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RESEARCH ARTICLE

IN VITRO-IN VIVO BIO-EQUIVALENCE CORRELATION STUDY OF METRONIDAZOLE, AND ITS BRANDS OF IMMEDIATE RELEASE TABLET UNDER BIO-WAIVER CONDITIONS

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Abstract

Objective: The aim of present study is to examine the *in-vitro in-vivo* correlation (IVIVC) of immediate release product. Metronidazole 500 mg and its brands of immediate release dosage forms. Metronidazole is clearly classified into BCS class I, and could be evaluated under bio waiver conditions.
Methods: The *in vitro* parameters employed were hardness, weight uniformity, friability, disintegration time, absolute drug content, dissolution rate (in 0.1 N Hydrochloric acid, phosphate buffer and acetate buffer at 37ºC), and dissolution efficiencies were also analyzed. The *in-vitro* dissolution study was performed on the brands, according to FDA,USP dissolution profile in three different PH (1.2), (4.5), and (6.8) at 37ºC, using the USP apparatus II, then f1, f2 were determined for the time intervals of 10, 15, 30, 45 and 60 minutes, and dissolution efficiencies were calculated. MINITAB 14 statistical program used for *in vitro in vivo* correlation, level A was done for reference product.
Results: A non linear relation was established which is typical for immediate release formulation, of class 1. There was significant relationship between *in vitro* and *in vivo* data of reference metronidazole product, Correlation and distribution of data with correlation coefficient (r=0.724, 0.837, 0.707), nonlinear relationship with *p*-value (>0.05) = (0.167, 0.098, 0.182), there is no out lines, no lake of fits at *p*-values=0.0040, 0.006, 0.026.
Conclusion: Study concluded that there is no linear correlation between percent of drug released and percent of drug absorbed ,this may be due to uncontrollable gastric emptying rate for class one Metronidazole.
Keywords: Bioavailability, bioequivalence, biopharmaceutical classification system, bio-waiver correlation.

INTRODUCTION

Bio-equivalence:

Is defined as "the absence of significant differences in the extent and rate to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study"[1]. If two medicines are bioequivalent there is no clinically significant difference in their bioavailability. *In vitro* testing, preferably based on a documented "*in-vitro/in-vivo* correlation" may some-times provide the same indication of bioequivalence between two pharmaceuticals. Bioequivalence is determined based on the relative bioavailability of the innovator medicine versus the generic medicine[2]. It is measured by comparing the ratio of the pharmacokinetic variables for the innovator versus the generic medicine where equality is 1. Bioequivalence studies focus on the release of drug from dosage form, formulation and subsequent absorption into the systemic circulation. Bio-equivalence studies may involve both *in-vivo* and *in-vitro* studies[3].

In vitro- in vivo correlations:

Formulation design, development and optimization of the product is an integral part of manufacturing and marketing of any therapeutic agent which is indeed a time consuming and costly process. Optimization processes may require alteration in formulation compositions, manufacturing processes and equip-ments. If these types of changes are applied to a formulation, studies in human healthy volunteers may be required to prove that the new formulation is bio-equivalent with the old one[4]. Certainly, implementation of these requirements not only halts the marketing of the new formulation but also increases the cost of the optimization processes. It would be, desirable, therefore, to develop *in vitro* tests that reflect bioavailability data. A regulatory guidance for both immediate- and modified-release dosage forms has been, therefore, developed by the FDA to minimize the need for bioavailability studies as part of the formulation design and optimization[5].

IVIVC can be used in the development and optimazation of pharmaceuticals to reduce the number of human studies during the formulation development.

Correlation definitions:

The term correlation is frequently employed within the pharmaceutical and related sciences to describe the relationship that exists between variables. Mathematically, the term correlation means interdependence between quantitative or qualitative data or relationship between measurable variables and ranks[2]. From biopharmaceutical standpoint, correlation could be referred to as the relationship between appropriate *in vitro* release characteristics and *in vivo* bioavailability parameters, Two definitions of IVIVC have been proposed by the USP and by the FDA[3,4].

Metronidazole, is an antibiotic and antiprotozoal medication. It is used either alone or with other antibiotics to treat pelvic inflammatory disease, endocarditis, and bacterial vaginosis. It is effective for dracunculiasis, giardiasis, trichomoniasis, and amebiasis. It is an option for a first episode of mild-to-moderate *Clostridium difficile colitis* if vancomycin or fidaxomicin is unavailable[5].

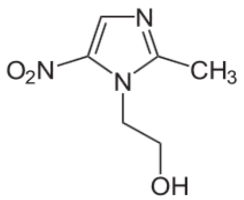

Figure 1: Chemical Structure of Metronidazole.

Metronidazole is available by mouth, as a cream, and by injection into a vein[5]. The aim of present study is to examine the *in-vitro in-vivo* correlation of Metronidazole 500 mg and its brands of immediate release dosage forms.

MATERIALS AND METHODS

Metronidazole reference standard USP, Mfg. August 2015, Exp. July 2020 (Azal Industries, Khartoum, Sudan), and three different brands of Metronidazole tablets 500 mg obtained from local market. The brands under study were selected based on frequency of prescription, DW and Methanol 99.8% (Sharlau, Spain).

Physical Test:

Uniformity of Weight Test:

Twenty randomly selected tablets were weighed. The average weights were determined. The tablets were weighed individually and the percentage of deviation of its weight from the average weight was determined for each tablet[6]. The deviation of individual weight from the average weight should not exceed the limit given in Table 1.

Hardness test:

The hardness of ten tablets randomly selected from each batch was determined on an automatic tablet hardness tester. The crushing strength of uncoated tablets is accepted within 4-8 kg/cm^2.

Friability Test:

Twenty tablets previously freed of dust were weighed together before transferring to a frabilator set to run for 4 min at 25 r.p.m. Thereafter they were removed, dusted and reweighed[7]:

$$\%\ \text{Friability} = \frac{\text{Wi} - \text{Wf}}{\text{Wi}} \text{X100}$$

Where;

Wi is the initial weight and Wf the final weight of the tablets.

Disintegration time test:

According to official monograph determination of disintegration time for uncoated tablets was adopted using a disintegrating apparatus and the medium was distilled water at 37±1ºC. Six tablets were used for the determination. Accepted range for the uncoated tablet up to 30 minutes[8].

Absolute drug content:

Five pre-weighed tablets were crushed; the equivalent weight of a tablet was weighed out and dissolved in 500 ml of 0.1 M NaoH in a volumetric flask, and filtered. The absorbance reading was determined using UV-visible spectrophotometer at 319 nm.

***In vitro* dissolution test:**

Volume of 900 ml of each buffer was employed. Dissolution testing was performed using Tablet Dissolution Tester (USP Apparatus 2) at 75 rpm for class I, test and reference products, temperature will be adjusted to 37ºC ± 0.5ºC. Twelve dosage units of each product test and reference were evaluated in the three media. Sample aliquots of 10 ml were taken manually with syringes. Samples were withdrawn at specified time intervals (10, 15, 30, 45, and 60 min) and replaced with 10 ml of appropriate medium. With drawn samples were filtered using 0.45 µm Millipore Filters, then 5 ml taken after filtration by volumetric pipette (3 ml taken when use HCL buffer solution, and 1 ml taken in case of acetate and phosphate buffer, and diluted to 50 ml). A UV–visible spectrophotometer was used to analyze dissolved drug in dissolution testing. Scanning of wavelength done in each buffer, and spectrum recorded between 200-800 nm, and percentage % of drug dissolved calculated[9].

Buffers preparation:

Simulated gastric fluid (SGF), simulated intestinal fluid (SIF), and acetate buffer pH (4.5) were prepared according to instructions in USP test solution. All media were prepared without enzymes, as follow:

a. Simulated Gastric Fluid (SGF) pH (1.2):

To prepare hydrochloric acid 0.1N, 8.5 ml was taken from concentrated HCL (37%) and volume completed to 1000 ml by distilled water.

b. Simulated Intestinal Fluid (SIF) pH (6.8):

Potassium phosphate monobasic KH_2PO_4 0.2 M was prepared by dissolving 27.22 g in water, and volume diluted to 1000 ml by distilled water. Then sodium hydroxide 0.2 M prepared by dissolving 8 g in water and volume diluted to 1000 ml by distilled water. Total 250 ml from Potassium phosphate monobasic KH_2PO_4 0.2 M was placed into 200 ml volumetric flask, also 112 ml taken from sodium hydroxide 0.2 M and volume completed to 1000 ml with distilled water[10].

c. Acetate Buffer pH (4.5):

Firstly acetic acid 0.2N was prepared from concentrated acetic acid 99.93%. Total 116 ml was taken and diluted with distilled water. Then 2.99 g of sodium acetate ($NaC_2H_3O_2$) taken, and placed in 1000 ml volumetric flask,14 ml from acetic acid was added and volume completed to 1000 ml by distilled water.

Preparation of Standard Stock Solutions:

Standard stock solutions of Metronidazole in HCL, phosphate and acetate buffers were prepared by dissolving 500 mg of standard in 100 ml volumetric flask using HCL, acetate and phosphate buffers as solvents to give concentration of 5 mg/ml, one ml taken by volumetric pipette in 100 ml volumetric flask to give concentration of 50 µg/ml, using 50 ml volumetric flask to give serial concentration of standard curve[10].

Data Analysis:

All dissolution data evaluated using Excel spread sheet, and the results will be plotted for each brand[6].Average of % content of active pharmaceutical ingredient (API) dissolved in each media of 12 tablets will be taken and a plot of % of (API) dissolved against time will be drawn to represent the dissolution profile .The dissolution profile for local brand will be compared to that of the reference drug[11].

If they are similar the similarity factor, f2 equal to or more than 50. This means that they are equivalent, if it's less than 50 they are not equivalent.

f1 = {[3t=1n | Rt - Tt|]/[3t=1n Rt]}C

f2 = 50 C log {[1+(1/n)3t=1n (Rt - Tt)2] -0.5C 100}……… (2)

Similarity factor f2 has been adopted by FDA and the European Agency for the Evaluation of Medicinal Products (EMEA) by the Committee for Proprietary Medicinal Products (CPMP) as a criterion to compare the similarity of two or more dissolution profiles. Similarity factor f2 is included by the Centre for Drug Evaluation and Research (CDER) in their guidelines such as guidance on dissolution testing of immediate release solid oral dosage forms[7], and guidance on Waiver of *in-vivo* Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System[7]. The area under the dissolution-time curve method was used in calculating the dissolution efficiency (DE), and this was calculated at 30 min .The higher the dissolution efficiency (DE) is, the better the release efficiency of the tablets' active ingredient, according to equation:

$$DE=\left\{\left[\int_{t_1}^{t_2}\% D_t \cdot dt\right]/\left[\% D_{max}\cdot(t_2-t_1)\right]\right\}\cdot 100 =$$

$$[AUC_{0-T}/\% D_{max}\cdot T]\cdot 100$$

Where % D is the percentage dissolved at time t, % D (max) is the maximum dissolved at the final time T, and AUC(0-T)is the area under the curve from zero to time T2.

Correlation calculation will carried on using MINITAB14 specific statistical program.

In vivo percent absorbed of reference product was calculated from equation:

$$\frac{A_t}{A_0}=\frac{C_t+K_{el}\bullet AUC_0^t}{K_{el}\bullet AUC_0^\infty}$$

Where, $\frac{At}{A0}$denotes the fraction of drug absorbed at time t, Ct is the plasma drug concentration at time t, Kel is elimination rate constant, AUC0-t and AUC0-∞ are the area under the plasma concentration– time profile curve at time t and ∞ respectively[13].

Then the values of percent of drug released were plotted against the percent of drug absorbed for reference products of Metronidazole using MINITAB14 analysis program to find out the relationship between data (correlation). Amount of drug released in the three different pH was plotted against amount of drug absorbed.

RESULTS AND DISCUSSION

A summary of the results of weight uniformity, hardness, friability, disintegration and assay are shown in Table 1 and Table 2. Weight uniformity may serve as a pointer to amount of the active pharmaceutical ingredient (API) contained in the formulation. All the brands complied with the compendial specification for weight uniformity.

Table 1: Weight uniformity of atenolol tablets.

Average weight of tablets	Deviation (%)	Number of tablets
Less than 80 mg	± 10.0 ± 20.0	Minimum 18 Maximum 20
80 mg to 250 mg	± 7.5 ± 15.0	Minimum 18 Maximum 20
More than 250 mg	± 5.0 ± 10.0	Minimum 18 Maximum 20

Hardness is referred to as non-compendial test. The hardness or crushing strength assesses the ability of dosage form to withstand handling without fracturing or chipping. It can also influence other parameters such as friability and disintegration. Hence, the dosage forms of all brands were satisfactory for hardness. Friability test is used to evaluate the tablets resistance to abrasion. Friability is now included in the United States Pharmacopeia as a compendia test. The compendial specification for friability is less or equal to 1%. Friability for all brands of Metronidazole were below 1%.

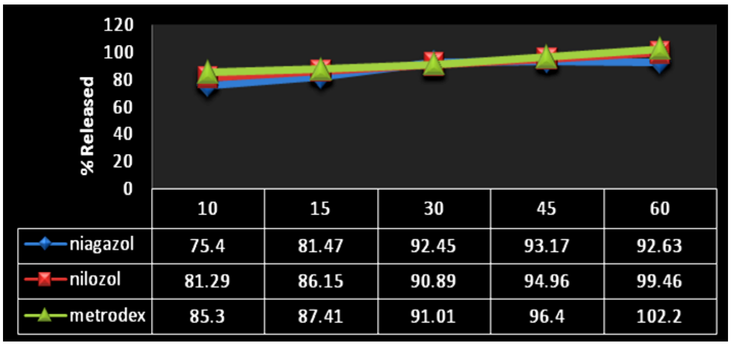

Figure 2: Dissolution profile of metronidazole (pH 4.5).

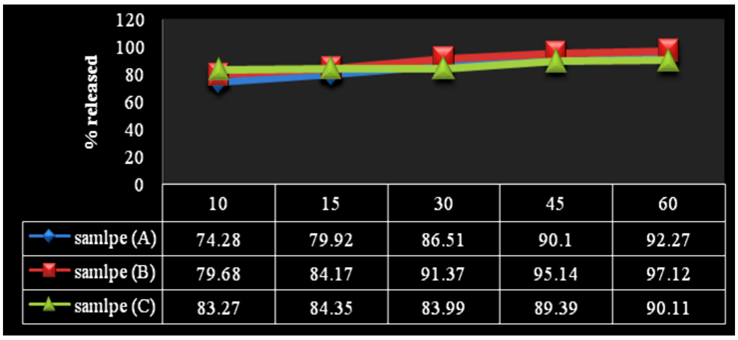

Figure 3: Dissolution profile of metronidazole in pH (6.8).

A drug will be released rapidly as the dosage forms disintegrate. British Pharmacopeia specifies that uncoated tablets should disintegrate within 15 min and film coated tablet disintegrate within 30 min while USP specification for disintegration is 30 min for both uncoated and film coated tablets. All the brands were complied with both BP and USP specifications for disintegration as maximum disintegration time[14].

Table 2: Quality control results of Metronidazole.

Brands	Hardness (Kg/cm)	Weight variation (RSD)	DT min	%F	Assay %
Sample (A)	12.0	0.00386	8:27	0.01158	99.88
Sample (B)	12.5	0.0419	2:22	0.1843	98.75
Sample (C)	10.7	0.0243	3:20	0.0184	99.97

%F=Friability, DT=Disintegration time

Potency is the average amount of the active ingredient present per tablet. All the brands complied both BP and USP specification, as USP specification is that the content of active ingredient should not be less than 90% and not more than 110% while BP specifies that the content should not be less than 95% and not more than 105%.

The results of dissolution studies are graphically represented in the dissolution profile figures. All dissolution data are based on the actual drug content of the test dosage form as calculated from the assay results. All the Metronidazole brands released >90% drug in acidic media (pH 1.2) within 30 min, and pH (4.5).

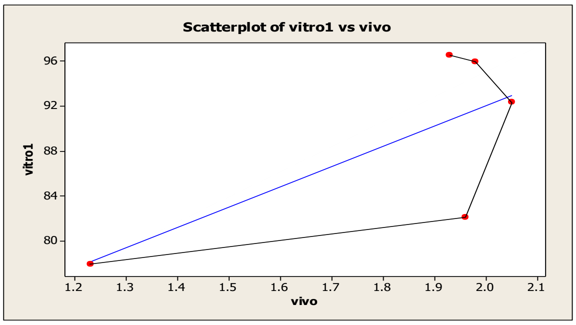

Figure 4: Metronidazole correlation in pH (1.2).

Amount released in phosphate buffer PH (6.8) were about 84% for reference drug and 91.4%, 86.5% for test brands, This may be due to the pH depended solubility of Metronidazole.

Table 3: F1 and F2 Values.

Samples	pH 1.2		pH 4.5		pH 6.8	
	F1	F2	F1	F2	F1	F2
Sample (B)	4	64	5	66	6	63
Sample (C)	5	63	7	58	4	66

Analysis of Dissolution Data: To compare the dissolution profiles of the brands, a model independent approach of difference factor f1 and similarity factor f2 were employed. Difference factor f1 is the percentage difference between two curves at each point and is a measurement of the relative error between the two curves. The similarity factor (f2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between two curves.

Two dissolution profiles to be considered similar and bioequivalent, f1 should be between 0 and 15 while f2 should be between 50 and 1007.

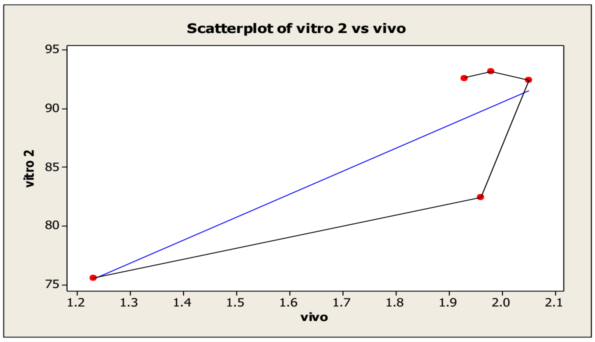

Figure 5: Metronidazole correlation in pH (4.5).

All the values for f2 and f1shown in tables 29 for metronidazole, as mentioned in previous tables, all brands f2 values were more than 50 and f1 values were less than 15. Which mean that all brands are equivalent with the innovator brand. *In-vitro* AUC in three pH (1.2), (4.5), (6.8) for class I product were found three times *in vivo* bioequivalence AUC calculated before, which is acceptable result because the *in-vitro* dissolution studies were carried out in ideal conditions without any factors that could affect their performance, such as volunteers internal biological inconsistency.

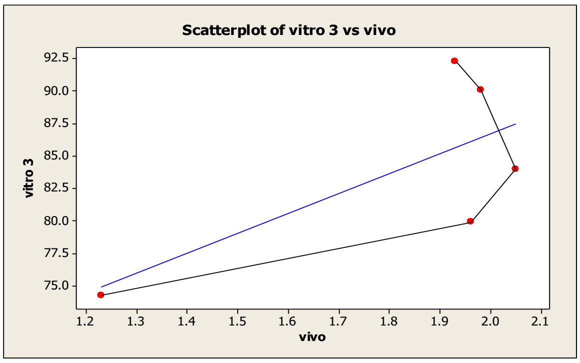

Figure 6: Metronidazole correlation in pH (6.8).

Dissolution efficiency (DE) was also employed to compare the drug release from various brands. The reference and the test product can said to be equivalent if the difference between their dissolution efficiencies are within appropriate limits (±10%, which is often used)2. Dissolution efficiency of all the brands (class I) differed by less than 10% from the innovator brand. So, we can say that all the brands are pharmaceutically equivalent with the innovator brand.

Table 4: Dissolution efficiency for Metronidazole brands.

Samples	pH 1.2		pH 4.5		pH 6.8	
	AUC	Difference with reference	AUC	Difference with reference	AUC	Difference with reference
Sample A	356.37	-	361.96	-	357.84	-
Sample B	364.14	-7.77	350.14	11.82	355.03	-3.19
Sample C	361.02	-4.65	345.85	16.11	364.51	-12.73

Table 5: Relative dissolution efficiency of Metronidazole brands.

Brand	pH 1.2	pH 4.5	pH 6.8
Brand B	102.18%	96.73%	**100.91%**
Brand C	101.30%	95.45%	**103.62%**

In vitro- in vivo Correlation Data Analysis

As IVIVC is a predictive mathematical model describing the relationship between variables (an *in vitro* property of a dosage form and a relevant *in vivo* response). According to MINITAM 14 statistical program, there was significant relationship between *in vitro* and *in vivo* data of reference metronidazole product, correlation and distribution of data with correlation coefficient (r=0.724, 0.837, 0.707), nonlinear relationship with *p*-value (>0.05)=(0.167, 0.098 , 0.182), there is no out lines, no lake of fits at *P*-Values=0.0040, 006, 0.026. By analysis of variance (ANOVA) the data points have significant relationship with *p*-value (> 0.05) for the three pH (1.2), (4.5), (6.8) respectively. Estimating the uncertainty in predicted correlation between *in vitro* and *in vivo* data was also performed. The interval is represented by the curved lines on either side of the regression line and gives an indication of the range within which the ‘true’ line might lie. Note that the confidence interval is narrowest near the center (the point x, y) and less certain near the extremes.

Using MINITAM 14 statistical program, there was significant relationship between *in vitro* and *in vivo* data of reference Atenolol product, Correlation and distribution of data with correlation coefficient (r= 0.798, 0.815, 0.967), nonlinear relationship with *p*-value (>0.05)=(0.106, 0.93, 0.009), there is no out lines, no lake of fits at *p*-values=0.106, 0.040, 0.056 (>0.05) for the three pH (1.2,4.5,6.8) respectively.

Estimating the uncertainty in predicted correlation between *in vitro* and *in vivo* data. The interval is represented by the curved lines on either side of the regression line and gives an indication of the range within which the ‘true’ line might lie. Note that the confidence interval is narrowest near the center (the point x, y) and less certain near the extremes. By applying analysis of variance (ANOVA) for the dissolution data using MINITAB 14 we concluded that the test products are bioequivalent to reference products of metronidazole and atenolol and could be interchangeable.

CONCLUSIONS

The bio waiver study has emphasized that pharmaceutical equivalence indicate that product have same drug molecule with approximately same pattern of dissolution release profile. By making fine turning in bioequivalent study we can reduce the time, cost, avoid Ethical, Ethnical consideration by unnecessary exposure of healthy subjects to medicines and finally to market the quality generic drug product. By applying level an *in-vivo in-vitro* correlation, we might concluded that there is no linear correlation between percent of drug released and percent of drug absorbed, this may be due to uncontrollable gastric emptying rate for class one Metronidazole. Metronidazole is an immediate release formulations. As dissolution is not a rate-limiting step in IR products, the fraction of drug absorbed against the fraction of drug released profile would be non-linear type which was obtained in present study. So it may be concluded that the *In vitro-In vivo* correlation is well established and justified for reference formulation by level A correlation.

By applying analysis of variance (ANOVA) for the dissolution data using MINITAB 14 we concluded that the test products are bioequivalent to reference products of Metronidazole and could be interchangeable.

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AUTHOR'S CONTRIBUTION

Ahmed EM: clinical work, writing. **Ibrahim ME:** methodology, investigation. **Magbool FF:** formal analysis, data curation, conceptualization. All authors revised the article and approved the final version.

DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

No conflict of interest is associated with this work.

REFERENCES

1. Amidon GL, Lennernas H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. Pharm Res 1995; 12:413-420. *https://doi.org/10.1023/a:1016212804288*
2. Anderson NH, Bauer M, Boussac N, Khan-Malek R, Munden PSM. An evaluation of fit factors and dissolution efficiency for the comparison of *in vitro* dissolution profiles. J Pharm Biomed Anal 1998; 17 (4-5): 811-822. *https://doi.org/10.1016/S0731-7085(98)00011-9*
3. Chen JC, Chiu MH, Nie RL, Cordell GA, Qius SX. Cucurbitacine and cucurbitane glycosides: structure and biological activities. Nat Prod Rep 2005; 22(3): 386-99. *https://doi.org/10.1039/B418841C*
4. Jayaprakasam B, Seeram NP, Nairs MG. Anticancer and anti-inflammatory activities of cucurbitacins from *cucurbita andreana*. Cancer Lett 2003; 189(1): 6-11. *https://doi.org/10.1016/s0304-3835(02)00497-4*
5. The American Society of Health-System Pharmacists. Archived from the original on 6 September 2015. Retrieved 31 July 2015.
6. Raimar L, Nadia BC, Erika S, *et al*. Toward Global standards for comparator pharmaceutical products: case studies of moxicillin, metronidazole, and zidovudine in the America. J American Ass Pharm Sci 2012; (14):462–472. *https://doi.org/10.1208/s12248-012-9350-9*
7. FDA, Center for drug evaluation and research, guidance for industry: immediate release solid oral dosage forms. *In vitro* dissolution testing, and *in vivo* bioequivalence documentation [SUPAC-IR], (1995).
8. Gupta E, Barends DM, Yamashita E, Lentz KA, Harmsze AM, Shah VP, *et al.* Review of global regulations concerning biowaivers for immediate release solid oral dosage forms. Eur J Pharm Sci 2006; 29(3–4):315–24. *https://doi.org/10.1016/j.ejps.2006.05.001*
9. Al Naimi RK, Khan SA: Comparative *in-vitro* pharmaceutical evaluation of four brands of metronidazole tablets marketed in Gulf region. Jordan J Pharm Sci 2014; 7(2):144-151.
10. Bendari A, Al-Shehi B, Ahuja. A comparison of pharmaceutical properties of different marketed brands of metronidazole tablets available in Oman. Int J Pharm Arch 2015. Mar 20; 4(2).
11. Porta V, Nunes DSG, *et al*. Biowaiver monographs for immediate release solid oral dosage forms: Metronidazole. J Pharm Sci 2011; 100 (5): 1618-1627. *https://doi.org/10.1002/jps.22409*
12. Ibezim E, Attama A, Obitte N, Onyishi V, Brown S. *In vitro* prediction of *in vivo* bioavailability and bioequivalence of brands of metronidazole tablets in eastern Nigerian drug market. Scientific Res Ess 2008; 3 (11): 552-558.
13. Olusola AM, Olubukola OO, Emeka OH, Lilian AE. Equivalence of two generic brands of amlodipine besylate under biowaiver conditions. Int J Pharm and Pharmaceut Sci 2012; 4 (2): 265-268.
14. Ahmed EM, Ibrahim ME, Magbool FF. *In vitro-in vivo* bio-equivalence correlation study of atenolol, and its brands of immediate release tablet under bio-waiver conditions. Universal J Pharm Res 2019; 4(6): 25-29. *https://doi.org/10.22270/ujpr.v4i6.332*