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Physico-chemical and Metal Impurity Assessment of Some Brands of Ciprofloxacin Hydrochloride Tablets Marketed in Kano Metropolis, Nigeria

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ABSTRACT

This research was carried out to assess the quality and compare the physico-chemical equivalence of twenty samples of ciprofloxacin hydrochloride tablets marketed in Kano metropolis using standard analytical methods. The physico-chemical and chemical equivalence were assessed through the evaluation of uniformity of weight, disintegration test, friability test, assay for percentage concentration, metal impurities, pH and ionic strength. The product assay was carried out using UV/Visible spectrophotometric method while atomic absorption spectrophotometer was used to determine the possible metal impurities. All the samples complied with the official specifications for uniformity of weight, friability test while one sample failed the disintegration test of 15mins. Eighteen samples conformed to specifications 90% - 110% w/w of stated amount, one sample was above the limit, 111.66$\pm$0.57% w/w, while another sample was below the limit, 87.65$\pm$0.70 w/w. Eighteen of the samples evaluated in this study could be regarded as being physico-chemically and chemically equivalent while two samples could be regarded as substandard and fake product. All the samples have the metal impurities within official specifications except for one which has high concentration of lead.

Keywords: Ciprofloxacin tablet, counterfeit, fake drug, physic-chemical and UV Spectrophotometer

INTRODUCTION

The World Health Organization (WHO) at the International Conference of Primary Health Care, Alma Ata 1973, identified the supply of good quality essential drugs as one of the basic pre-requisites for the delivery of health care and thus promulgated the WHO certification scheme on the quality of pharmaceutical products in international commerce. Some 128 countries participated in the WHO certification scheme, yet fake, adulterated and sub-standard drugs are exported from manufacturing countries into the non-manufacturing developing countries because of the conditions of sales. It was in view of this fact that World Health Organization (WHO) issued guidelines for global standard and requirements for the registration, assessment, marketing authorization, and quality control of generic pharmaceutical products (WHO, 1996, 2005). The quality of these drugs and the threat of counterfeit pharmaceuticals have been largely ignored (Shakoor *et al*., 1997). There is mounting evidence that counterfeit pharmaceuticals pose a serious threat to public health, especially in developing countries (Pecoul *et al*., 199).

Pharmaceutical counterfeiting is a pervasive problem, impacting nations of every description (Aluba 1994, Graviela, 2001). There are many reports of the availability of counterfeited medicines, not only in developing countries but also in Europe and USA (Shakoor *et al*., 1997).Indication shows that there are substandard drugs circulating in the market in different developing countries, widely reported in Africa, Asia and Latin America (Shakoor *et al*., 1997).Antibiotics are the most frequently used, misused, abused and counterfeited class of drugs worldwide (Global Forum, 2002). The presence of substandard antibiotics in various parts of Nigeria as reported by some authors includes tetracycline capsules and ampicillin oral suspension (Aluba, 1994). This contributed to the problem of increasing resistance among previously sensitive bacterial species to common antimicrobial agents in Nigeria (Philip *et al*., 2005). The most common and widely spread dangers associated with the use of substandard antibiotics are waste of resources, microbial resistance and the complication of diseases (Oliphant and Green, 2002).

Ciprofloxacin developed by Bayer in 1981, is the first oral antimicrobial drug with broad spectrum activity for treating severe infections caused by both gram-negative and gram-positive bacteria including pseudomonas spp. and staphylococcus spp. (Nayaz *et al*., 2013). It is one of the 4- quinolone carboxylic acid derivatives as drug for its chemical activity. It is relatively non-toxic, well tolerated and has proven especially

useful for oral therapy of chronic gram-negative infections such as osteomyelitis and recurrent cholangitis, and for acute exacerbations of pseudomonas infection in cystic fibrosis (Shahnaz *et al*., 2014). It is soluble in water, slightly soluble in methanol, very slightly soluble in ethanol, practically insoluble in acetone, ethyl acetate and methylene chloride (Susmita *et al*., 2009). There has been a proliferation of different brands of these antibiotics in Nigeria, many of which are incredibly cheap compared with ciprofloxacin by Bayer pharmaceutical limited, hence the need for the assessment of their quality (Philip *et al*., 2005).

In parts of the world, the evaluation and assessment of different brands of Ciprofloxacin tablet marketed were reported, (Mai, 2015, Jaman *et al*., 2015, Kholoud, 2009). A good number of assessment and evaluation of the quality of ciprofloxacin marketed in some Africa countries have been reported, (Getu, 2010, Mus'ab *et al*., 2010, Tadesse and Shibesi, 2015). Different authors have also undertaken various studies in the ciprofloxacin available in the Nigerian environment, (Ngozi *et al*., 2007, Bagbi *et al*., 2014).

Nigeria imports a large proportion of its pharmaceutical requirements from various regions of the world. This has led to indiscriminate dumping of fake, adulterated and counterfeit medicines in the Nigerian drug market. The problems of fake, substandard and counterfeited drugs threaten the survival and effective functioning of the society.

Pharmaceutical tablets are composed of number of different materials, each of which is designed to improve performance at the targeted site. Metallic particles (mostly heavy metals) are common contaminants in the pharmaceutical manufacturing process, a problem that should be addressed before the product is released to market (Mary and Kent, 2010).

Kano drug market has about five thousand registered pharmaceutical shops, some in Sabon – Gari market while others are located outside the market (NAFDAC, 2005). Drugs are distributed from the manufacturing companies through the medical representatives to the distributors, to the retailers and finally to the consumers.

The aim of the research is to assess the quality of the various brands of Ciprofloxacin tablets sold in Kano metropolis to ascertaining their effectiveness and establishing baseline information on the level of substandard ciprofloxacin hydrochloride tablets in Kano drug market.

MATERIALS AND METHODS

Cleaning of Materials

All glass wares and plastics containers used in this work were washed with detergent, soaked in potassium dichromate solution then washed with tap water and finally rinsed with de ionized water and dried in an oven at 105^{O}C.Wooden spatula was used throughout the work. All the salt chemicals used are of analar grade and the nitric acid from sigma Aldrich (specific gravity-1.42, percentage concentration-70%).

Sample Collection

The samples selected were from three drug producing regions of the world; Africa, Asia and Europe. Ciprofloxacin hydrochloride tablets were purchased from retail outlets mainly from private pharmaceutical and drug stores in Kano. The drug samples were obtained in their original package as supplied by the manufacturers and protected from direct sunlight.

Weight Uniformity

Twenty tablets of each sample were individually weighed using an electronic analytical balance (model APX – 100 Denver Instrument, England). The mean tablet weight and standard deviation were calculated.

Friability Test

The weight of 20 tablets of all the samples was taken individually using electronic analytical balance, model APX – 100 Denver Instrument, England. The tablets were placed in the drum of Erweka type TA friability testing machine. The machine was switched on and operated at a speed of 25 revolutions per minute for four minutes. The tablets were dusted and their weight taken again to ascertain the percentage friability,

Disintegration Time Test

To determine disingration time, 900cm^3 distilled water was poured into a 1000cm^3 capacity beaker and then placed in the disintegration machine, (IP STD. Tablet Disintegration Machine, Lab Sales Cooperation, New Delhi, India). The temperature of the machine was maintained at 37^{o}C$\pm$0.5^{o}C with thermostatic heater.

Six tablets of each sample were placed into the basket rack assembly and placed into the beaker containing the disintegration medium and hung on the metal holder. The machine was placed in position and the basket oscillated in an upward and downward manner until the tablets fragmented. The time taken for each tablet to break into fragments was recorded and the average time calculated.

Determination of Wavelength of Maximum Absorption (λmax)

For determination of λmax, 4.0cm^3 of 5µgcm^{-3} solution of the ciprofloxacin hydrochloride standard solution was taken into a 1cm quartz cell and placed in the sample compartment of the UV/Visible spectrophotometer (model UV 757 GRT B – BRAW Scientific Instrument Company, England). The solution was scanned between 200nm – 500nm wavelength to obtain the absorption spectrum.

Preparation of Calibration curve

A 4.0cm^3 standard solution of Ciprofloxacin hydrochloride of various concentrations were taken in quartz cell and placed in the sample compartment of UV/Vis spectrophotometer and the machine was set at the obtained λmax (wavelength) of 276nm. The absorbance of each solution (i.e. 1,2,3,4,5,6,7,8,9,10) µgcm^{-3} were taken in triplicate and recorded. The average value of the absorbance was taken and a calibration curve was plotted. A regression equation was obtained from the plot. The calibration curve regression equation was used to calculate the percentage concentration of each test sample solution.

Assay for Ciprofloxacin Hydrochloride tablet

The weight of twenty (20) tablets of each sample was taken and average weight noted. The weighed tablets were crushed into fine powder using pestle and mortar.

A 0.006g of the powder was weighed and transferred into a 1000cm^3 volumetric flask. 50cm^3 of water was added and shaken for 30 minutes mechanically to attain complete dissolution. The volume was made up to 1000cm^3 mark in volumetric flask with distilled water. The solution was filtered and the absorbance taken at wavelength of 276nm using UV spectrophotometer (Adepoju, 2010).

Sample Digestion

To digest the sample, 2.00g of the powdered ciprofloxacin hydrochloride tablet of each sample was weighed and transferred into a round-bottom flask. The beaker used in weighing the powder was rinsed with 20cm^3 of 5M trioxonitrate V acid and poured into the flask. Additional 30cm^3 of the acid was transferred into the content of the round bottom flask and refluxed at 80^{o}C for one hour on a thermostatically controlled heating mantle. The solution was allowed to cool to room temperature and made up to 100cm^3 mark with deionized water. This was filtered with no. 42 Whatman filter paper and stored in a clean dry plastic sample bottle. The digested sample was aspirated into the atomic absorption spectrophotometer (AAS, Bulk scientific model 216VGP) at the individual metal wavelength and the absorbance values were recorded against a blank. Calibration curves for the different metals were plotted from metal standard solutions and from the result the concentrations of metals were calculated (Alsante *et al*., 2004).

RESULTS AND DISCUSSION

The results of the physicochemical properties with respect to the sample weights, disintegration time, friability and percentage concentration for the various brands of ciprofloxacin hydrochloride tablets analysed are presented in Table 1.0

Table 1.0: The Physicochemical and quantitative results obtained for twenty samples of Ciprofloxacin hydrochloride tablets.

Sample	Average Weight of Tablet in Gram ± SD	Disintegration Time (minutes) ± SD	% Friability ± SD	%Concentration± SD
A	0.6061±0.01	5.70 ± 0.01	0.23±0.00	100.93±0.01
B	0.7663±0.00	4.55 ± 0.05	0.09±0.01	99.07± 0.09
C	0.6902±0.01	16.0. ± 0.55	0.30±0.00	91.84± 0.47
D	0.9645±0.01	5.00 ± 0.03	0.10 ±0.01	105.59±0.24
E	0.8445±0.00	6.42 ± 0.05	0.40 ±0.00	111.66±0.57
F	0.7750±0.00	4.17 ± 0.07	0.25± 0.01	. 106.53±0.30
G	0.7842±0.00	3.37± 0.11	0.22± 0.00	102.56 ±0.11
H	0.7771±0.00	1.72 ± 0.20	0.01 ±0.01	106.76± 0.31
I	1.0566±0.01	2.50± 0.16	0.05± 0.01	103.96±0.16
J	0.6920±0.01	3.67 ± 0.10	0.72± 0.02	102.33±0.10
K	0.9392±0.01	13.12 ±0.40	0.21± 0.00	99.53 ±.0.07
L	0.6599±0.01	4..25± 0.07	0.09± 0.01	87.65± 0.70
M	0.9900±0.01	2.33 ± 0.17	0.60± 0.01	108.39±0.39
N	0.7840±0.00	2.08± 0.18	0.35 ±0.00	109.09±0.44
O	0.9465±0.01	5.17± 0.02	0.38± 0.01	98.32 ± 0.13
P	0.6994±0.01	4.67± 0.04	0.03 ±0.01	99.16 ± 0.09
Q	0.8996±0.00	4.37± 0.06	0.14 ±0.00	97.90 ± 0.20
R	0.8718±0.00	6.92± 0.08	0.29 ±0.00	98.18 ± 0.14
S	0.7814±0.00	7.78± 0.12	0.72 ±0.02	98.18 ± 0.14
T	0.7985±0.00	6.00 ± 0.03	0.11 ± 0.01	90.44 ± 0.55
BP Limit		15.00	1.00	90.00-110.00

The wavelength of maximum absorption (ʎmax) exhibited by the ciprofloxacin hydrochloride standard, Fig.1.0, was an indication that the ciprofloxacin standard was 99.80% pure, (Adepoju, 2010). The linear plot of the calibration curve, (Fig.2.0) indicated that ciprofloxacin obeys Beer-Lambert law.

The uniformity of weight determination for all the samples showed compliance with the official specifications (BP, 2005) as none of the samples deviated by up to 5% from their mean (Table 1.0). This indicated that the weights of the tablets in each batch within each sample are within the expected official specifications.

Similarly, all the samples gave less than 1.0% w/w loss in weight with the friability test determination and within the official limit of 1.0% (Fig. 3.0, Table 1.0), (BP, 2005, USP, 2004). High value of friability could result to loss of tablet weight there by lowering the concentration of the active ingredient (BP, 2005, USP, 2004).

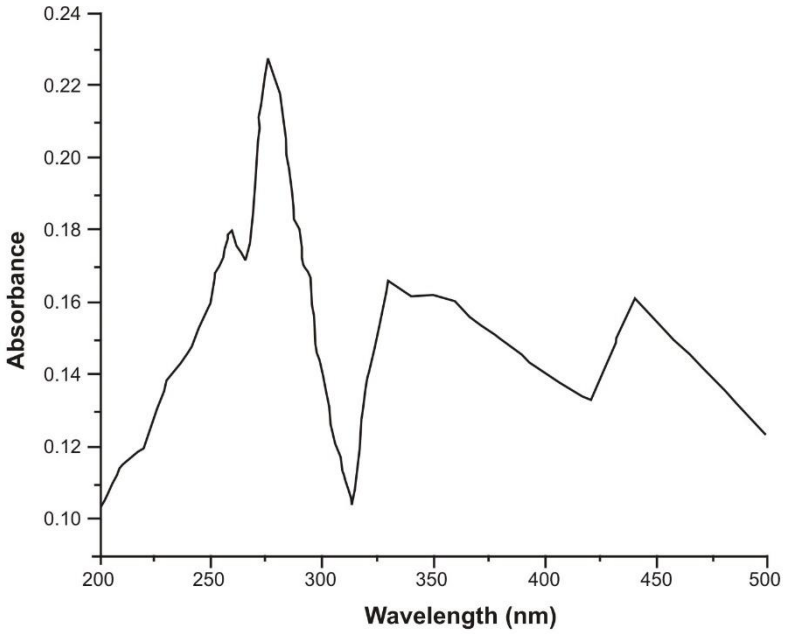

Fig. 1.0: Graph of Wavelength of Maximum Absorption of Ciprofloxacin Standard

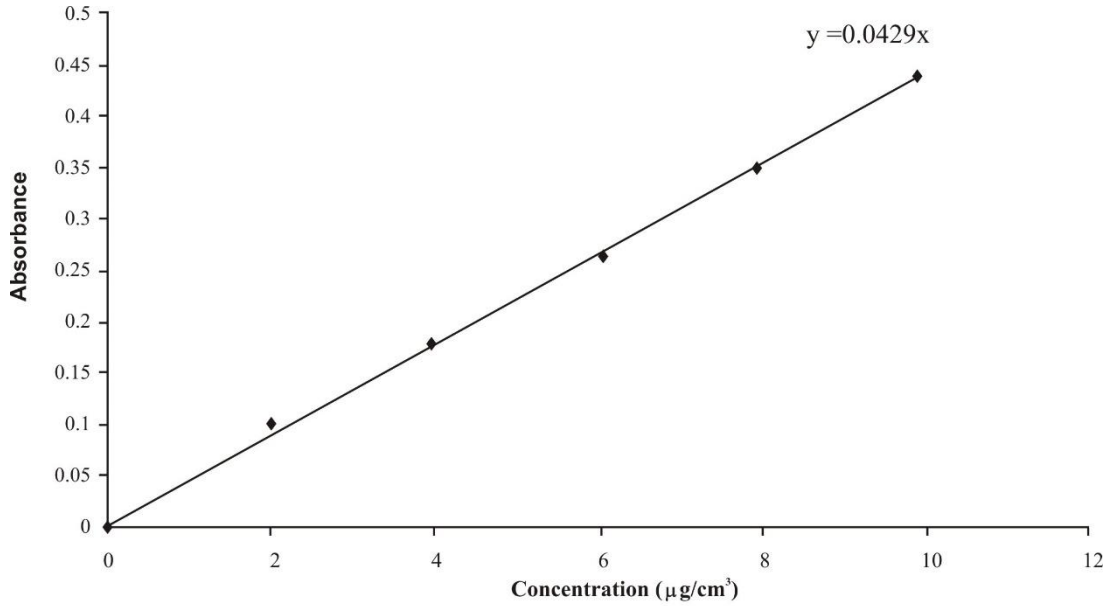

Fig. 2.0: Calibration curve for Ciprofloxacin hydrochloride Standard Solutions

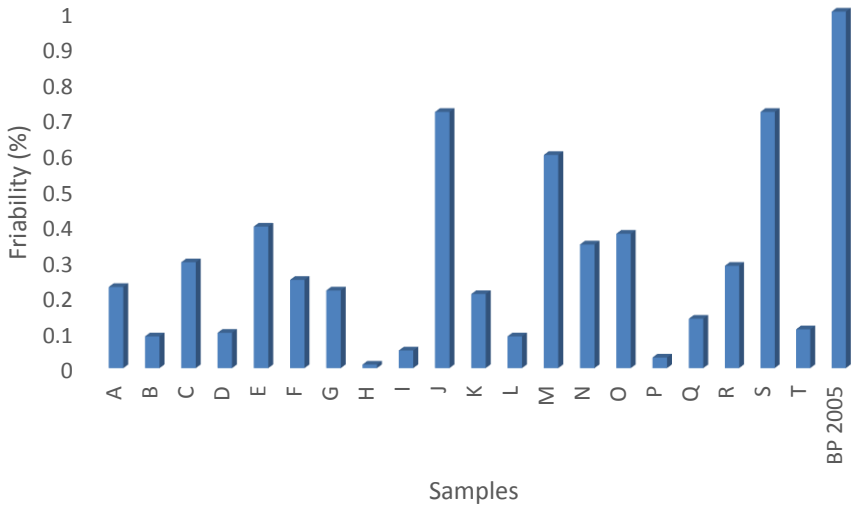

Fig. 3.0: Bar Chart of Mean Friability of Samples

All the samples passed the disintegration time test except sample C (Fig. 4.0) which fall outside the official limit of 15 minutes. This may be due to excess binder and pressure applied to the tablet during compressing that delayed its dissolution and would result in delaying its absorption when taken (BP, 2005).

The assay of ciprofloxacin hydrochloride indicated that eighteen samples gave values that conform to the USP (2010) specification of 90 – 110% w/w while sample E was above the limit with the value 111.66±0.53%w/w, sample L was below the limit with the value 87.65±0.698% w/w, (Table 1.0). These indicated that samples E and L can be regarded as substandard and fake respectively, since neither can provide the required concentration needed for effective pharmacological activities. The reasons for high and low result seen in samples E and L respectively may be due to excess of 1% of active ingredient added to take care of loses and improper mixing of the wet granules during processing (Susmita *et al*., 2009).

The calcium level in all the samples ranged between 0.006mg/g – 0.016mg/g, (Table 2.0) and falls within the specification of 3mg/g for the drug. The level of calcium in the product results from the nature of the excipient used which is usually calcium phosphate.

The sodium level in all the samples ranged between 0.012mg/g – 1.975mg/g (Table 2.0) and falls within the specification of 23.4mg/g, Webiner (2010) which must have been incorporated as a result of sodium methyl hydroxybenzoate, sodium propyl hydroxybenzoate and sodium benzoate used as preservatives, (Onlinelibrary, 2011).

Copper levels were found to be within specification 0.25mg/g (Table 2.0) and must have been sourced mostly from the water and processing vessels, (Webiner 2010). Iron and zinc levels were also found to be within specification and that the only major source being the processing equipment, (FDA, 2002; BP, 2005),

The potassium level in all the samples was within the limit specified by the official standard, 3.6mg/g (table 2.0) with the major source coming from the commonly used preservative, potassium sorbate (Onlinelibrary, 2011). The level of potassium in some of the samples ranged between 0.071 – 0.214mg/g while in samples B, J and Q the potassium concentration was below the detection limit.

Manganese concentration was found to be within the official limits in some samples, 0.25mg/g (Table 2.0), (IAPT, 1997) though in 14 of the samples the manganese concentration was below the detection limit. The manganese contents could come as impurities in the raw materials and the processing equipment.

Lead concentrations in some of the samples were found above the official limits of 0.001mg/ with the highest concentration found in sample Q (Table 2.0, Fig.5.0). The major source of lead in pharmaceutical products have been related to the nature of the water used in the manufacturing process (Webiner 2010).

After computing the t-test for both Africa/Europe it was observed that at 5% probability and 6 degrees of freedom, the table t-test (t Critical one-tail) value was 2.44691 and the calculated t-test (t Stat) value was 0.43418 (Table 3.0). This shows that the calculated t value was less than the table t-value, thus, it can be suggested that there was no significant difference between samples from the two continents.

For Africa/Asia at 5% probability and 10 degrees of freedom, the calculated t-value (1.11759) was less than t-value (1.81246). This indicated that there was no significant difference between samples from the two continents (Table 4.0).

For Europe/Asia, at 5% probability and 12 degrees of freedom, the calculated t-value (2.2317) was greater than the table t-value (1.78229). This indicated a significant difference between samples from these continents, (Table 5.0).

In the determination of the effect of temperature on the absorbance of ciprofloxacin hydrochloride, it was observed that there was no effect since the melting point of the compound is 318-320^{0}C (Chemblink, 2011).

The pH in both acidic and basic medium does not show any effect on the absorption of ciprofloxacin hydrochloride since it remained unionized in both basic and acidic medium being an acidic drug (Rui *et al*., 2003).

The ionic strength of the solution does not have any effect on absorption properties of the ciprofloxacin hydrochloride solution. This is an indication that ciprofloxacin hydrochloride does not form complex with sodium ion (Na^+) or that only divalent and trivalent metal ions form complexes (Gammeira *et al*., 2007).

Table 2.0: Concentration of Elemental Impurities (mg/g) in Ciprofloxacin Hydrochloride Tablets

Sample	Elements Concentration in mg/g							
	Ca	**Na**	**Cu**	**Fe**	**K**	**Mn**	**Pb**	**Zn**
A	0.010	0.012	0.001	0.026	0.071	ND	ND	0.007
B	0.006	0.302	0.001	0.028	ND	0.013	0.001	0.007
C	0.049	0.652	0.001	0.030	0.071	0.013	0.001	0.004
D	0.010	0.411	0.001	0.024	0.071	0.013	ND	0.002
E	0.013	0.409	0.001	0.015	0.213	ND	ND	0.004
F	0.010	0.471	0.001	0.026	0.143	ND	ND	0.002
G	0.016	1.975	0.001	0.019	0.214	ND	ND	0.007
H	0.013	0.691	0.001	0.056	0.214	ND	ND	0.007
I	0.100	0.504	0.001	0.002	0.071	ND	ND	0.004
J	0.016	0.385	0.001	0.013	ND	ND	ND	0.002
K	0.010	0.572	0.001	0.017	0.071	0.001	ND	0.004
L	0.010	0.481	ND	0.011	0.142	ND	ND	0.002
M	0.010	0.385	0.001	0.030	0.071	ND	ND	0.004
N	0.006	0.403	0.001	0.026	0.071	ND	0.001	0.002
O	0.013	0.739	0.001	0.050	0.071	ND	ND	0.002
P	0.006	0.802	0.001	0.013	0.143	0.001	ND	0.002
Q	0.006	0.554	0.001	0.048	ND	0.013	0.009	0.002
R	0.009	0.676	0.001	0.028	0.143	ND	ND	0.004
S	0.006	0.802	ND	0.013	0.071	ND	ND	0.002
T	0.006	0.700	0.001	0.030	0.071	ND	ND	0.004
Standard	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**

Table: 3.0. t-test for samples from Europe and Africa

t-Test: Two-Sample Assuming Unequal Variances

	Europe	*Africa*
Mean	103.903	102.603
Variance	4.14789	47.4992
Observations	4	6
Hypothesized Mean Difference	0	
Df	6	
t Stat	0.43418	
P(T<=t) one-tail	0.33967	
t Critical one-tail	1.94318	
P(T<=t) two-tail	0.67934	
t Critical two-tail	2.44691	

Table: 4.0. t-test for samples from Africa and Asia

t-Test: Two-Sample Assuming Unequal Variances

	Africa	*Asia*
Mean	102.603	98.684
Variance	47.4992	43.8224
Observations	6	10
Hypothesized Mean Difference	0	
Df	10	
t Stat	1.11759	
P(T<=t) one-tail	0.14494	
t Critical one-tail	1.81246	
P(T<=t) two-tail	0.28987	
t Critical two-tail	2.22814	

Table: 5.0. t-test for samples from Europe and Asia

t-Test: Two-Sample Assuming Unequal Variances

	Europe	*Asia*
Mean	103.903	98.684
Variance	4.14789	43.8224
Observations	4	10
Hypothesized Mean Difference	0	
Df	12	
t Stat	2.2417	
P(T<=t) one-tail	0.02233	
t Critical one-tail	1.78229	
P(T<=t) two-tail	0.04466	
t Critical two-tail	2.17881	

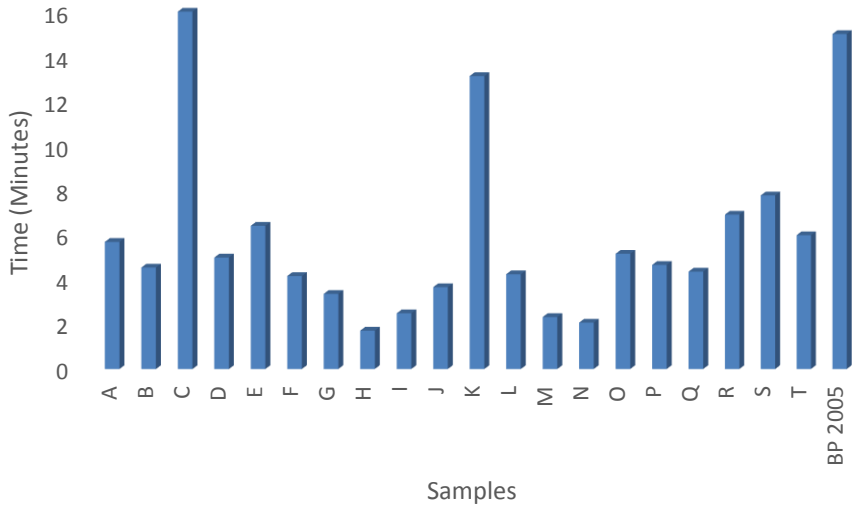

Fig.4.0: Bar Chart of Mean Disintegration time of Samples

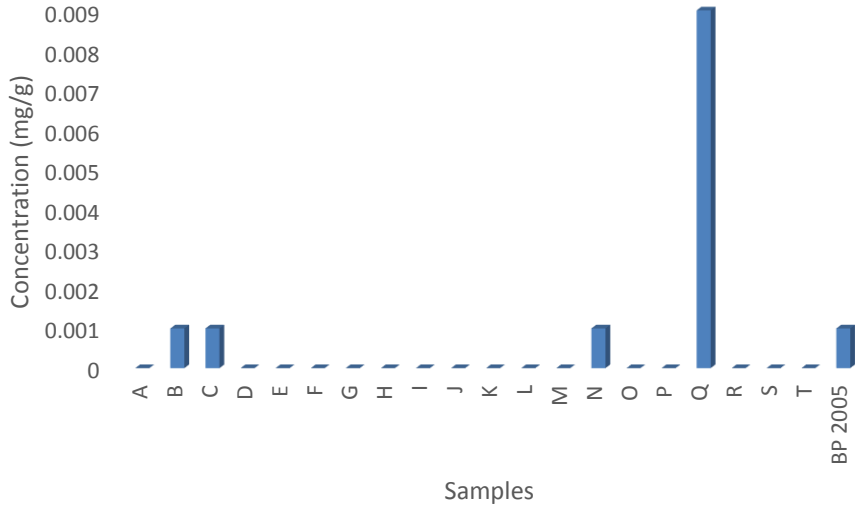

Fig. 5.0: Mean Concentration of Lead in Ciprofloxacin Hydrochloride Tablet

RECOMMENDATION

Further work should be carried out using high performance liquid chromatography (HPLC) or gas chromatography mass spectrophotometer (GC-MS) and compare the result with that of the UV/VIS spectrophotometer so as to see the level of accuracy.

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