KAMPALA INTERNATIONAL UNIVERSITY –WESTERN CAMPUS

SCHOOL OF PHARMACY

A PHARMACEUTICAL EQUIVALENCE STUDY OF THE SELECTED AZITHROMYCIN 500 mg BRANDS ON THE UGANDAN MARKET

DONE BY

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A RESEARCH PROJECT REPORT SUBMITTED TO THE SCHOOL OF PHARMACY IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE AWARD OF A BACHELOR OF PHARMACY OF KAMPALA INTERNATIONAL UNIVERSITY.

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APRIL, 2018.

DECLARATION

I KALAMUZI PAUL M declare in my full sanity that this research report contains results obtained by me under the guidance of my supervisor. It is not a copy of someone else's project report in any university or other institution, and therefore it has never been submitted by any student for the award of any qualification.

Signature..28/05/2018..... Date..28/05/2018.....

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I whole heartedly thank God Almighty whose Grace has carried me all the way through. May His name be praised immeasurably and worshiped in ways uncountable, AMEN.

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LIST OF ABBREVIATIONS

FDA	Food and Drug Administration
BP	British pharmacopoeia
USP	United States Pharmacopoeia
ANDA	Abbreviated New Drug Application
Wt	Weight
NCCLS	National Committee for Clinical Laboratory Standards
SPSS	Statistical Package for Social Sciences.
HCL	Hydrochloric

ABSTRACT

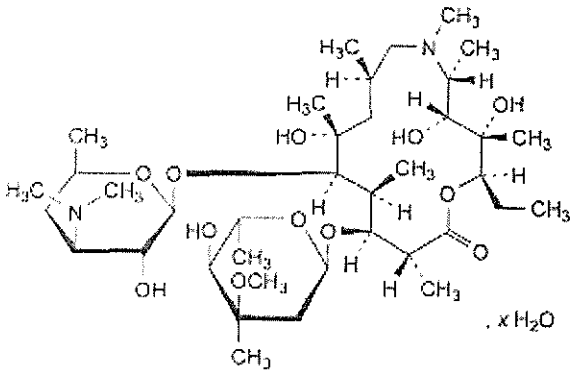
Azithromycin, being a very important antibiotic, is manufactured by different pharmaceutical companies and available in numerous brands. Therefore, it requires a quantitative evaluation and assessment of tablets' chemical, and physical properties to determine their pharmaceutical equivalence. In this study, three brands of 500mg azithromycin on the Ugandan market that is: brand X from U.K, Y from Egypt, and Z from U.S.A were tested for pharmaceutical equivalence irrespective of their large differences in cost. The physicochemical quality parameters tested included: weight variation, size, hardness, friability and disintegration time of three brands of azithromycin tablets. Assay was done using UV spectrophotometry to determine the content of the active ingredient in each and percentage label claim was calculated. The different brands of tablets showed variations in weight not exceeding 5% of standard value. Similarly, hardness of all the brands was less than 5kg/f and friability ranged from 0.2 to 0.5%. All the brands tested disintegrated in less than 6 minutes. Percentage labelled claim for drugs X, Y and Z were 100.079%, 98.733%, and 96.827% respectively. All the physiochemical quality parameters of three brands of azithromycin tablets were found to be within the pharmacopeial specifications therefore all the brands were pharmaceutically and chemically equivalent.

CHAPTER ONE

1.1 INTRODUCTION

1.11 Background

Azithromycin is a macrolide antibiotic, semi synthetic product derived from erythromycin. It is a 15-atom lactone macrolide ring compound, derived from erythromycin by addition of a methylated nitrogen into the lactone ring (Katzung and Trevor, 2012 Pg.825).



Azithromycin is active against *Mycobacterium avium* complex and *Toxoplasma gondii*, slightly less active than erythromycin and clarithromycin against staphylococci and streptococci and slightly more active against *Haemophillus influenza"* (Katzung, 2012, p. 829*)*.

Azithromycin is highly active against *Chlamydia sp.* The drug is slowly released from tissues (tissue half-life of 2 4 days) to produce an elimination half-life approaching 3 days. These unique properties permit once-daily dosing and shortening of the duration of treatment in many cases. For example, a single 1-gdose of azithromycin is as effective as a 7-day course of doxycycline for chlamydial cervicitis and urethritis. Community-acquired pneumonia can be treated with azithromycin given as a 500-mg loading dose, followed by a 250-mg single daily dose for the next 4 days (Katzung, 2012, p. 829).

Azithromycin is the most prescribed and effective macrolide antibiotic in the treatment of *Chlamydia trachomatis, Haemophilus influenza* infections and prophylaxis of disseminated *Mycobacterium avium* complex (MAC) disease (Zuckerman et al, 2011).

The availability of numerous brands of azithromycin in our drug market today places clinicians and pharmacists in a difficult situation of choice of a suitable brand or the possibility of

alternative use. Most of these drugs are sold at very cheaper retail prices than the innovator drug, making their qualities, safety and efficacy oblivious to scrutiny among physicians and pharmacists. Quality of product defines to its confining to the standards pre-set to assure the desired purpose and it is the most important factor for efficacy and safety of product.

It is necessary to ensure that drugs products are chemically and pharmaceutically equivalent. They must be identical in strength, quality, purity, active ingredient release profile and also in the same dosage form, for the same route of administration (Singh et al. 2017). Though this information is collected during clinical trials and to some extent by scientific literature but the data obtained by post marketed monitoring helps in product improvement, development of standards and regulations. It is therefore imperative to conduct post marketing surveillance or monitoring of approved medicines in order to assess their quality, therapeutic effectiveness and safety of medicines for the public.

In this research, the percentage content and physicochemical quality parameters like weight variation, size, friability, disintegration time profile of azithromycin tablets were assessed by performing various test procedures according to established methods. The brands selected for the study have big differences in cost, different manufactures and are among the commonest in pharmacies, hospitals and drug shops; that is brand X from U.K, Y from Egypt and Z from U.S.A. The three brand above have big differences among their costs yet all are generics which draws the question as to whether they have equal effectiveness and their physical properties meet the specified ranges in the pharmacopeias. More so patients and some medical personnel find trouble choosing which drug to use among the different brands in fear that the cheaper one may be less effective yet the other options are not affordable by the majority.

There is increased number of various brands of drugs from multiple sources in the developing countries due to attempts to improve overall healthcare delivery. This however has also increased the number of fake and substandard drugs on the market. The healthcare providers find trouble trying to select genuine and good quality brands from among the many that are allegedly pharmaceutically equivalent (Chika et al., 2011).

This study was aimed to answering the question of cheaper azithromycin brands being substandard or not, and provide the ultimate evidence based decision of opting for cheaper ones

if equally effective or going for the more expensive brand because it is superior and better. Hence confirming or disproving the prescriber's undocumented complaints that U.S.A is less effective than azithromycin from Teva when treating Chlamydia infections.

1.2 Problem statement

The increase in the number of brands of drugs in developing countries from different sources has paved way for an increase in substandard and fake drugs (Chika. Et al., 2011). According to research carried out by a student in India, some brands of the same drug that are supposed to be pharmaceutically equal contained less of the active ingredient (Pervin., Most., & Shahnaj, 2014) and conclusions showed that they were not all pharmaceutically equivalent. This is very dangerous because it causes therapeutic failure and development of resistance by microorganisms.

According to FDA, pharmaceutically equivalent products must: contain the same active ingredient, be of the same dosage form and same route of administration, and be identical in strength and concentration. The different generics are therefore expected to be related in cost with just slight differences due to different costs of production in different areas. This raises the question as to whether a drug costing 25,000 pharmaceutically equal and can be interchanged with the drug costing 4,500 shilling while retaining the same therapeutic effect.

According to WHO 2011, the consequences of substandard drugs are: relatively cheap drugs which are ineffective, drug resistance, reduced confidence in public health systems, health care professionals and government agencies involved in drug distribution

1.3 Aim of the study

This study was purposed to determine if different azithromycin 500mg tablet brands on the Ugandan market are pharmaceutically equal despite the large differences in their cost.

1.4 Significance of the study

Many health care centers, hospitals and pharmacies procure expensive brands of azithromycin drugs using a large portion of the budget yet it can be reduced by opting for the cheaper and more affordable brand of the same drug if they are equally effective. Patients can also buy the same drug at a cheaper cost with confidence it works just effectively. If some generics are below the standard and this being the reason for their differences in prices, this research will expose the

inferiority and they can be scrapped off the list of azithromycin brands used hence guarding patients' safety.

1.5 Objectives of the study

1.51 General objective.

To determine the pharmaceutical equivalence of the selected azithromycin 500mg brands sold on the Ugandan market.

1.52 Specific objectives.

- To determine friability of tablets of each of the selected azithromycin 500 mg brands.
- To carry out the weight variation test of tablets in each of the three azithromycin 500 mg brands.
- To determine disintegration time of tablets of the three selected azithromycin 500 mg tablet brands.
- To carry out hardness test on the selected azithromycin brands.
- To determine active ingredient concentration in each selected azithromycin 500mg tablet brands.

1.6 Research question

- Are the tablets in the selected azithromycin 500mg brands pharmaceutically equivalent?
- Do all the selected azithromycin 500mg brands meet the pharmacopoeial specifications?

1.7 Inclusion procedure

- Only brands with big differences in retail price are selected.
- Only 500mg tablets of each brand will be included.
- Only tablet that still have at least 6 months left on their shelf life will be included.
- Only tablets whose primary packaging materials are still intact will be included.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Azithromycin

Mechanism of Action: Azithromycin acts by binding to the 50S ribosomal subunit of susceptible microorganisms and, thus, interfering with microbial protein synthesis. Nucleic acid synthesis is not affected (Katzung. 2012, p. 829). It concentrates in phagocytes and fibroblasts as demonstrated by *in vitro* incubation techniques. Using such methodology, the ratio of intracellular to extracellular concentration was >30 after one-hour incubation. *In vivo* studies suggest that concentration in phagocytes may contribute to drug distribution to inflamed tissues.

Antibacterial effect

Azithromycin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section of NDA. Aerobic Gram-Positive Microorganisms: *Staphylococcus aureus, Streptococcus agalactiae, Streptococcus pneumoniae,* and *Streptococcus pyogenes*. Azithromycin demonstrates cross-resistance with erythromycin-resistant gram-positive strains. Most strains of *Enterococcus faecalis* and methicillin-resistant staphylococci are resistant to azithromycin. Aerobic Gram-Negative Microorganisms include: *Haemophilus influenzae and Moraxella catarrhal is.* "Other"Microorganisms include *Chlamydia trachomatis*.

Furthermore, Beta-lactamase production should have no effect on azithromycin activity. Azithromycin has been shown to be active *in vitro* and in the prevention and treatment of disease caused by Mycobacteria mainly; *Mycobacterium avium* complex (MAC) consisting of: *Mycobacterium avium* and *Mycobacterium intracellulare* (Katzung, 2012, p. 829)

2.2 Pharmaceutical equivalence

The nonproprietary drugs must be identical in content, purity, uniformity of weight, disintegration and dissolution time before chemical equivalence is considered (olaniyi et al, 2001).

Research done in India in 2014 revealed that only four of the five azithromycin brands studied were pharmaceutically equivalent. One brand had less of the active ingredient (Most., Shahnaj., Pervin, 2014, p.35).

There are several reports of differences in clinical efficacies by the chemical equivalents that could only be due to different manufacturers (Remington et al, 1990)

The availability of numerous brands of azithromycin in our drug market today places clinicians and pharmacists in a difficult situation of choice of a suitable brand or the possibility of alternative use. Most of these drugs or products are sold at highly cheaper retail prices than the innovator drug, making their qualities, safety and efficacy oblivious to scrutiny among physicians and pharmacists. Quality of product defines to its confining to the standards pre-set to assure the desired purpose and it is the most important factor for efficacy and safety of product. It is necessary to ensure that drugs products are chemically and pharmaceutically equivalent (Singh R. et al. 2017). The generic drug is a copy of the brand-name drug, that is, it has the same active ingredients, dosage form, strength, route of administration, and intended use as the brand drug. The generic drug must be **therapeutically equivalent** to the brand drug and be approved as Abbreviated New Drug Application (ANDA) by the FDA (Chisholm et al. 2009).

2.2 Friability test

Friability is the ability of tablets to withstand both shocks and abrasion without crumbling during manufacturing, packing, transportation and consumer handling. Friability can be evaluated by means of friability test apparatus (Singh R. 2017). Conventional compressed tablets that lose not more than 1% (after 100 revolutions) of their weights are generally acceptable (BP, 2009). Drugs that fail this test show physical instability and easily lose parts during transportation, storage or handling by patients and dispensers leaving them with less strength. Most., Shahnaj., & Pervin, 2014, revealed failure of some azithromycin brands on the Indian market that failed this test.

2.4 Weight variation

Weight variation test is used to determine content uniformity of drug distribution when tablets contain 50% or more of drug (U.S.P 2009). Tablet weight variation is mainly affected by factors like tooling of the compression machine, head pressure, machine speed and floor properties of the powder. Inconsistent powder or granulate density and particle size distribution are common sources of weight variation during compression (Tahaineh, & Gharaibeh. 2012).

Table 1: Acceptable weight variation

IP/BP	LIMIT	USP
80mg or less	±10%	130mg or less
80mg-250mg	±7.5%	130-324mg
Beyond 250mg	±5%	Beyond 324mg

2.5 Hardness test

Hardness can be defined as the crushing strength of the tablet to withstand the pressure applied. The crushing strength will be determined with a tablet hardness tester. It is expressed in kg/cm2. Five tablets are randomly selected from each brand for this test. The tablet to be tested is held between a fixed and a moving jaw of the Hardness Tester. The force applied to the edge of the tablet is gradually increased by moving the screw knob forward until the tablet breaks. The reading is noted from the scale which indicates the pressure required to break the tablet. Mean for hardness is also calculated for each brand (Awofisayo et al. 2010). Acceptable hardness for oral tablets according to USP is in the range of 4 to 10 kg/cm^2.

2.6 Disintegration test

The disintegration time is the time required for a tablet to break up into granules of specified size, under carefully specified test conditions. The disintegration time for six tablets per brand was determined by placing one tablet in each tube, using the distilled water at 37°C±2°C as a disintegration media in the disintegration test apparatus. The time taken for all the tablets to fully disintegrate and pass through the mesh was measured in minutes and seconds. They must disintegrate within 15 minutes (B.P, 2009; Lahdenpaa. et al.,1997) while U.S.P acceptable disintegration time is within 30 minutes using stimulated gastric fluid.

CHAPTER THREE

3.1 MATERIALS AND METHODS

3.11 Equipment: Hardness tester, Friabilator, Disintegration machine, Electronic balance, UV-Vis spectrophotometer, Mortar and pestles.

3.2Study area

The research was conducted at Kampala International University- Western Campus, Ishaka town Bushenyi District-Uganda.

3.3Study design

The study was comparative.

3.41 Inclusion criteria

Only azithromycin 500mg tablets from the NDA approved list of drugs were used. All brands selected are on the Ugandan market and can be found in pharmacies and health care centers.

3.42 Exclusion criteria

Expired, cracked and tablets whose primary packaging material was broken.

3.5 Laboratory analysis

Azithromycin tablet brands were bought from retail pharmacies in Ishaka town-Bushenyi District and Kireka town- Kampala District.

Table 2: **Brands used in the study**

npany	Strength	Retail Price(Ugx)	Drug Code	Dosage form
a UK	500mg	25,000	X	Tablet
)un pharmaceutical co.)t	500mg	10,000	Y	Tablet
madras pharmaceuticals	500mg	4,500	Z	Tablet

3.51 Weight variation

Ten tablets of generic drug X were taken and weighed together and then individually by an analytical balance. The average weight of the tablets was calculated (BP, 2009). Then percentage of weight variation was calculated by using the following;

% of weight variation {(individual weight –average weight)/average weight} × 100.

The process was repeated for generics Y, and Z. and results were compared with the acceptable ranges in the USP

3.52 Disintegration test

The disintegration apparatus was heated and maintained at 37°C. One tablet of brand x was placed in each of the six chambers of the basket and closed by the disc. The apparatus was operated using distilled water as the immersion fluid. The time taken for the tablets to fully disintegrate was recorded. The procedure was repeated for tablet brands Y and Z

3.53 Friability test

Ten tablets of generic drug X were deblistered and weighed. Their weight was recorded as initial weight. The tablets were put in the friability test apparatus which was switched on to run for 4 minutes at 25rpm.Tablets were removed, dedusted and weighed to give the final weight. The process was repeated on another set of 10 tablets of the same brand and mean initial and final weights calculated. Percentage weight loss was calculated as; %friability = {(W1-W2)/W1} x 100. Where W1 is mean initial weight and W2 is final weight.

3.54 Hardest test

The test was carried out using Monsanto-Stroke's hardness tester. Five tablets from each brand were randomly selected and each tablet was placed between the jaws of the hardness tester and force was applied by adjusting the knob of the tester until the tablet cracked. The results were recorded in Kg/f (Kg/cm^2) (Lahdenpaa. et al., 1997).

3.55 Assay of the active ingredient

3.551 Preparation of standard calibration curve

Stock solution was prepared by dissolving 100mg of accurately weighed Azithromycin standard in 10ml of ethanol and the final volume made up to 100ml with 0.1 M HCl. After that, 1 ml of stock solution was further diluted with 0.1 M HCl in 100ml to get 10µg/ml (working standard). Then 2, 4, 6, 8, 10ml of working standard was taken in 10 ml standard volumetric flask and made up the volume with 0.1M HCl to prepare 2µg, 4µg, 6µg, 8µg and 10µg drug per ml solution. Then the absorbance was measured by systronic smart double beam UV spectrophotometer at 210 nm against 0.1 M HCl as blank. The standard calibration curve was plotted. The standard sample gave a linear graph of absorbance against concentration (Singh. et al, 2017). A standard

calibration curve was plotted and the equation of the line of best fit noted. 20µg/ml concentrations for each sample was measured and its absorbance noted. Actual concentration for each brand was calculated from the equation of the line of best fit on the standard calibration curve. Alternatively, actual concentrations of the solutions can also be noted from the standard curve by noting the concentration that corresponds to the absorbance given. Percentage labeled claim was calculated for all the three brands and compared to the standard USP range.

3.6 Data analysis

All data obtained from the sample analysis was tabulated using Microsoft Excel and then uploaded to SPSS version 13. Each test was carried out in triplicate and one way- ANOVA was used to test for significance

CHAPTER FOUR

4.1 RESULTS

4.11 Weight variation

Table 3: Weight variation

Code	Number (n)	Weight(mg)(Mean±SD)
X	10	716.1±2.071
Y	10	701.7±1.735
Z	10	754.0±2.000

Table 4: Hardness, friability, and disintegration

Code	Hardness (Kg/f) (Mean±SD, n= 5)	Friability (%) , n= 10)	Disintegration time (minutes, n= 6)
X	4.3±0.167	0.321	4 min 51 sec
Y	4.82±0.172	0.285	4 min 33 sec
Z	5.3±0.141	0.400	5 min 05 sec

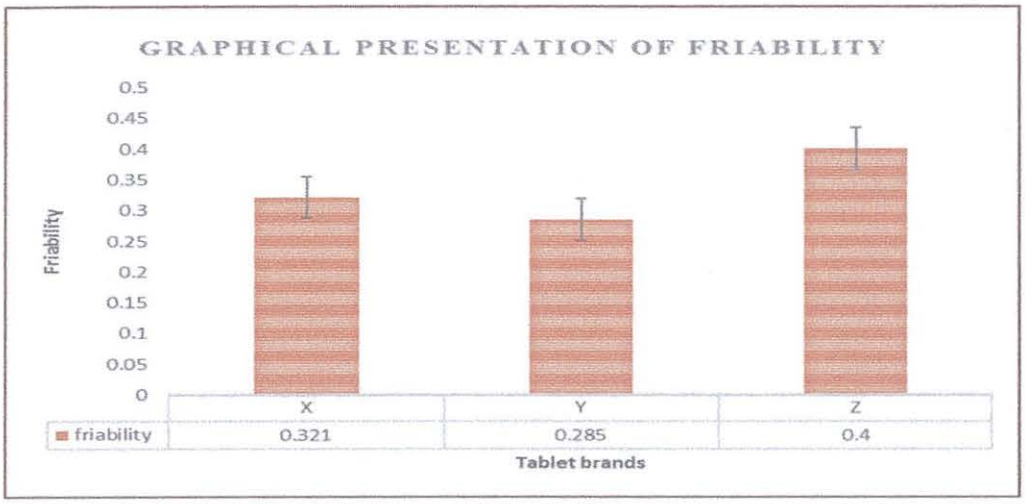


Figure 1: Friability of the three brands

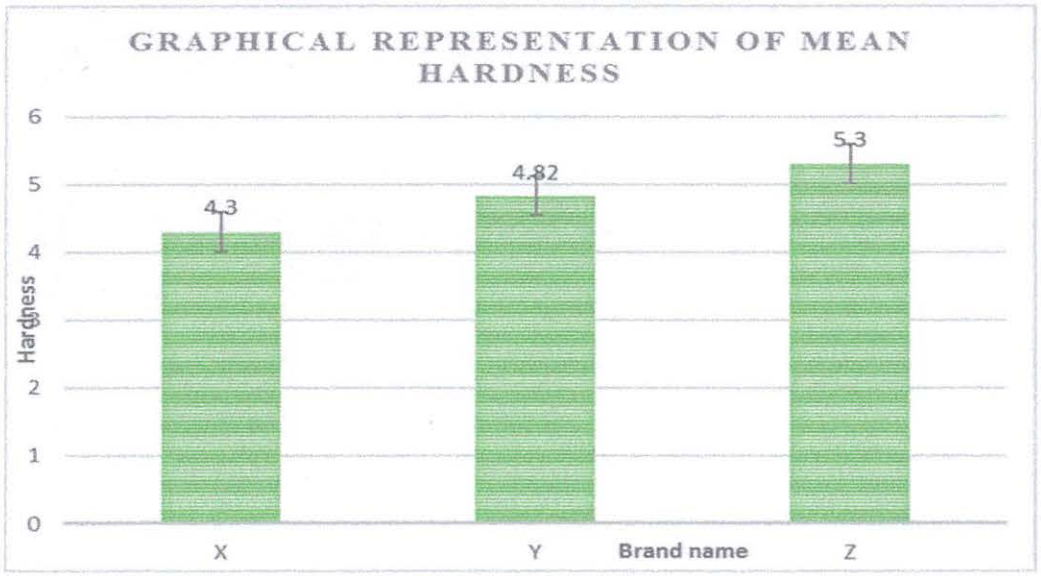


Figure 2: Mean hardness of the three brands

Table 5: Absorbance

Standard		Sample		
CONCENTRATION (µg/ml)	ABSORBANCE		CONCENTRATION (µg/ml)	ABSORBANCE
2	0.1292	X	20	0.927
4	0.205			
6	0.291	Y	20	0.915
8	0.394			
10	0.496	Z	20	0.898
20	0.923			

Table 6: Calculated concentration and percentage labelled claim

Sample	Measured concentration(µg/ml)	Absorbance	Actual concentration x=(y-0.0343)/0.0446.	Percentage labelled claim (potency) =(100x/20)
X	20	0.927	20.0157	100.079%
Y	20	0.915	19.7466	98.733%
Z	20	0.898	19.3655	96.827%

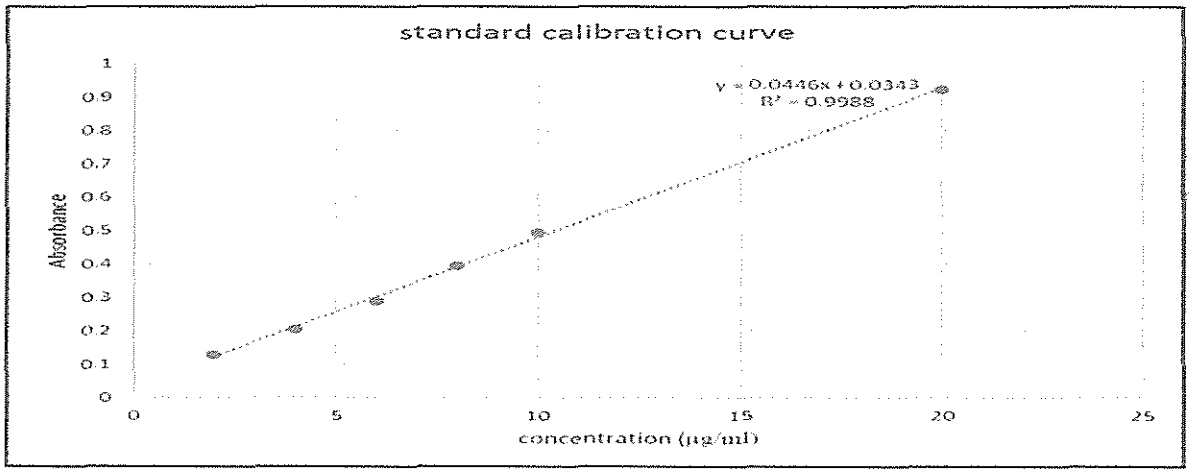


Figure 3: Standard calibration curve.

Calibration equation: y=0.0446x+0.0343. Where y- absorbance, x-actual concentration.

x=(y-0.0343)/0.0446.

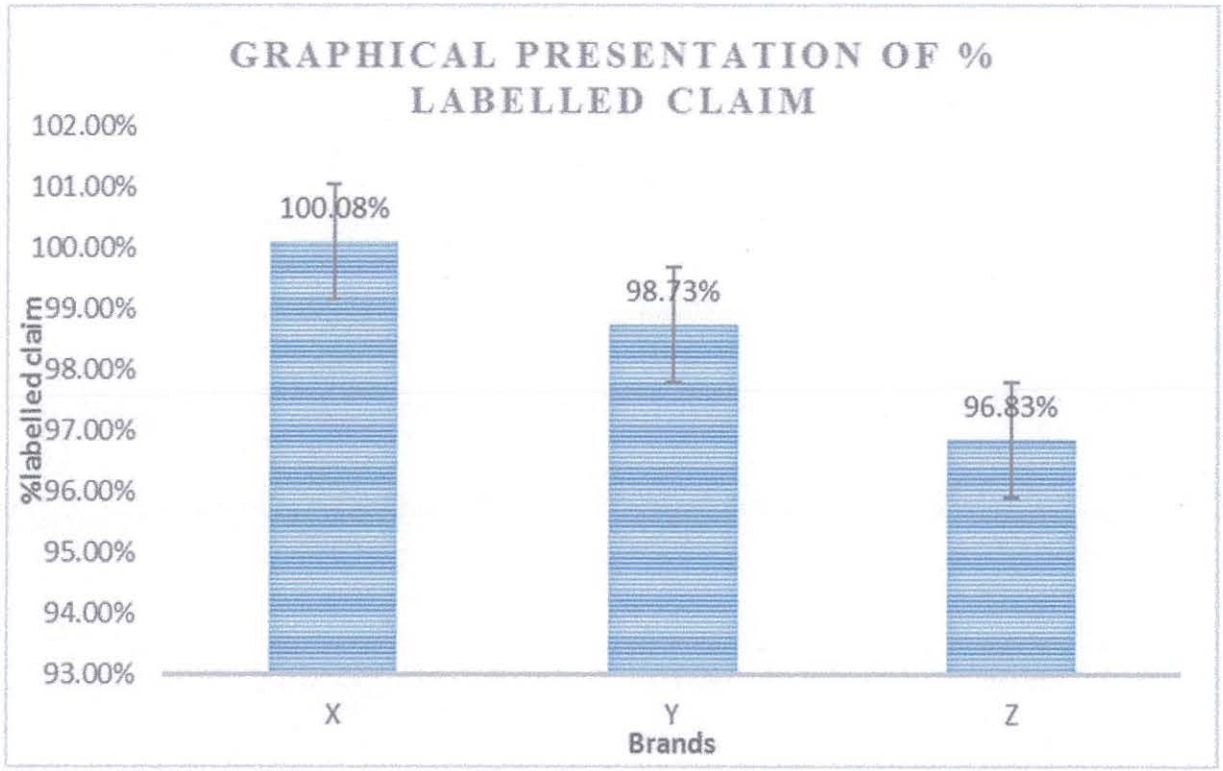


Figure 4: percentage labelled claim for the three brands

CHAPTER FIVE

5.1 DISCUSSION

5.11 Weight variation

All brands showed acceptable uniformity of weight as none had percent deviation in weight greater than 5% as stipulated by the USP. The significance of this test is to ensure that the tablets of each are within the appropriate size range.

There were inter brand weight variations were significant with P = 0.364888 which were due to the different excipients used by the different companies that manufacture the drugs. Weight variation of tablets is an important in-process control evaluation of tablets and it is a valid indication of the corresponding variation in the drug content. A small variation beyond what is acceptable does not ensure good content uniformity between dosage units while a large weight variation precludes good content uniformity (Lahdenpaa. et al., 1997). So good quality products must pass weight variation tests

5.12 Hardness

All brands had acceptable hardness according to U.S.P. This is an essential criterion in the determination of the ability of the tablets to resist chipping, abrasion or breakage under conditions of storage, transportation and handling before storage (Lahdenpaa. et al., 1997).

Hardness ranged from 4.3 to 5.3 kg/f with brand X having the least crushing force. The difference in this hardness was significant with P = 0.949292. It is due to differences in the method of manufacture and the different excipients used like the binding agent type and amount in each brand.

5.13 Disintegration

The disintegration test measures the time required for tablets to disintegrate into particles. This is a necessary condition for dissolution and could be the rate-determining step in the process of drug absorption. All the three brands passed the disintegration test which has to be less than 15 minutes. Brand Z had the highest disintegration time and far above the time of brand X and Y. inter brand disintegration time difference was significant with P=0. 411322. This can be caused by several factors like type and amount of binders, lubricants, tablet hardness, manufacturing

procedure etc. can significantly affect the disintegration time of compressed tablets (Lahdenpaa. et al., 1997).

5.14 Friability

All three brands passed friability test. According to USP, a maximum loss of weight not greater than 1.0 per cent is acceptable for most of the tablets. In our study, the friability values for Azithromycin for all the brands were ranged from 0.2 to 0.4% which ensures that all the tablets of each brand were mechanically stable. Friability was highest in brand Z and lowest in brand Y with the differences were significant with P= O.509 probably caused by differences in excipients like type and concentration of binders used by different companies during manufacture. Tablet friability may also be profoundly affected by the moisture content of the tablet depending on granulation method used.

5.15 Assay

Percentage potency (labelled claim) ranged from 96.8 to 100.0. Azithromycin tablets must contain an amount of Azithromycin equivalent to not less than 90.0 percent & not more than 110.0 percent of the labeled amount of Azithromycin. From the result, it is evident that all brands of Azithromycin tablet meet the specification of potency as per USP range. Brand X was very close to actual labeled claim while Z fell the furthest among the three. Deviations can be caused by several factors like amount used during manufacture, deterioration of the active ingredient after manufacture, or errors during the experiment (Cruz & Blanco. 2011). All the brands had acceptable potency according to their percentage labeled claim calculated.

5.2 CONCLUSION

Friability, disintegration, weight variation and hardness were all in acceptable ranges as specified by the pharmacopoeias for the three tablet brands tested. Percentage label claim was also in the required range stipulated in the USP. Basing on these results alone, the three brands are pharmaceutically equal.

5.3 RECOMMENDATIONS

Further studies on the bacterial susceptibility to each brand of azithromycin studied to asses if they all have the same MIC. More so, bioavailability studies should be carried out on all the brands.

REFERENCES

American Society of Health-System Pharmacists. (October 15, 2012). "Azithromycin". *MedlinePlus*. United States National Library of Medicine. Retrieved February 19, 2018.

Awofisayo O, Oladoja A, Awofisayo N. (2010). Comparative assessment of the quality control measurements of multisource ofloxacin tablets marketed in Nigeria. Disso Tech. 6:20-5.

Chika, A., Bello, S. O., Jimoh, A. O., and Umar, M.T. (2011). The menace of fake drugs: Consequences, causes, and possible solutions. *Research Journal of Medical Sciences*, 5(5) 257-261.

Chisholm, S. A.; Neal, T. J.; Alawattegama, A. B.; Birley, H. D. L.; Howe, R. A.; Ison, C. A. (2009). "Emergence of high-level azithromycin resistance in Neisseria gonorrhoeae in England and Wales". *Journal of Antimicrobial Chemotherapy.*

Cruz, J., and Blanco, M. (2011). Content uniformity studies in tablets by NIR-CI. *Journal of Pharmaceutical and Biomedical Analysis,* 29(4), 408-412.

Hoepelman IM, Schneider MM. (1995). Azithromycin: the first of the tissue-selective azalides. *Int J Antimicrob Agents,* 5(3), 145-167.

Katzung, B.G., Masters, S.B., & Trevor, A.J. (2012). Basic &clinical pharmacology (12th edition.). New York; New Delhi: TataMcGraw-Hill education.

Lahdenpaa, E., Niskanen, M., and Yliruusi, J. (1997). Crushing strength, disintegration time, and weight variation of tablets compressed from three Avicel PH grades and their mixtures. *European Journal of Pharmaceutics and Bopharmaceutics,* 43(3) 315-322.

Mac Dougall C, Chambers HF. (2011). Protein synthesis inhibitors and miscellaneous antibacterial agents. Brunton LL, Chabner BA, Knollmann BC. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 12th Ed. New York, Mc Graw-Hill,1529-1530.

Pervin, Most. Shahnaj. (2014). A comparative study of different brands of azithromycin tablets, p.35.

Singh R, Saxena M, Sahay D, Singh S. In-vitro study of quality control parameters of three different brands of azithromycin tablets. *Int J Basic Clinical Pharmacology,* 2 (6),1572-1576.

Tahainch, L.M., and Gharaibeh, S. F. (2012). Tablet splitting and Weight Uniformity of Half Tablets of 4 Medications in Pharmacy Practice. *Journal of Pharmacy Practice,* 25(4), 471-476.

Zuckerman JM, Qamar F, Bono B. (2011). Review of macrolides (azithromycin, clarithromycin), ketolids (telithromycin) and glycylcyclines (tigecycline). Med Clin North Am, 95:761-791.