as the two indices of recigno [5,9] were utilized to comparatively measure the similarity or dissimilarity between an innovator product which is the reference and a test product which can be considered a generic brand based on the concentration of drug released as a function of time.

The dissolution efficiencies (DE) were calculated using the area under the dissolution curve up to a certain time *t*, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time as shown in Equation 3 where y is the percentage of drug dissolved at time t.

$$DE = \{ \int_0^t y \times \partial t / y_{100} \times t \} \times 100 \qquad \text{Equation 3}$$

3. RESULTS AND DISCUSSION

From the results obtained all the tablets passed all the routine quality control tests; uniformity of weight, hardness, tablet thickness, disintegration, friability tests and assay of drug content. All the tablets complied with the official requirements for tablets in their category. However in order to assess the bioequivalence and the interchangeability of the brands of metronidazole with the innovator brand, the dissolution tests was subjected to different statistical analytical models.

3.1 Discussion

The National agency for food and drug administration and control (NAFDAC) prior to giving specific identification numbers to new brands of antibiotics, utilizes varying assessment parameters to ensure the overall quality of these brands. Quality assessment requirements must be met to ensure registration of these brands in Nigeria [1]. Varying parameters are utilized by NAFDAC to ensure that at the end of the production chain, adequate bioavailability of the drug in the blood stream of the patient is assured after the drug product has been administered. In this study, compendial standards disintegration time, hardness, friability and assay/drug content were used as a basis of comparison of the generics with the innovator product MZ-1. Table 2 shows the physicochemical characteristics of the varying brands of metronidazole tablets studied, reflecting that even though the same API (active pharmaceutical ingredient) was utilized in the production of the generic form of metronidazole tablets, disparities in parameters such as disintegration time, hardness and friability existed. MZ-2 and MZ-13 had very high disintegration times which were not consistent with the time reported for the innovator brands and deviated from the overall mean disintegration times for all the batches which fell between 0.33 and 1.75 minutes. Disintegration does not however imply complete dissolution of the tablet or it's API (IP 2014), it is an intrinsic parameter which links the first in a series of steps to drug release from the dosage form prior to dissolution. The BP 2014 gives the general requirement for disintegration for uncoated tablets as 30 minutes, thus it can be said that within these limits all brands passed the disintegration test amidst large variations between the innovator brand (1.4±0.21 minutes) and MZ-2 & MZ-13 (29.67±0.79 and 18.0±0.99 minutes respectively).

There was a large variation in average tablet weights amongst all the brands studied (Table 2), which could be as a result of differing manufacturing processes as well utilization of varying spectrum of excipients, and varying modes/mechanisms of incorporation of theses excipients into the dosage form i.e. tablets. The assay results showed that all the brands had APIs within specified official limits except MZ-2 and MZ-13 that reflected drug content of 81.5 and 81.9% respectively. Since the potency of the drug is a direct indication of how much API is present in the formulation and available for release and BP 2014 specification for metronidazole assay states that the drug content should not be less than 90% and not more than 110%, MZ-2 and MZ-13 did not pass the assay for drug content.

The ability of the individual brands to withstand mechanical stress was also evaluated via hardness testing, values obtained ranged from 2.65 kg/cm^2 for MZ-12 to 10.16 kg/cm^2 for MZ-2, with the innovator brand exhibiting a hardness values of 4.82 kg/cm^2. However friability being a more objective and absolute indication of tablet strength was also assessed. The ability of the dosage form to resist abrasion due to mechanical handling/agitation via oscillatory tumbling motion that may be experienced during coating, packaging and necessary transportation to the end user was evaluated via friability testing. A weight loss of 1% or less was deemed acceptable [18]. MZ-4 and MZ-5 reported friability values of 1.91% and 1.16% respectively, reflecting appreciable loss of excipient and possibly APIs that could occur during handling of these brands as they did not comply with compendial standards. Formulation factors arising from varying impaction forces utilized in tablet production which comprises of insufficient compression forces as a result of equipment inconsistencies, variations arising from excipient sources, ratios/techniques via which these excipients are combined (i.e. binders and disintegrant ratios) have been known to give rise to friable tablets which may negatively impact on tablet quality.

The study of dissolution *in vitro* is considered a fundamental requirement in the pharmaceutical industry in order to assure the quality of solid pharmaceutical dosage forms for oral use, guarantee the quality from batch to batch, orientate the development of new formulations and secure the uniformity in quality and performance of the drug even after modifications [19]. On a parallel basis, this allows formulation optimization in the development phase and, in the same way, it allows stability studies, manufacturing process monitoring, and the establishment of in vivo/in vitro correlations [20,21,22]. Various procedures have been proposed for statistical assessment of similarity or dissimilarity of dissolution profile. Dissolution studies were carried out for twelve generic brands MZ-2 to MZ-13 and comparisons made with the innovator brand MZ-1 manufactured by Sanofi Aventis®. These studies were carried out in two different dissolution media pH 1.2 (Fig. 4) and pH 6.8 simulated intestinal fluid (Fig. 5)

which characterized the environment in the stomach and the small intestine. Metronidazole (Fig. 1) is a BCS class 1 drug having high solubility and high permeability, thus it is expected to have excellent bioavailability (the brands assessed were not sustained release tablets).

The rate-limiting step being its ability to go into solvation within seconds of ingestion. The dissolution efficiency (DE) (Equations 3) was used to compare the release profiles (Table 3). The difference in DE of the generic tablets compared with the innovator brand was in the range of 5.11% to 59.44% in pH 1.2 and about 3.88% to 64.80% in pH 6.8 indicating that not all the formulations can be interchangeably used in lien of the innovator brand MZ-1 as a difference between DE of less than 10% is assumed to indicate bioequivalence [23], Ngwuluka et al. 2012. MZ-3, MZ-4, MZ-10 and MZ-13 showed difference in DE of 50.89%, 16.89%, 13.14% and 59.44% respectively in pH 1.2 and 64.80%, 20.89%, 15.8% and 48.77% in pH 6.8 respectively and as such these brands should not be interchangeably used with the innovator brand due to disparities in the release of metronidazole from these dosage forms. Table 3 also shows the comparison of similarity, dissimilarity index as well as lower and upper rescigno indices.

Table 2. Physicochemical characteristics of the varying brands of metronidazole tablets are as stated below

Brand code	Average weight tablet (grams±SD)	Disintegration time (minutes ±SD)	Hardness test (kg/cm^2)	Friability test (%)	Thickness (mm)	Assay (90-110%)
MZ-1	667±0.02	1.4±0.21	4.82	0.22	5.27	99.03
MZ-2	489±0.13	1.75±0.21	10.16	0.15	4.89	101.06
MZ-3	544±0.06	29.67±0.79	9.97	0.14	5.61	81.05
MZ-4	498±0.14	0.27±0.2	8.72	1.91	4.8	98.4
MZ-5	561±0.17	1.75±0.43	4.06	1.16	5.58	100.6
MZ-6	491±0.28	0.33±0.08	7.91	0.15	4.81	93.08
MZ-7	401±0.19	0.67±0.11	7.82	0.12	4.12	90.2
MZ-8	496±0.03	0.67±0.06	4.94	0.2	4.46	98.02
MZ-9	592±0.11	0.42±0.5	4.28	0.38	3.6	97.14
MZ-10	602±0.18	0.5±0.46	7.42	0.16	4.34	96.62
MZ-11	588±0.32	0.42±0.08	4.33	0.19	4.6	90.14
MZ-12	522±0.41	0.42±0.65	2.65	0.58%	4.5	93.3
MZ-13	316±0.15	18.0±0.99	7.32	0.71%	4.14	81.9

Table 3. Statistical analysis of dissolution data showing, similarity and difference factors (f_2&f_1), recigno indices (Ç1& Ç2) and dissolution efficiency (DE)

	Metronidazole in 0.1N HCL						Metronidazole in simulated intestinal fluid pH 6.8					
	% dissolved* (mean±SD)	f_1	f_2	Ç1	Ç2	DE*	% dissolved* (mean±SD)	f_1	f_2	Ç1	Ç2	DE*
MZ-1	100.1±0.08	-	-	-	-	89.43	99.95 ± 0.09	-	-	-	-	88.78
MZ-2	95.75±0.21	4	65	0.023	0.098	84.32	98.99±0.04	4	62	0.039	0.1	79.43
MZ-3	85.34±0.32	33	20	0.201	0.432	38.54	83.5±0.11	36	19	0.39	0.4	23.98
MZ-4	94.87±0.03	8	50	0.020	0.933	72.54	89.99±0.07	10	46	0.023	0.1	67.89
MZ-5	93.78±0.43	8	51	0.036	0.102	79.4	100.98±0.61	1	85	0.029	0.099	81.98
MZ-6	95.99±0.72	4	70	0.029	0.096	80.43	98.76±0.66	3	73	0.022	0.092	84.90
MZ-7	91.74±0.28	9	51	0.034	0.097	79.09	97.83±0.32	2	78	0.028	0.111	80.32
MZ-8	94.89±0.11	8	50	0.033	0.092	82.54	98.87±0.56	2	80	0.029	0.11	79.99
MZ-9	95.43±0.29	4	66	0.048	0.100	80.03	98.04±0.19	3	69	0.040	0.182	78.55
MZ-10	95.89±0.03	9	48	0.034	0.098	75.99	88.9±0.22	9	52	0.029	0.178	72.98
MZ-11	95.76±0.12	6	61	0.029	0.093	78.43	95.87±0.54	4	69	0.027	0.189	83.90
MZ-12	95.89±0.06	5	62	0.034	0.11	79.06	100.96±0.54	2	77	0.036	0.136	78.89
MZ-13	83.8±0.33	37	18	0.210	0.399	29.99	80.76±0.43	30	25	0.41	0.409	40.01

**% Drug dissolved and dissolution efficiency were evaluated after 30 minutes*

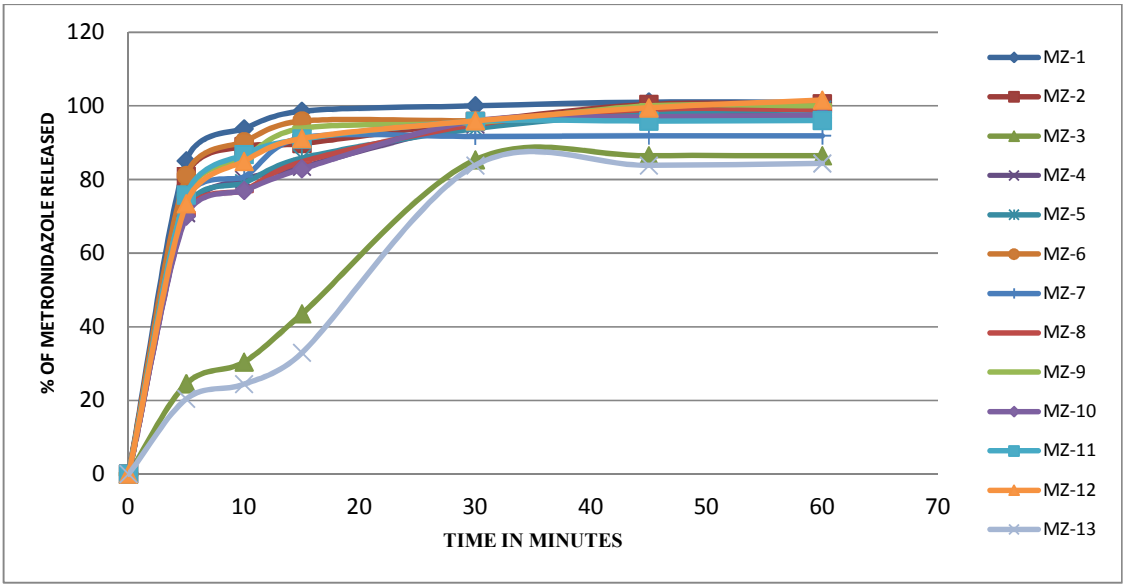


Fig. 4. Dissolution profile of the innovator brand MZ-1 and twelve generics of metronidazole tablets in pH 1.2

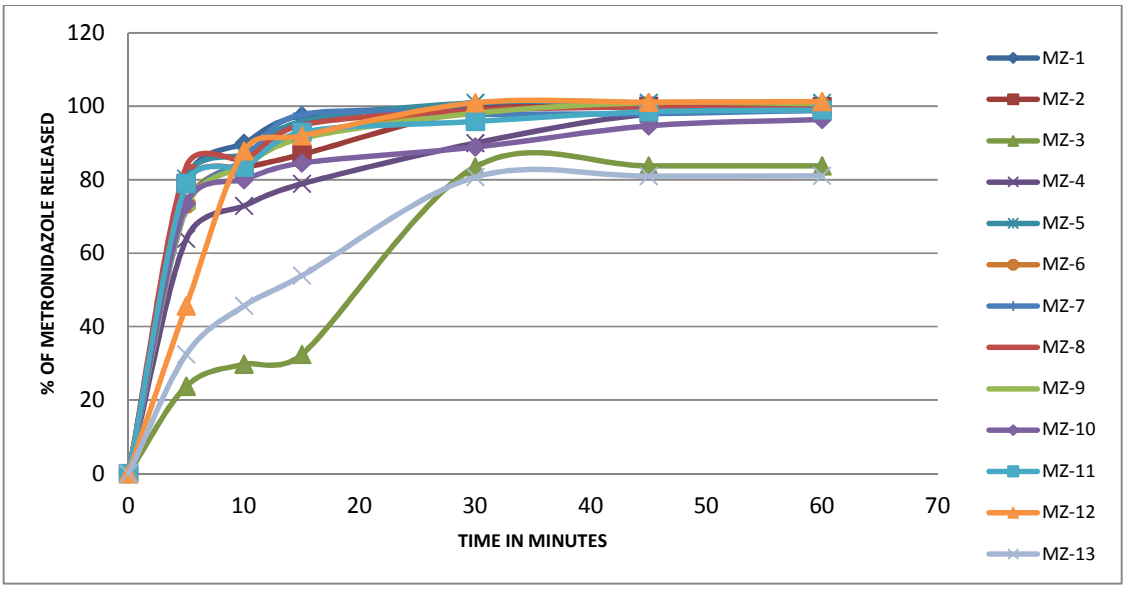


Fig. 5. Dissolution profile of the innovator brand and twelve generics of metronidazole tablets in simulated intestinal fluid pH 6.8

According to the FDA guidance [4] values of f_1 between zero and 15 and of f_2 between 50 and 100 ensure equivalence of two dissolution profiles. Based on the similarity and dissimilarity criterion for dissolution profile, MZ-6 dissolution profile best suits the profile of the innovator brand, MZ-1. All other formulations were not altogether fitted to the criteria of similarity and dissimilarity. The formulations with the highest variability were MZ-3, MZ-13, MZ-10 and MZ-4 in both pH 1.2 and pH 6.8. This approach was simple to apply but the disadvantage is that both equations do not take into account the variability or correlation structure of the data. They are sensitive to the number of points used, and, from a statistical point of view, this method seems to be less discriminating than other methods. The literature revealed several issues relevant to the

invariant property of f_2 with respect to the location change, shape of the curve, and the unequal spacing between the sampling time points. The similarity factor is a sample statistic that cannot be used to formulate a statistical hypothesis for the assessment of dissolution similarity. Therefore, it is impossible to evaluate false positive and false negative rates of decisions for the approval of drug products based on f_2 [5,23]. However the results from the comparison of dissolution data utilizing f_1 and f_2 factors in both simulated gastric and intestinal pHs revealed a similar pattern when compared with the difference in the DE between the innovator brand, as the same brands failed to meet the required standards. The bioequivalence index that is used to measure the dissimilarity between a reference and a test product based on plasma drug concentration time profile was applied to dissolution concentrations via rescigno indices. Table 3 showed lower indices of rescigno ς1 for MZ-3. MZ -13 gave a much larger value than the other generic brands obtained in both media. The upper indices ς2 in both media studied gave much higher values than ς1 but were roughly same for all generic formulations except MZ-3 and MZ-13. Varying storage conditions obtainable in the community pharmacies where these generics were purchased from could also account for the high variability in the release data obtained. In the tropical regions of the world such as Nigeria where extreme temperatures and humidity of storage areas occur and are improperly managed, degradation of the API is likely to occur thus affecting amount of drug released. Adequate resources should be put not only in monitoring of the generic production but also in ensuring that these drugs at individual pharmacies have access to optimum storage conditions.

4. CONCLUSION

In this study, the *in vitro* equivalence studies involving dissolution comparison between the innovator brand and twelve generic brand of metronidazole were evaluated in varying simulated dissolution media. The twelve generics brands were within compendial specified limits for hardness, friability, drug content and disintegration. Four of the brands MZ-3, 4, 10 and 13 were assessed not to be pharmaceutically equivalent to the innovator brand MZ-1 based on the results obtained from model-dependent method via dissolution efficiency where the release profile as a function of time was compared, the f_1 and f_2 deciding the difference or similarity between dissolution profiles and the recigno indices. The extent to which these differences affected the amount of active constituent released over time in comparison with the innovator product was evident as only 8 of the brands MZ-2, 5, 6, 7, 8, 9, 11,12 could be considered to be bioequivalent and thus interchangeably used with the innovator product.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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