Full Length Research Paper

In vitro prediction of *in vivo* bioavailability and bioequivalence of brands of metronidazole tablets in Eastern Nigerian drug market

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The objective of this study was to carry out pharmaceutical equivalence studies on ten different brands of commercially available samples of metronidazole tablets from different manufacturers. The *in vitro* parameters employed were dissolution rate (in 0.1 N Hydrochloric acid at 37°C), hardness, weight uniformity, friability, disintegration time, absolute drug content and dissolution efficiency were also analyzed. Results obtained showed that there were wide variations in the various tablet parameters among the different brands, with some of the brands having acceptable tablet characteristics while others did not. Only two batches indicated evidence of predictable bioequivalence. This is significant in therapy where drugs are expected to not only conform to their label claims but also have satisfactory bioavailability.

Key words: Metronidazole, bioequivalence, bioavailability, prediction, dissolution efficiency.

INTRODUCTION

Some *in vitro* experimental models and data do not always ideally validate the active ingredient label claim on drug formulations. Neither does an *in vitro* profile often congruently corroborate with *in vivo* experience. This chasm in *in vivo* behavior between two or more brand products of the same active drug with similar label claims or physicochemical results is called bioinequivalence. A generic product, which is bioequivalent to same active drug but different brand name, implies similar bioavailability. Bioavailability of a drug may be regarded as the quantity of the administered doses, which arrives in a suitable form and concentration at the sites within the body where it will exert its biological effect (Effraim et al., 2002). The U.S food and Drug Administration (FDA) defines bioavailability as the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action (U.S Food and Drug Administration). In general bioequiva-

lence evaluations involve comparisons of dosage forms that are pharmaceutical equivalents (James and Marvin, 2002). Such dosage forms are defined as drug products that contain identical amounts of the identical active drug ingredient, that is, the same salt or ester of the same therapeutic moiety, in identical dosage forms, but do not necessarily contain the same inactive ingredients, and that meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and where applicable content uniformity, disintegration times and/or dissolution rates (U.S Food and Drug Administration).

Small difference in the manufacturing process could consistently alter the disintegration, dissolution and consequently the bioavailability of the active ingredients in a product (WHO, 1974). Routine random sampling and regulatory checks on drugs to ensure physicochemical consistencies will at least control the influx of too many iso-generic drugs with conflicting bioequivalence data. CGMP tends to have bias for *in vitro* than *in vivo* tests while other regulatory bodies rely on both. In Nigeria, there is suspicion that our regulatory bodies carry out *in*

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vitro without adequate *in vivo* tests before approval of drugs for distribution and consumption. Effraim et al. (2002) also believe that in Nigeria official standards and enforcement agencies for the quality control of drugs manufactured or imported into the country are not very effective. Consequently a wide array of iso-generics is out there with discrepant therapeutic efficacies arising from bioinequivalence. Panadol for instance has maintained a unique patient-effectiveness far enjoyed by some paracetamol brands.

Metronidazole is an amoebicide indicated against, *Giardia lamblia*, *Trichomonas vaginalis* (Aguwa, 1996) and is clinically effective in trichomoniases, amebiases, giardiases, bacteroides, *Clostridium* and *Helicopter* spe-cies. It is a prodrug, requiring reductive activation of the nitro group by susceptible organisms. It is usually com-pletely and promptly absorbed after oral intake, reaching concen-trations in plasma of 8 - 13 μg within 0.25 - 4 h after a single 500 mg dose (Hardman and Limbird, 2001). Consequently its biopharmaceutics would depend much on its dissolution and physicochemical characteristics. Therefore strict adherence to CGMP during manu-facturing is a prelude to a predictable bioavailability and bio-equivalence of similar generics. Furthermore, a preserva-tion habit instituted on its post manufacturing formulations is another matter of concern. Metronidazole loses its aesthetic and pharmacological activity on expo-sure to light (British Pharmacopoeia, 1980). Some of our markets and some commuter buses are awash with mobile drug hawkers that unwittingly or deliberately precondition these drugs to high vulnerability to photo degradation. Also, fake, adulterated and under-dose for-mulations have been known to find their way to the shelves of some drug stores, most of which are controlled by charlatans and business men.

The task of ensuring drug bioavailability via dissolution rate studies has long been studied (Wurster et al., 1965). Furthermore the goal of many workers in this area has been centered on designing *in vitro* tests that could quantitatively predict or at least predict ranks of perfor-mance *in vivo* (Ofoefule et al., 2001). Dissolution and some physicochemical properties can therefore approxi-mate bioavailability.

One of the early approaches to relate *in vivo* bioavail-ability data to *in vitro* measurements employed testing based on the time required for a solid dosage form to disintegrate in a particular solvent (James and Marvin, 2002) using a USP official apparatus (Committee of Revi-sion. Monograph 701, 2000). The drawback is that disin-tegration time may not necessarily relate to the tablets' dissolution rate. However the USP XXIV describes one official *in vitro* disintegration apparatus and two official dissolution apparatus for the evaluation of solid dosage forms (Committee of Revision. Monograph 701, 2000). These methods have reportedly been used extensively, but only few *in vitro/in vivo* correlations between dissolution data and human bioavailability data have been esta-blished (James and Marvin, 2002). However the work of

some reporters showed that the *in vitro* drug release pro-files correlated with the *in vivo* bioavailability parameter (Sarat et al., 1991).

Therefore the aim of this work is to predict bioavai-lability and bioequivalence of 10 brands of metronidazole tablets sampled from some eastern Nigerian drug mar-kets and shops, using *in vitro* tests.

MATERIALS AND METHODS

Drugs and chemicals

Hydrochloric acid (M and B, ENGLAND), metronidazole powder (KIND GIFT FROM RAJRAB NIG LTD,), sodium hydroxide (Merck, USA), metronidazole tablets (Lacure Nig Ltd, Eurogem Lab, Emzor Nig Ltd, M and B plc, Michelle Lab., Adson pharm, krka, Maxheal Pharm, Emmjay Lab, and Juhel Nig-Ltd). The tablets were bought from open drug markets in Onitsha, Aba, Nsukka, hospitals, patent medicine shops and pharmacies. Ten different company products of metronidazole, arbitrarily selected and coded as A – J, were used.

Uniformity of weight test

The British Pharmacopoeia (1998) method was adopted. Twenty randomly selected tablets from each batch were tested.

Hardness test

The hardness of 5 tablets randomly selected from each batch were determined on an automatic tablet hardness tester (Erweka, TBH, 28 Heusenstamn)

Friability test

Five tablets previously freed of dust were weighed together before transferring to a frabilator (Erweka - TAR) set to run for 4 min at 25 r.p.m. Thereafter they were removed, dusted and reweighed:

$$\% \text{ Friability} = [(W_i - W_f)/ W_i] \times 100 \qquad (1)$$

Where W_i is the initial weight and W_f the final weight of the tablets.

Disintegration time test

The British Pharmacopoeia (1998) method for the determination of disintegration time for uncoated tablets was adopted using a disintegrating apparatus (Grucka, Model T.D 88 T175) and the medium was 0.1 N HCl at 37±1°C. Six tablets were used for the determination.

Absolute drug content

Five pre-weighed tablets were crushed; the equivalent weight of a tablet was weighed out and dissolved in 100 ml of 0.1N HCl in a volumetric flask and filtered. The absorbance reading was determined using a spectrophotometer (Pye Unicam, model SP6-450 UV/VS) at 277 nm.

Dissolution rate

The magnetic stirrer/beaker method was used while the medium

Table 1. Results of hardness and friability tests of different brands of metronidazole tablets.

Batch	Mean tablet hardness (kgf) ± SD	Mean tablet friability (%)	CSFR
A	4.90±0.10	0.79	6.2
B	13.10± 1.02	0.18	72.78
C	2.88±0.08	5.96	0.34
D	3.94±0.05	0.84	4.69
E	3.96±0.11	2.36	1.68
F	4.92±0.13	0.70	7.03
G	3.14±0.11	2.20	1.43
H	3.96±0.11	1.67	2.37
I	3.96±0.09	2.55	1.55
J	6.82±0.29	0.29	24.36

was 250 ml of 0.1N HCl maintained at 37±1°C by a hot plate (Fischer scientific co, model 14). A basket assembly supported the tablet within the beaker, as the magnetic stirrer rotated at a speed of 100 rpm. At predetermined time intervals 1 ml of the medium was sampled which, was immediately replaced by fresh 0.1N HCl, and diluted appropriately and filtered prior to spectrophotometric assay.

Dissolution efficiency

The dissolution efficiencies (DE) (Ana et al., 2005; Costa and Lobo, 2001; Brazil Resoluciao, 2004; FDA Guidance for Industry, 1995; James and Ali, 2002; Reddy et al., 2004; Khan, 1975; Anderson et al., 1998) of the 10 batches were calculated using the calculus method to determine the area under the dissolution-time curve.

Beer lamberts plot

A 100 mg sample of pure metronidazole powder was weighed out and dissolved in 60 ml of 0.1N HCl and later made up to the 100 ml mark in a beaker. From this stock solution dilutions equivalent to 1, 2, 3, 4, 5, 6, 7 and 8 mg % (w/v) of the drug were made. A plot of absorbance against concentration was used to determine the slope K.

RESULTS AND DISCUSSION

Hardness and friability

Results of the hardness and friability values are shown in Table 1. The highest and least hardness values were recorded by batch B, 13.10 kgf and batch C, 2.08 kgf, respectively. Similarly, batch B had the least friability while batch C gave the highest friability value of 5.96%. The crushing strength for batch B was quite high, as high as to have resulted to the least friability and highest disintegration time. This high crushing strength is attributed to a high compression force, high binder concentration or excess volume of granulating fluid. Batch C with the least value may be due to the reverse of the aforementioned reasons. The implication of these is that CGMP was not

adhered to and quality control may have eluded these batches of tablets. According to The British Pharmacopoeia (2004) maximum loss of 1% of the mass of the tablets tested (for friability) is considered acceptable. Based on this, batches C, E, G, and I failed the friability test. It is also possible that for economic reasons the companies may have been reluctant to exclude these batches of tablets or that there was no friability test carried out at all.

The least friability exhibited by batch C may have been because of the absence of a binder, the addition of one with low adhesive strength, addition of insufficient granulating fluid or tableting done under low compression pressure. The ability to withstand shock during shipping, transportation and handling is a regulatory and official requirement for tablets. This batch C, on getting to retail points would have experienced a lot of piecing off and breakages which is not only an immediate loss to the retail drug vendor or pharmacist but a negative blow to the company's integrity. There was an inverse correlation between friability and crushing strength. Batch C that was most friable had least crushing strength. The ratio of crushing strength to friability (CSFR) is an index of measuring the mechanical properties of tablets; the higher the CSFR, the stronger the tablet (Odeku and Itiola, 2003). Batch B recorded the highest CSFR of 72.78 while batch C had the least.

Weight uniformity

Batch H weighed highest (0.701+0.009 g) while batch D weighed least (0.374±0.006 g). The British Pharmacopoeia (1998) specifies that not more than two of the individual weights should deviate from the average weight by more than 5%, and none should deviate by more than 10%. All the batches passed the test. The differences in inter batch weights could be attributed to the variations in percentage of excipients especially diluents or bulking agents, which is usually the decision of the formulation pharmacist.

Disintegration time

In Table 2, batch B indicated the longest disintegration time of 18.0 ± 0.03 min while batch J, the least value of 0.40 min. USP disintegration allowance for uncoated tablets is within 15 min; this means that batch B had a slightly longer time while others recorded acceptable values. This above fifteen minutes disintegration time correlates with its low friability and high hardness values.

Batches A and J with very low values are possibly attributed to the presence of large amounts of disintegrants. Batch J was second to batch B in crushing strength and friability. It should therefore be expected that its disintegration time be second or close to that of B. Nevertheless a striking least disintegration time of 0.4 ± 0.04 min was recorded. Onyekweli et al. (2004) made a similar obser-

Table 2. Results of uniformity of weight and disintegration time tests of different brands of metronidazole tablets.

Batch	Mean tablet weight ± SD (min)			Mean tablet Disint. Time+ SD (min)		
A	0.684	±	0.0.008	0.55	±	0.03
B	0.588	±	0.008	18.00	±	0.03
C	0.617	±	0.015	4.00	±	0.03
D	0.374	±	0.006	4.51	±	0.28
E	0.517	±	0.005	1.35	±	0.07
F	0.358	±	0.008	1.17	±	0.01
G	0.492	±	0.003	5.30	±	0.05
H	0.701	±	0.009	1.56	±	0.15
I	0.552	±	0.017	4.13	±	0.06
J	0.470	±	0.014	0.40	±	0.04

Table 3. Results of absolute drug content of different brands of metronidazole tablets: drug released after 45 minute and dissolution efficiency.

Batch	Absolute drug content (mg)	% Drug released at 45 min	Dissolution effficiency at T30 (min)
A	70	60.7	48.2
B	190.1	26.2	18.2
C	157.6	75.6	68.6
D	58.3	82.2	80.4
E	141.0	79.2	72.4
F	141.1	93.3	81.4
G	170.0	76.7	70.6
H	199.8	75.6	48.6
I	196.9	84.8	50.2

vation; tablets with high compression force and increased hardness values surprisingly recorded faster disintegration. Contrary to this, the observation of other workers (Ejiofor et al., 1986; Iwuagwu and Onyekweli, 2003) was that increase in compression pressure, which should expectedly increase the crushing strength led, to increase in disintegration time. In essence the therapeutic response of batch J is expected to be faster and better than that of B. This is because the disintegration of a tablet in the gastrointestinal tract (GIT) is a crucial step to absorption and bioavailability through the epithelial membranes.

Absolute drug content

Table 3 shows the results of the absolute drug content of the various batches, with their different values. Batch D had the least value of 58.3 mg while H, the highest value of 199.8 mg. The British Pharmacopoeia does allow some deviations i.e. ± 5% of the stated value of the active ingredient. Since the label claim is 200 mg, the contents are required to fall within 190-210 mg. Going by this, it was only batches B, H and I that met this official require-

ment. The implication is obvious; in spite of good hardness, disintegration or friability profile such sub-optimal content of metronidazole tablets may never achieve therapeutic plasma or cellular minimum effective or inhibitory concentration. Although the development of resistance to metronidazole has not proven to be a therapeutic problem (Aguwu, 1996), clinical resistance is well documented for *Trichomonas vaginalis*, *Giardia lamblia* and a variety of anaerobic bacteria but has yet to be shown for *Endamoeba histolitica* (Hardman and Limbird, 2001). Yet the intake of sub-lethal doses of tablets is likely to increase the risk of tolerance and resistance.

Dissolution studies

Figures 1 - 3 show the dissolution behaviors of the various batches. The official British Pharmacopoeia specification is that not less than 70% of the stated or prescribed drug amount should be contained by samples taken at 45 min (British Pharmacopoeia, 2004). With the exception of batches A, B and J (which failed the test.), the rest of the batches, C, D, E, F, G, H and I, released at least 75% of their content within 45 min. The corresponding t_{75} for batches C, F, E, D, G, H and I which were approximately ≤45 min is not conclusive of adequate bioavailability unless the drug content is also within official stated values.

For instance batch D that had a very poor absolute drug content of 58.2 mg witnessed an excellent drug release of 82.2% within 45 min. The systemic bioavail-ability of this batch will be low in addition to precarious therapeutic efficacy. Any unfortunate patient who is placed on such tablets may report back to the doctor that the drug is not working. The doctor may quickly resort to a higher expensive fluoroquinolone antibiotic or increase the initial drug dose. This may predispose to hepatotoxicity, drug resistance and/or economic loss.

Dissolution efficiency

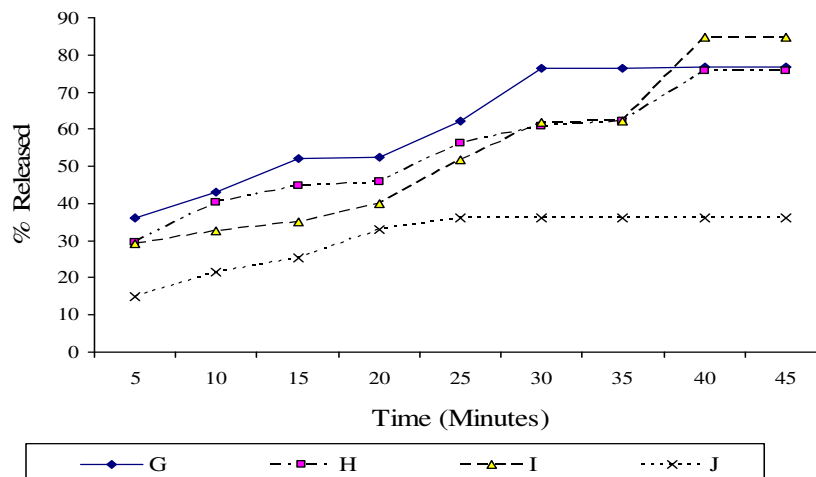The area under the dissolution-time curve method was
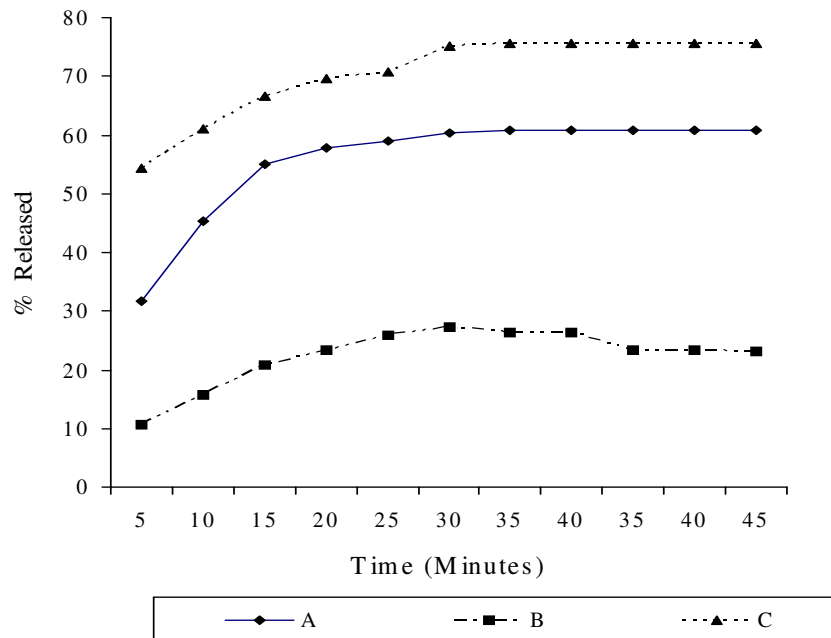
Figure 1. Metronidazole drug release (%) released vs time (min) for batches A, B and C.
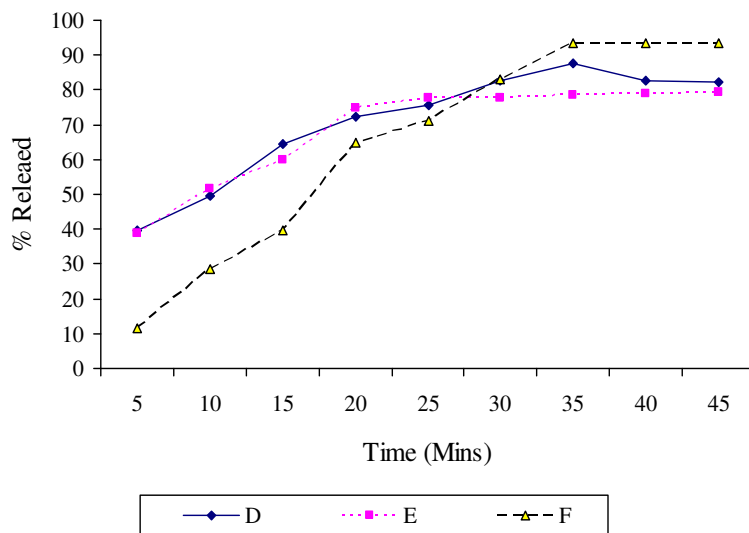
Figure 2. Metronidazole drug release (%) released vs time (min) for batches D, E and F.

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. Table 3 shows the dissolution efficiency (DE) values at 30 min. Batch F had the highest value of 81.4% while B recorded the least value of 18.2%. Batches C, D, E and G had (DE) above 50% at time (30 min) which is good enough for anticipated efficient bioavailability while batches A, H and I had marginal values. Batch D with a dissolution efficiency of 80.4% may not likely achieve optimum therapeutic response because its absolute drug content was 58.3 mg. Even if it achieves good bioavailability it may not measure measure up to the minimum tissue concentration enough for prompt bactericidal action; besides its duration of action will be impaired. This is because a 500 mg dose ingested orally attains a plasma concentration of 8 - 13 µg/ml within 0.25 - 4 h and its minimum effective concen-

Figure 3. Metronidazole drug release (%) released vs time (min) for batches G, H, J and I.

tration (MEC) is ≤ 8 µg/ml. It has also been reported that a linear relationship between dose and plasma concentration pertains for doses of 200 - 2000 mg (Hardman and Limbird, 2001). On the other hand the batch B that indicated an excellent absolute drug content of 190.1 mg could only release 26.2%, hence its poor DE of 18.2%.

DE has been shown to be a quantitative approach to assess drug release profile unlike the fit factors, f_1 and f_2 method (Reddy et al., 2004), which are at best qualitative in nature. However a better assessment and prediction of good bioavailability should include absolute drug content, drug release profile (especially T_{50} and T_{70}) and dissolution efficiency.

A tablet may have a very high crushing strength to friability ratio (CSFR), a good minimum crushing strength of 4 kgf (Banker and Rhodes, 1979) and yet not have a good DE, as was the case with batch B with the highest CSFR. Therefore while not neglecting the usefulness of mechanical properties, the release characteristics, absolute drug content and DE are good enough to attempt a prediction of favorable correlation with *in vivo* studies. Some workers have demonstrated Brand-brand inequivalence with the innovator product (Oluleye and Familusi, 2005) and correlated *in vitro* and *in vivo* studies to predict bioavailability and bioequivalence (Sarat et al., 1991; Babalola et al., 2001).

Some of the brands (that is, batches B and J) did not show evidence of predictable satisfactory bioavailability and bioequivalence based on their dissolution efficiency values of 18.2 and 24.2%, respectively. The major cause of the latter's poor DE is attributed to its slow % release, probably occasioned by adsorption of the drug to one of the tablet excipients. This same batch recorded the least disintegration time of 0.4 min. Similarly for batch B, the reason for its least DE value is likely to be due to its high CSFR, disintegration time and hardness which culminated in a delayed release of the drug.

The difference in the metronidazole brands calls for a step-up of quality control and cGMP efforts by drug manufacturers and post-distribution-routine market-sampling *in vitro* quality control and *in vivo* tests by regulatory agencies. Quality assurance (Hudson, 2004) system involves complex options with checks, tests and inspection carried out at all levels and includes quality control procedures, the purpose of which is to ensure an absolute quality (a zero-defect) product such that each tablet will contain the amount of active drug claimed on the tablet within limits.

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