

*Full Length Research Paper*

# Effect of process parameters on the properties of some metronidazole tablet and capsule formulations

Mbah C. C.\*, Emosairue C. O., Builders P. F., Isimi C. Y., and Kunle O. O.

Department of Pharmaceutical Technology and Raw Materials Development, National Institute for Pharmaceutical Research and Development, Idu, PMB 21 Garki, Abuja, Nigeria.

Accepted 26 March, 2012

This work was aimed at evaluating the properties of metronidazole capsules and tablets formulated by different methods in comparison with some commercially available tablet brands to ascertain the influence of formulation parameters and the unpopularity of clinical use of the capsule in Nigeria. Three batches of metronidazole 200 mg tablets were formulated by wet granulation, dry granulation and direct compression methods. Metronidazole 200 mg capsules were formulated by hand filling technique. The formulations and two commercially available tablet brands (M & B, Cardinal) were evaluated following standard procedures. All the formulated tablets passed the uniformity of weight and content, disintegration and dissolution tests but failed the friability test to a significant degree in the order: Dry > Direct Compression > Wet. The release profiles were in the order: Wet > Direct Compression > Dry > M & B > Capsule > Cardinal, with significant ( $P < 0.05$ ) difference between the highest and the lowest. The results indicated that variations in formulation parameters had important influence on the qualities of solid dosage formulations of metronidazole. Except for one commercial brand, all the tablet formulations tested generally performed better than the capsule formulation, probably supporting its unpopularity in Nigeria.

**Key words:** Metronidazole, capsules, tablets, granulation, dissolution profile.

## INTRODUCTION

Capsule formulations of metronidazole can hardly be seen in use in Nigerian health institutions despite the avalanche of other dosage forms, including tablets, suspensions and infusions. Whether this unpopularity is connected with effectiveness, instability, production cost, patient apathy or lack of compliance, remains to be answered. However, solid dosage forms, of which tablets and capsules are predominant, are presently the most common means of drug delivery (British Pharmacopoeia (BP), 2004). The BP defines capsules as solid preparations with hard or soft shells of various shapes and capacities usually containing a single dose of active substance. Capsules are usually prepared by filling the shells with the desired material by hand or using capsule filling machine. Tablets, on the other hand, are solid

preparations each containing a single dose of one or more active substances and usually obtained by compressing uniform quantities of particles. They may contain excipients such as diluents, binders, disintegrants, glidants, lubricants, colouring matter and flavouring substances which should be used in quantities that do not affect stability, dissolution rate, release and bioavailability (Swarbarick and Boylan, 2002).

Formulation parameters have been identified to influence tablet characteristics. Variations in the manufacturing process could consistently alter the disintegration, dissolution and consequently the bioavailability of the active ingredients in a product (WHO, 1974). Tablets are usually prepared by either granulation or by direct compression methods. Granulation is a process in which small particles of powdered drug material are made to adhere to form larger particles called granules (Aulton, 2002), with or without excipients, using a granulating fluid or binder solution or by pre-compression. This process improves the shape and size distribution

\*Corresponding author. E-mail: mbaccc@yahoo.com. Tel: +234 8087716982.

**Table 1.** Formula for preparation of tablets.

Material	Value
Metronidazole powder	200 mg
Maize starch powder	5% w/w*
Microcrystalline cellulose (Avicel® PH-101)	3% w/w
Magnesium stearate powder	1% w/w
Lactose powder qs	250 mg

\*w/w = weight in weight.

of the bulk material with resultant increase in the packing and flow properties. Also individual granule strength and porosity are improved (Lachman et al., 1987), all of which are important factors that affect quality of tablets produced. In the direct compression method of tableting, the ingredients are mixed together and compressed, in a single-stage process (Aulton, 2002).

Metronidazole is a nitroimidazole compound known to be clinically effective in protozoan infections such as trichomoniasis, amoebiasis, and giardiasis, as well as in a variety of infections caused by obligate anaerobic bacteria including *Bacteroides*, *Clostridium*, and *Helicobacteria* species. It is also used as cream or gel for treatment of propionibacterium acnes (Hardman and Limbird, 2001). Metronidazole is a pro-drug, requiring reductive activation of the nitro group by susceptible organisms. It is usually completely and promptly absorbed after oral intake, reaching concentrations in plasma of 8 to 13 mg within 0.25 to 4 h after a single 500 mg dose. Therefore its pharmacokinetic behavior would depend much on the dissolution as well as physicochemical characteristics, and adherence to Current Good Manufacturing Practice (CGMP) during manufacturing is paramount to predictability of its bioavailability and bioequivalence (Ibezim et al., 2008). Furthermore, preservation of metronidazole post manufacturing formulations is another matter of concern as it loses its aesthetic and pharmacological activity on exposure to light (BP, 1980). Solid dosage forms of metronidazole are usually available in Nigeria as tablets in strengths of 200, 250, 400 and 500 mg. It has been found that out of 10 brands of metronidazole tablets purchased from different Nigerian drug markets, there were wide variations in the various tablet parameters, with some of the brands having acceptable tablet characteristics while others does not (Ibezim et al., 2008). Only two batches indicated evidence of predictable bioequivalence. The major goal for *in vitro* dissolution tests is to quantitatively predict *in vivo* bioavailability (Ofoefule et al., 2001). Some reported works showed that the *in vitro* drug release profiles correlated with the *in vivo* bioavailability parameter (Sarat et al., 1991).

In this work, it was intended to formulate metronidazole capsules and tablets, and compare their properties with those of two commercially available tablet formulations

supposedly containing equivalent amounts of labelled metronidazole so as to evaluate the feasibility of therapeutic use of the capsules in Nigeria. The preparation of metronidazole tablets by three different methods namely: wet granulation, dry granulation and direct compression was also intended to evaluate how process parameters affect the properties of the formulation.

## MATERIALS AND METHODS

Metronidazole powder (Sigma, Germany), maize starch (Sigma, Germany), magnesium stearate (BDH, England), microcrystalline cellulose 90% (Avicel® PH-101) (MCC), lactose (Sigma, Germany), Loxagyl® 200 mg tablets (May and Baker Nig. PLC, Lagos) (M & B) and Metronidazole 200 mg tablets (Cardinal Drugs Ltd., Nigeria) (Cardinal) were purchased from a registered retail pharmacy in Abuja, Nigeria. Other reagents used were of analytical grade and were used without further purification.

### Preparation of tablets

The procedures outlined in the British Pharmacopoeia (BP) were followed in the preparation of tablets (BP, 2004). Table 1 shows the formula used for all the batches prepared by different methods. A total of 60 tablets each were prepared for the wet and dry granulation methods while 48 were prepared by direct compression. All the tablets were stored in well closed and light resistant containers at laboratory temperature.

Maize starch powder was used because starch (especially maize starch powder) is one of the most widely used disintegrants in tableting. MCC was used as a binder because it is the most effective dry binder especially for tablets prepared by direct compression (Swarbarick and Boylan, 2002). Magnesium stearate is a boundary and water-insoluble lubricant. It has surfactant properties which aids dissolution. It also reduces tablet crushing strength. Lactose is the most common filler used in tablets preparation (especially those prepared by wet granulation method). It possesses a series of good filler properties e.g., it dissolves readily in water which makes it suitable for active ingredients of low water solubility such as metronidazole. It has a pleasant taste, is non-hygroscopic, reasonably inert and showed good compactability (Swarbarick and Boylan, 2002).

### Wet granulation

The wet granulation method was adopted (Aulton, 2002). A 12 g quantity of metronidazole powder, 80% of maize starch powder (intragranular addition) and 1.65 g of lactose powder were triturated together in a mortar in increasing amounts. A 3% dispersion of the binder (MCC) was prepared and few drops mixed with the powder to form a wet mass. The wet mass was forced through a standard granulating sieve (BSS 16), to produce wet granules which were dried in an oven at 50°C for 1 h. The dried granules were sieved again and then mixed with the remaining maize starch (20%, extragranular addition) and magnesium stearate. Sequential addition of the disintegrant was done since it is required between the granules as well as within them so that the disintegrating action will not only force the tablet apart into the original granules but will also break down the granules. Quantities weighing 250 mg of the granules were compressed into tablets at compression pressure of 9.5 kgf using the single punch tableting machine (Tianxiang Chentai Pharm. Machinery Co. Ltd., China).

### Dry granulation

A 12 g quantity of metronidazole, 0.75 g of maize starch, 0.45 g of MCC, 0.15 g of magnesium stearate powders were triturated together with 1.65 g of lactose powder in a mortar. A 250 mg quantity was weighed out and slugs were produced using a compression pressure of 5 kgf. The slugs were sieved to produce dry granules. Another 250 mg were again weighed out and re-compressed into tablets using a compression of 9.5 kgf.

### Direct compression

A 9.6 g quantity of metronidazole, 0.6 g of maize starch, 0.36 g of microcrystalline cellulose, 0.12 g of magnesium stearate and 1.32 g of lactose powders were triturated together in a mortar. After trituration, 250 mg was weighed out and compressed into tablets using the single punch tableting machine at a compression pressure of 9.5 kgf.

### Preparation of capsules

Metronidazole granules were prepared by wet granulation method, as in tablet preparation, and used as fill material for the capsules. A 250 mg quantity was weighed using an analytical balance and poured into the capsule shells using the hand filling technique, since the number of capsules required for this study was below the number that the encapsulating machine could accommodate at a time.

### Tablet and capsule evaluation

All measurements were carried out in triplicates and mean calculated.

#### Weight uniformity test

The BP method was adopted (BP, 2004).

#### Crushing strength/hardness test

The BP method was adopted (BP, 2004), using the Erweka® hardness tester.

#### Friability test

The BP method was followed using the friabilator (BP, 2004). The percentage weight loss was calculated as a percentage of the initial weight. The crushing strength to friability ratio (CSFR) of all the tablets were also calculated using the equation:

$$CSFR = CS/F \quad (1)$$

Where, CS is the crushing strength and F is the friability.

#### Content uniformity test

The BP method was adopted using the dissolution test apparatus (BP, 2004). 5 tablets randomly selected from each of the 3 batches of formulated tablets were crushed and grinded to powder by triturating vigorously in a clean and dry mortar. The mean weight from the weight uniformity test was weighed out and dissolved in 100 ml of 0.1 N HCl (pH 1.2) in a beaker. To ensure proper

dissolution of the solid particles, the beaker was placed in a water bath to warm the solution. Afterwards, the solution was filtered using a filter paper (Whatman No.1). Then 1 ml of the filtrate was pipetted and made up to 100 ml with 0.1 N HCl. A 1% solution of the pure sample was prepared and double-fold dilutions made. These solutions were used to obtain a calibration curve spectrophotometrically, using a spectrophotometer (UV-160A, Shimadzu, Japan), for analysis of the metronidazole-containing samples at 277 nm absorption maximum. The test solutions were then analysed using the UV. The standard solution was also prepared by dissolving 200 mg of pure metronidazole sample in 100 ml of 0.1 N HCl and 1 ml pipetted and made up to 100 ml with 0.1 N HCl. The absorbances and concentrations were recorded and the percentage metronidazole released then calculated using the equation:

$$\% \text{ drug released} = [C_s (\times \text{Dilution factor})/C_m] \times 100 \quad (2)$$

Where  $C_s$  is the concentration of metronidazole in the withdrawn sample,  $C_m$  is the concentration in the medium.

### Disintegration test

The United States Pharmacopoeia (USP) method was adopted (USP, 2003) using the Erweka® disintegration tester. This test was carried out using 6 tablets from each batch. 900 ml of 0.1 N HCl (pH 1.2) was used as disintegration medium. The equipment was maintained at a temperature of  $37 \pm 2^\circ\text{C}$ . One tablet was placed on the mesh screen at the bottom end of each of the 6 glass tubes. The basket maintained an up and down movement in and out of the medium at a frequency of 28 to 32 cycles per min. Disintegration time was noted by means of a stopwatch. All the tablet particles passed through the screen. The test was repeated two additional times.

### Dissolution test

The rotating basket method was adopted (BP, 2004). A 0.1 N HCl solution (pH 1.2) was used as the dissolution medium. *In vitro* release of metronidazole from the tablets and capsules was measured at  $37 \pm 2^\circ\text{C}$  and 100 rpm in 900 ml of the medium. Samples (5 ml) were withdrawn at predetermined time intervals of 5, 10, 15, 20, 45 and 60 min, diluted suitably (1 in 10 dilution) and analysed spectrophotometrically at 277 nm absorption maximum. An equal volume of fresh dissolution medium, maintained at the same temperature, was added after each withdrawal to maintain the volume. The test was repeated thrice.

### Statistical analysis

The results were analyzed by analysis of variance (ANOVA) and Student's *t*-test using Microsoft Office Excel 2007 and values at ( $P < 0.05$ ) considered significant.

## RESULTS

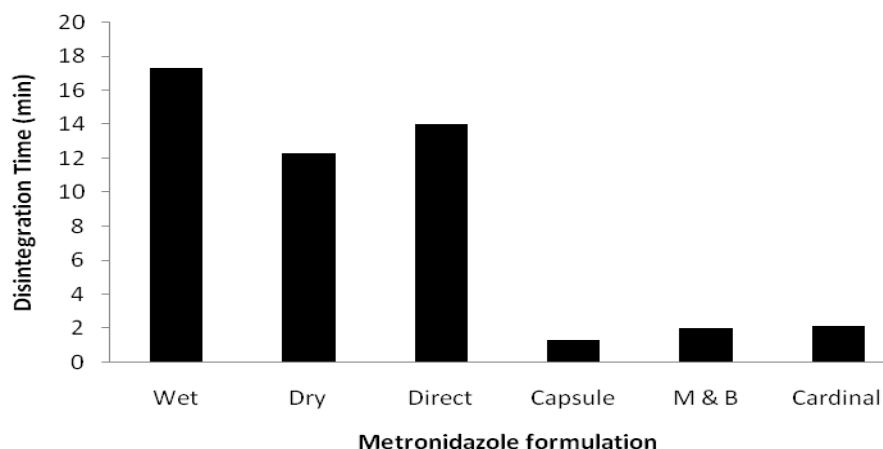
Results of the evaluation tests are shown in Table 2 and Figures 1 and 2, respectively.

### Weight uniformity

All the formulations tested passed the test for uniformity of weight (Table 2). There was greater extent of variation

**Table 2.** Mean tablet and capsule characteristics.

Parameter	Wet granulation	Dry granulation	Direct compression	M&B	Cardinal	Capsules
Mean Weight (mg) (250 mg for wet, dry and direct)	245.78 ± 4.2	243.49 ± 3.2	240.63 ± 4.6	342.49 ± 10.3	552.09 ± 13.2	
Crushing strength [CS] (kgf)	2.65 ± 1.5	0.68 ± 0.2	2.32 ± 1.6	6.49 ± 0.63	4.5 ± 0.97	
Friability [F] (%)	4.97 ± 0.02	9.37 ± 0.01	8.08 ± 0.04	0 ± 0.00	0.48 ± 0.01	
CSF Ratio	0.533	0.073	0.29	6.49	9.38	
Disintegration time (min)	17.33 ± 0.04	12.33 ± 0.16	14.00 ± 0.37	2.03 ± 0.04	2.18 ± 0.03	1.36 ± 0.03
Content uniformity (%)	96.10 ± 0.17	95.9 ± 0.46	96.2 ± 0.4	95.3 ± 0.17	96.7 ± 0.85	96.3 ± 0.2

**Figure 1.** Graph showing disintegration times of metronidazole formulations.

in weight in the two commercial brands of metronidazole tablet. The variation in weight of the tablets was in the order: Cardinal > M & B > Direct > Wet > Dry.

### Crushing strength

Except for the dry granulation, the other formulated and commercial brands of metronidazole tablets passed the test for hardness with the values lying within the range of about 2 to 6.5 kgf (Table 2). The M & B brand had the highest while the tablet formulated by direct compression method had the least value. The value obtained for the dry granulation tablets, which failed the test, differed significantly from other formulated tablets and the commercial brands.

### Friability

All the formulated tablets failed the friability test in the order: Dry > Direct > Wet, as the percentage weight losses were greater than the BP requirement of less than

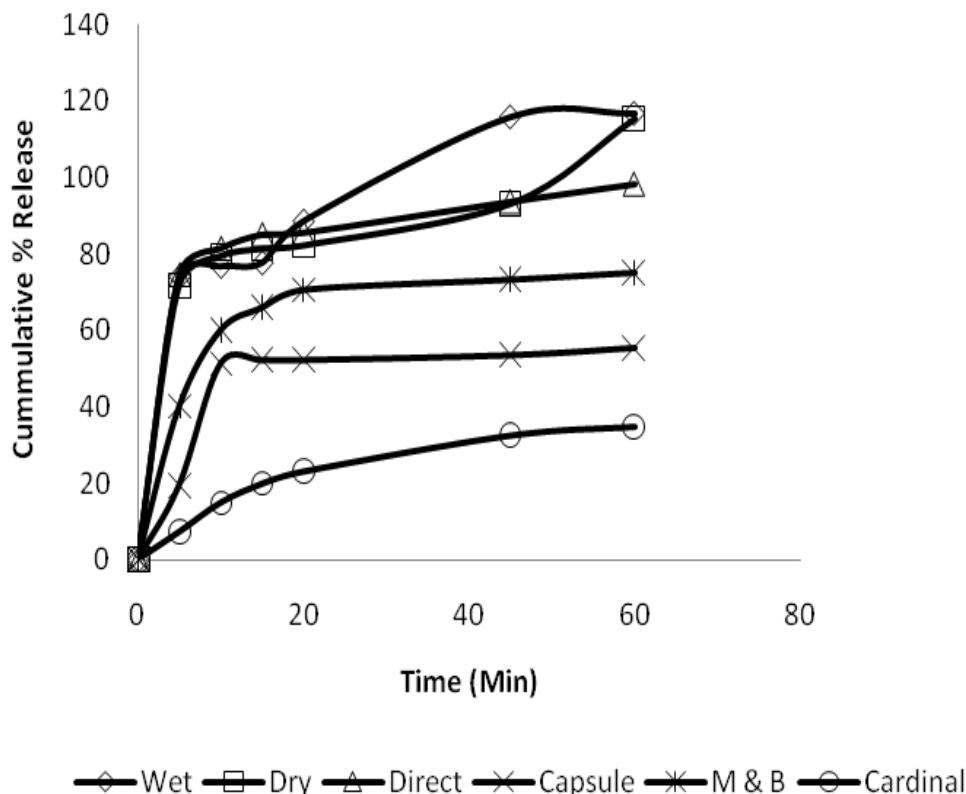
or equal to 1 and differed significantly from those of the commercial brands (Table 2). The commercial brands tested passed the test in the order: M & B > Cardinal.

### Crushing strength/friability ratio (CSFR)

The CSFR calculated (Table 2) was of the order: Cardinal > M & B > Wet > Direct Compression > Dry. This implies that the Cardinal Drugs tablets were the hardest, while those prepared by dry granulation had the least ratio.

### Disintegration time

Both the commercial brands and the new formulations generally passed the test for disintegration. The formulations disintegrated fast in the order: Capsule > M & B > Cardinal > Dry > Direct Compression > Wet (Table 2). Except for the tablets formulated by wet granulation which disintegrated at 17.33 min, all the others disintegrated in less than 15 min. The formulated capsule and the commercial brands disintegrated significantly (*P*



**Figure 2.** Dissolution profiles of the metronidazole formulations.

< 0.05) faster than the formulated tablets. The capsule formulation had the fasted disintegration time of 1.36 min. It was observed that the formulated capsules started disintegrating within the first 1 min. At that time the shells started dissolving from the ends where the drug content then began to lick (release). Figure 1 illustrates clearly the results of the disintegration test.

### Content uniformity

All the formulations, including the capsule and the commercial tablet brands, had approximately uniform concentration of about 96% metronidazole (Table 2). This value fell within the BP requirement of 85 to 115%, indicating that appropriate quantities of metronidazole were approximately weighed and used in the formulations.

### Dissolution test

Table 2 and Figure 2 illustrate results of the dissolution test. As shown in Figure 2, the three batches of tablets formulated exhibited significantly faster release rates than the capsule and the commercial brands throughout the period of the test. The release rates were in the order:

Wet > Direct > Dry > M & B > Capsule > Cardinal. The batch of tablets prepared by wet granulation, though slowed down around the 10<sup>th</sup> to 15<sup>th</sup> minute, eventually released more than all the tested products. The Direct Compression tablets progressively released faster than the Dry granulation tablets up to the first 45 min but at 60 min the latter surpassed. At 45 min of the test, while the Cardinal Drugs tablet released only 32.2% and the Capsule formulation, 53.6%, the Loxagyl<sup>®</sup> (M & B) and other tablet formulations tested had released well over 70% of their metronidazole contents. The brand from Cardinal drugs depicted significantly very poor release properties under the experimental conditions.

## DISCUSSION

### Weight uniformity

The formulated tablets and the commercially available brands passed the weight uniformity test as the standard deviation from the mean was within the specifications given in the International Pharmacopoeia (IP) (IP, 1994). The variations in the weights of individual tablets may be attributed to accuracy of weighing and die filling procedures. Inaccurate weighing and uneven filling of the die during tableting might have contributed to the observed

variations in the tablet weights.

### Crushing strength

Tablet hardness, or more appropriately crushing strength (CS), is a measure of the force required to break or crush the tablet. It gives an indication of how stable the tablet could be to stress in the course of handling. Hardness test, though not official, is an important in-process means of assessing whether the tablets being produced are firm enough to withstand breakage, chipping or crumbling, and yet not so hard as to delay disintegration (Aulton, 2002). Crushing strength is dependent on the amount of binder solution used, compression pressure and also the tablet dimensions. It is also a function of the weight, density and porosity of materials used and the space between the upper and the lower punches at the moment of compression. Excess amount of binder solution and compression pressure may make the compressed tablet too hard such that it may not disintegrate within desired time. On the Monsanto tester, soft and just handleable tablets would give a reading of 1 to 2 kgf while well compacted tablets would give up to 6 or more (Rawlins, 1984). A range of 4 to 8 kgf had also been given as values obtainable for CS of tablets (Remington's Pharm. Scs., 1980). The Erweka Hardness Tester used, operates by the same principle.

On the average, the results showed that the processes involved in the various unit operations, complied with CGMP with respect to producing good CS for the tablets formulated by wet granulation and direct compression. Both batches passed the test for CS. Similarly, the two commercial brands passed the test for CS, indicating that their formulation processes also complied with CGMP. However, the observations clearly indicate that the process of dry granulation may not be particularly suitable for the preparation of metronidazole tablets. This, however, requires further verification. The M & B brand having the highest crushing strength might have been formulated with higher concentration of binder and/or higher compression pressure.

### Friability

This test measures resistance to shock and abrasion of tablets due to tumbling motion that may be encountered during coating, packaging or transportation (Aulton, 2002). Friability values are usually considered satisfactory when the product exhibits weight loss of less than 0.8%. For conventional compressed tablets, weight loss of 0.5 to 1.0% or less is considered acceptable (Lieberman *et al*, 1990; Remington's Pharm. Scs., 1980). As the result shows, the newly formulated tablets may lose reasonable amount of their constituents in the course of handling. Possible factors that could have

affected the results may include: insufficient binder solution/dispersion, compression pressure, air entrapment within the granules or powders during mixing or prior to compression. However, the commercial brand tablets passed the test, implying that the tablets will be resistant to shock and abrasive frictional forces in the course of handling.

### Crushing strength/friability ratio (CSFR)

It had been stated that CSFR is an index of measuring the mechanical properties of tablets; the higher the CSFR, the stronger the tablet (Odeku and Itiola, 2003). All the newly formulated tablets had very low values. The poor strength may imply that most probably, the compression pressure used was inadequate. The tablets prepared by Dry granulation with the least CS and highest friability, had the least CSFR. The highest value obtained for Cardinal Drugs tablets correlated with its poor dissolution profile. The observations indicated an inverse relationship between crushing strength and friability.

### Disintegration time

The disintegration time test measures the time it takes a tablet or capsule to break into granules and smaller particles in physiological media. This parameter is a basic step prior to release of the active ingredient for the desired pharmacodynamic activity. The BP general requirement for disintegration of uncoated tablets is within 15 min (BP, 2004) while the USP requirement is within 30 min (USP, 2003). The results therefore indicate that the formulated tablets will disintegrate fast enough to release the drug material. From the results, it would be expected that they will release their contents in the same order.

Factors that influenced crushing strength and friability might also have affected the disintegration times of the formulations. Other important factors include solubility of the formulation constituents in the disintegration medium. The observed fast disintegration of the capsule formulation would imply that it will dissolve quickly to release its content in the dissolution medium.

### Dissolution test

Dissolution rate test is an important parameter for assessing drug release from pharmaceutical dosage forms. It is used as an indirect method of measuring drug availability, especially in assessments of formulation factors and manufacturing methods that may affect bioavailability (Lachman *et al.*, 1987). The basket method of assessing dissolution rate mimics the kinetic conditions

to which solid dosage forms are subjected when ingested into the gastrointestinal tract. The dissolution profiles showed that all the formulations released their contents with time over the 60 min period. Within the first 10 min, all the samples tested exhibited relatively fast rates of dissolution, reaching the peak at about the 15<sup>th</sup> minute. This corresponded to the period within which disintegration of the tablets or capsules were completed which normally precedes complete dissolution. However, the rate was in the order: Direct > Dry > Wet > M & B > Capsule > Cardinal. After the initial period, the rate generally decreased in nearly the same order for all the tested samples with significant ( $P < 0.05$ ) differences between the fastest and the lowest. Towards the end of the test period, the tablets prepared by wet granulation showed the highest rate of release. The Cardinal tablets showed the overall lowest release rate.

The BP requires that at 45 min, not less than 70% of the prescribed or stated amount of active ingredient should have been released at completion of dissolution test (BP, 2004). The fact that both the Cardinal brand and the capsule formulation could not achieve 70% release even at the end of the 60 min test period raises some concern as to their effective clinical use. The poor release profile observed is in line with the report of an earlier study (Ibezim et al., 2008). This may be attributed to the poor aqueous solubility of metronidazole. However, it could be reasoned that the strength of the Cardinal tablet, as shown by the calculated CSFR value, may account for the poor release profile having obtained high value for the drug content. The slower release rate of the capsule than the tablet formulations, despite its faster disintegration time, poses a puzzle. However, it had been stated that fast disintegration time may not necessarily imply high bioavailability (Ibezim et al., 2008). Perhaps the capsule shell retarded release of metronidazole particles from the encapsulated granules. The relatively poor release profile may thus explain why its clinical use is not popular in Nigeria despite the taste-masking advantage. Notwithstanding, this, together with the very poor release profile observed on the Cardinal product under the experimental conditions, need to be further examined to underscore the influence of formulation parameters on the release profile of metronidazole solid dosage formulations.

## Conclusion

The observed differences in the characteristics of the tablets prepared by different methods underscore the influence of formulation parameters on the qualities of solid dosage formulations of metronidazole. Tablets prepared by wet granulation showed the best qualities compared to the direct compression and dry granulation tablets, respectively. All the tablet formulations tested, except for one commercial brand, generally performed

better than the capsule formulation. Therefore capsule formulation of metronidazole for oral administration may need to be re-evaluated to ascertain its therapeutic usefulness in Nigeria. The dissolution and other physicochemical tests could be employed in evaluating other generic pharmaceutical products for clinical use.

## ACKNOWLEDGEMENTS

The authors are grateful to Mr. Ledou Gilama and Mrs. Theresa Ettah of the Department of Pharmaceutical Technology and Raw Materials Development, National Institute for Pharmaceutical Research and Development (NIPRD), Idu, Abuja, Nigeria for their technical assistance and also to NIPRD for provision of the facilities used in the study.

## REFERENCES

- Aulton ME (2002). *Pharmaceutics: The Science of Dosage Form Design*. Intl. Student's Ed. Churchill Livingstone. Edinburgh, 360: 417-422, 451-453.
- British Pharmacopoeia (1980). Her Majesty's Stationery Office. The Pharmaceutical Press London, p. 105.
- British Pharmacopoeia (2004). The Pharmaceutical Press, Her Majesty's Stationery Office, London. Monograph A-Z. 1-4: 361, 1306, 2141, Appendix X1118 A259, X11D A261, X11J A273-A274, XV11G A358,
- Hardman JG, Limbird LE (2001). *Goodman and Gilman's The Pharmacological basis of Therapeutics*. 10<sup>th</sup> Ed. McGraw-Hill Medical Publishing Division New York, pp. 1105-1106, 1810.
- Ibezim EC, Attama AA, Obitte NC, Onyishi VI, Brown SA (2008). In vitro prediction of in vivo bioavailability and bioequivalence of brands of metronidazole tablets in Eastern Nigerian drug market. *Sci. Res. Essay*, 3(11): 552-558.
- International Pharmacopoeia (1994). 3rd Ed. WHO Geneva, 4: 24-27; 40-41; 46-48.
- Swarbarick J, Boylan JC (2002). *Encyclopaedia of Pharmaceutical Technology*. 2nd Ed. Marcel Dekker Inc. New York, 1-3: 720, 2649, 2715-2723.
- Lachman L, Lieberman HA, Kanig JL (1987). *The Theory and Practice of Industrial Pharmacy* 3<sup>rd</sup> ed., Varghese Publishing House Bombay, pp. 77, 88, 297-299.
- Lieberman HA, Lachman L, Schwartz JB (1990). *Pharmaceutical Dosage Forms: Tablets*. 2nd Ed. Marcel Dekker Inc. New York, 2: 148-150.
- Odeku OA, Itiola OA (2003). Evaluation of the effects of Khaya gum on the mechanical and release Properties of Paracetamol Tablets. *Drug Dev. Ind. Pharm.*, 29(3): 311-320.
- Ofoefule SI, Chukwu A, Ijezie PP (2001). *The Nig. J. Pharm.*, pp.32-38.
- Rawlins EA (1984). *Bentley's Textbook of Pharmaceutics*. 8<sup>th</sup> Ed. Baillie Tindall. East Sussex, pp. 298-299.
- Remington's *Pharmaceutical Sciences* (1980). 16<sup>th</sup> Ed. Marck Pub. Co. Pennsylvania, pp 1555-1557.
- Sarat CC, Sudip KD, Saroj kg, Bijan kg (1991). Controlled delivery of Theophylline from Methacrylic ester copolymers and computersupported Pharmacokinetic assessment, in *Pharmaceutical Technology*, Wells JI, Rubinstein MH (eds.), 2: 118-125.
- United States Pharmacopoeia (2003). Asian Ed. The United States Pharmacopoeial Convention, Inc. Rockville, 26: 399, 2125, 2407-2540.
- World Health Organization (1974). *Bioavailability of Drugs: Principles and Problems*, Techn. Rep. Ser. No. 536. Geneva. WHO, pp. 7-8.