MM Ahmed et al /J. Pharm. Sci. & Res. Vol. 8(1), 2016, 13-18

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Equivalent Assessment of Ciprofloxacin Tablets Available in KSA : A Post Market Surveillance Study for Cost Effective Treatment

MM Ahmed*[1], Farhat F[1], MJ Ansari[1], Fahad I Al-Saikhan[2], M Khalid. Anwer[1], S. Jamil[1], Ramadan Al-Shdefat[1], Baha E Ali[1], MH Fayed[1]. Mohammed Dakhalallah J Al Shelewi[3], Prakash Katakam[4]

*[1]*Department of Pharmaceutics, College of Pharmacy, Prince Sattam Bin Abdulaziz University, P.O.Box 173, Al-Kharj-11942, KSA.*

[2]*Dept. of Clinical Pharmacy, College of Pharmacy, Prince Sattam Bin Abdulaziz University, P.O.Box 173, Al-Kharj-11942, KSA.*

[3]*Undergraduate Student, College of Pharmacy, Prince Sattam Bin Abdulaziz University, P.O.Box 173, Al-Kharj-11942, KSA.*

[4]*Department of pharmaceutics,Priyadarshini Institute of pharmaceutical Education and Research, Guntur, Andhra Pradesh, India. Pin 522503*

Abstract

The aim of this study was to evaluate the physicochemical and pharmaceutical parameters in order to confirm the bioequivalence of the generic formulation available in Saudi Arabia with that of innovator 500 mg ciprofloxacin tablets. Assessment was done based on the compendia Physicochemical, pharmaceutical and microbiological parameters. Three selected brands under studies comply the official specifications for weight variation all the brands are within the 5 % specified limit, The disintegration time laid between 2.2 to 4.2, the dissolution profile shows more than 80 % release in first 30 minutes, and the kinetics study reflects all formulations followed First order release kinetics with f1 difference factor as per the pharmacopeia limit of less than ≤15. The *in vitro* antibacterial study revealed that the Brand B2 and innovator B3 have the same mean zone of inhibition against *S. aureus* & *E. coli* species i.e 14.77 mm. These results indicates that generic version of ciprofloxacin hydrochloride are bioequivalent which can be interchangeable for the cost effective treatment. This study may serve as a tool to monitor post market quality of broad spectrum antibiotic and give confidence to substitute the costly brands with bioequivalent generic ciprofloxacin for cost-effective treatment .

Keywords: Ciprofloxacin, *in vitro* antibacterial , first order kinetics , dissimilarity factor.

INTRODUCTION

Dosage forms are said to biopharmaceutical and chemical equivalent if they possess the identical quality, quantity, purity and release profile and intended for the same rout of administration.[1] The dissolution profile act as a versatile tool to predict the batch to batch variation and also used for indicating *in-vivo* bioavailability mostly for per oral drug products.[2,3]According to FDA bioavailability means, the rate and extant at which the drug is absorbed from the dosage form and becomes available at the site of action. Subsequently two products said to be bioequivalent in absence of significant difference in the rate and extent to which the active moiety becomes available at the site of drug action when administered under matching conditions.[4] Quinolones are a class of synthetic antimicrobial which were modeled after nalidixic acid. Ciprofloxacin, a fluoroquinolone antimicrobial agent, was approved in 1987 as a broad-spectrum relatively non-toxic and well tolerated antibiotic. It acts by interfering with microbial DNA synthesis. In general, the fluoroquinolones have an excellent activity against *Enterobacteriaceae, fastidious* gram-negative bacteria and *Pseudomonas aeruginosa,* good to moderate activity against *staphylococci, mycobacteria, chlamydia, mycoplasma and ureaplasma*: and little or no activity against *streptococci* (particularly group D *streptococci*), *enterococci,* and anaerobic bacteria.[5]It is broadly used in the treatment of bacterial diarrhoea, skin and soft tissue infections, bone and joint infections, gonorrhea, urinary tract infections, lower respiratory tract infections and in surgical prophylaxis.[6] In the majority of the cases, it would appear that for treatment of above said infections, physicians prescribe ciprofloxacin as a first choice of drug. More or less 400 ciprofloxacin brands are available round the globe from this approximately 12 ciprofloxacin 500 mg tablets are approved by SFDA for marketing in the kingdom of Saudi Arabia by various manufacturer of different origin with a huge variation in the price ranging from 13.8 SAR to 101.35 SAR for the strip of 10 tablets.[7] With the availability of such large number of brands the health care provider will be in dilemma to select an ideal brand for the cost effective treatment with the same efficacy as that of innovator product. Assessment of Bioavailability and Bioequivalence BABE studies are important to get rid of this type of confusions. The safety and efficacy of drug products can be assured when their quality is consistent and reproducible from batch to batch. To ensure the requisite quality, pharmaceutical companies are required to test their

products during and after manufacturing and at various intervals during the shelf life of the product.[8] Post-market surveillance or monitoring involves all assessments to obtain information of approved marketed product which can be utilized to report if any irregularity in the product to the regulatory body or for product developments and to improve the standards and regulations.[9] Under current Food and Drug Administration (FDA) regulation, a patient may switch from the brand-name drug to a generic drug if the generic shows the same result as that of innovator. Normally it is a general psychology that the quality of the generic are less effective than innovators, presently in many countries a new trend is set to get the generic medicine in place of branded one to lower the national health budget. Total pharmaceutical expenditure (TPE) in public sector was 13.5 billion SAR which account of 18% of total health expenditure in Saudi Arabia for 2010 fiscal year. Sometimes antibiotics are sold over-the-counter without a prescription. Substitution of generic equivalents at the point of dispensing is allowed in public and private sector facilities by the Saudi Food and Drug Authority.[10]
The objective of the present study was to assess the chemical and pharmaceutical equivalency of three ciprofloxacin 500 mg tablets available in the Al-Kharj region of Saudi Arabia.

MATERIALS AND METHODS

Reference Ciprofloxacin HCL was a kind gift sample from Al Jazeera pharmaceuticals-Riyadh. Three different brands of Ciprofloxacin were obtained from different retail pharmacies of Al-Kharj, Saudi Arabia.

Methodology

Price deviation

The data available in the excel sheet released by SFDA in 2014 revealed that there are many manufacturer and marketing agencies approved for promotion of ciprofloxacin 500 mg tablets in a range of price.[11] The percentage price differentiation was calculated and presented in Table No-1.

Physicochemical Evaluations

Weight variation: Three brands of tablets were evaluated for weight variation as per USP XXIV monograph. Twenty tablets of each brand of the same batch were weight individually mean and standard deviation was calculated.[12]
Dimension and hardness measurement: Ten tablets were automated individually measured for its thickness and length (Erweka MultiCheck V, Heusenstamn Germany) Results were reported as average mean (mm) and percentage relative standard deviation (%RSD) for thickness and length whereas hardness was reported in Kg/cm^2 .
Friability Test: The friability tests were conducted employing 10 tablets from each brand with 100 revolutions (i.e. 25 revolutions per minute for 4 minutes). The tablets were de dusted, weighed together (W1) and friability tested (Erweka TAR friability/ abrasion tester). The friabilated tablets were reweighed (W2) and compared with their initial weights and percentage friability was obtained. Percentage friability was calculated as [(W1-W2)/W1] x 100%.
Tablet Disintegration Test: Based on the British Pharmacopoeia, 2003 method for uncoated tablets.[13] The disintegration medium was 0.1 N HCI, maintained at 37 ± 0.5°C. Six tablets from each batch were used for the test ((Erweka- ZT120 series).The disintegration time was taken as the mean time needed for the tablets to break into particles small enough to pass through the screen into the disintegration medium.
Drug Content Assay: 3 Tablets from each brand were crushed and a sample equivalent to 100 mg of the drug was taken from each powdered sample dissolved it in 100 ml of 0.1N hydrochloric acid (HCl).The absorbance of each sample was taken at 277 nm against the blank reagent (0.1N HCl) with an (Jasco-V-750 UV-Visible/NIR) UV Spectrophotometer.

Dissolution Test

Dissolution tests were carried out on the tablets using the USP general method in 0.1M HCl (900 ml) at 37± 0.5°C with the aid of Erweka-D dissolution test apparatus (Erweka, U.K.) fitted with a basket rotated at 50 rpm. Samples were withdrawn from a zone midway between the surface of the dissolution medium and the top of the rotating basket, and replaced with fresh aliquot of dissolution medium, in order to maintain sink conditions. The samples were filtered and diluted appropriately with 0.1N HCl and measured 277nm using (Jasco-V-750 UV-Visible/NIR) UV Spectrophotometer. Cumulative % Ciprofloxacin HCL released against time (min) was plotted for each formulation. The amount dissolved in 45, 30 and 15 min was obtained for each brand of Ciprofloxacin HCL. All determinations were in quadruplicate.[14]

Drug release kinetics and Difference factor

A: Model dependent methods (Drug release kinetics):
Because qualitative and quantitative changes in a formulation may alter drug release and in vivo performance. The in vitro drug release mechanism of ciprofloxacin HCl from three branded tablets in 0.1 N HCL can be described by fitting the dissolution data in four different (zero order, first order, Higuchi, Korsmeyer-Peppas model) kinetic models. In Korsmeyer-Peppas kinetic model an (n) value which is a diffusional exponent represents the mechanism of drug release from tablet formulations.[15-17]
B: Model independent methods (Difference factor)
A simple model independent approach uses a difference factor (f1) to compare dissolution profiles. The difference factor calculates the percent difference between the two curves at each time point and is a measurement of the relative error between the two curves. [18] It is expressed as:

$$f_1 = \{[\sum_{t=1}^{n} | R_t - T_t |]/[\sum_{t=1}^{n} R_t]\} \cdot 100$$

where n is the number of time points, R is the dissolution value of the reference (pre change) batch at time t, and Tt is the dissolution value of the test (post change) batch t at time t.

Anti bacterial activity:

The agar medium was sterilized transferring 0.1ml of the test organism into the sterile Petri-Plate. After thorough mixing, the plate was allowed to set. Using the cork-borer provided, cups were cut into 4 sectors previously drawn on the back-side of the plate. Into each cup, 100µl of each 50mcg/ml concentration of the Ciprofloxacin HCL pure drug and braded tablets solution was added to its corresponding cup. Then a pre-diffusion time of thirty minutes was allowed before incubation at 37 ^{0}C for 24 h the zone of inhibition was measured in mm.[19-21]

RESULTS AND DISCUSSIONS

Randomly 25 % (3 brands out of 12) was selected by considering the same batch product from different manufacturer. As per the Human drug list released in 2014 by SFDA approximately 12 brands are approved for marketing in the Saudi Arabia, which are listed in Table No -01 and selected brands profile in Table.No-2. Ciprofloxacin HCL 500 mg tablets (within the expiry dates) were assessed for its physicochemical and pharmaceutical parameters.

Table No:1 :- Ciprofloxacin 500 mg Tablets approved for marketing by SFDA in Saudi Arabia

Trade name	Public price (SAR)	% price difference	Manufacturer name	Country of Manufacturer	Marketing Company	Nationality
CIPROBAY	**101.35**	**Innovator**	**Bayer pharma ag**	**Germany**	**Bayer Pharma**	**Germany**
BACTALL	23.4	78.26	Jordanian Pharma (JPM)	Jordan	Jordanian Pharma (JPM)	Jordan
CIFLOX	37.45	64.40	Kuwait Saudi Pharm industries	Kuwait	Kuwait Saudi Pharm Industries	Kuwait
CIPROCIN	29.1	72.64	Eipico	Egypt	Eipico	Egypt
CIPRODAR	46.95	55.03	Dar Aldawa	Jordan	Dar Aldawa	Jordan
CIPROFLOX	46.95	55.03	APM	Jordan	Apm	Jordan
CIPROGEN	40.7	61.19	Riyadh Pharma	Saudi Arabia	Riyadh Pharma	Saudi arabia
CIPROHEXAL	13.8	87.73	Hexal	Germany	HEXAL	Germany
CIPROMAX	62.05	40.13	Spimaco	Saudi Arabia	SPIMACO	Saudi arabia
CIPROQUIN	23.85	77.82	Hayat Pharm Industries	Jordan	Hayat Pharm Industries	Jordan
OMACIP	33.05	68.74	National Pharm Industries co	Oman	National Pharmindustries Co	Oman
SARF	55.85	46.24	Gulf Pharmaceutical Industries (julphar)	United Arab Emirates	Gulf Pharmaceutical Industries (julphar)	United Arab Emirates

Table No:2 :- Selected brand of Ciprofloxacin 500 mg Tablets for the assessment

Brand code	Manufacturer	Batch No	Mfg. Dt	Exp.Dt
B1	Jordanian Pharmaceutical .Co. (JPM)	1311226	11/2013	11/2016
B2	Kuwait Saudi Pharmaceutical Industries	ET400	07/2014	07/2017
B3	Bayer Pharma	BXGPAX1	01/2014	01/2018

Physiochemical Parameters

Table No:- 03 Physicochemical assessment of selected Ciprofloxacin Brands

Brand Code	Weight Variation (mg) (n=20)		Thickness (mm)		Length (mm)		Hardness (Kg/cm^2) (n=6)	Friability (%) (n=10)	Disinteg-ration (min) (n=6)	Drug Content (%) Mean ±SD
	Avg wt	RSD %	Avg	RSD %	Avg	RSD %	Mean ±SD			
B1	880.8	0.88	6.85	0.10	17.09	0.04	09.45±0.25	0.20	3.59±0.74	95.5±1.99
B2	773.7	1.57	5.00	0.28	19.61	0.00	10.15±0.24	0.11	4.2±0.65	99.5±1.95
B3	767.9	0.60	5.75	0.37	18.09	0.00	08.69±0.74	0.31	2.2±0.14	98.0 ±1.35

Price deviation

The percentage price difference was found to be 40.13 to 87.73% as tabulated in Table No-01.when compared with innovator which is considerable for the cost effective therapy with ciprofloxacin HCL.

Physicochemical Evaluations

Weight variation: The objective to access the weight variation was to ensure the good manufacturing practices (GMP), appropriate size of the tablets and dose of the drug. All three tablets passes the weight variation test. The

weight variation of the tablets plays an important role in terms of dose of the drug which in turn varies the therapeutic activity of the drug , as per compendia specification tablets of ≥324 mg, weighing of not more than two tablets should deviate from average weight by more than 5 %, all the results are within the permissible limits, Table.No-3.

Dimension and hardness measurement: Dimensions of the tablets were also determined and the results were given in Table No :03.As per the USP and BP 4-6 Kg/cm2 force required to break the tablets is an ideal, with this reference all three batches based the hardness test certain strength needed to retain the integrity of the tablets.

Friability Test: The % loss during transportation was evaluated by friability testing and all the brands shown the 0.11 to 0.31 which is within the permissible limit of less than 1%.

Tablet Disintegration Test: Disintegration test measures the time required for the formulation to break up in to the particles on contact with the gastrointestinal fluids. All brands under investigation complied the pharmacopeia standards, the results are ranged from 2.2 to 4.2 shown in Table no:3 which is within the limit of 15 minutes for uncoated tablets.

Drug Content Assay: The drug content uniformity test assures the proper mixing of active drug with excipient during manufacturing, the USP guidelines about ciprofloxacin HCl permits if the % drug content is within 95% to 105% for the tablets with average weight above 250 mg the results presented in Table No-3, are within the compendia limits .

Dissolution Test

In vitro dissolution testing provides meaningful and reliable information regarding the bioavailability of the products. Figure-1 express cumulative % drug released vs Time (min) and was found to be reasonable for all three brands under examination. Brand B1 represent the relatively highest release rate at the end of 45 minutes all brands had almost 99% drug release.FDA states that all the conventional BCS class III (Ciprofloxacin HCl) should have a release of 85 % within 30 minutes to comply the bioequivalence all brand passes this criteria except brand B2 which shows 82.6 % drug release presented in Fig-2.

Drug release kinetics and Difference factor

Table No:04:- Kinetic Models & dissimilarity factor f_1 for three brands of Ciprofloxacin Tablets under study

Brand Code	Zero Order	First Order	Higuchi Model	Kormeyer Model	N[a]	[b]Difference factor f_1
B1	0.692	0.956	0.692	0.408	0.08	10.09
B2	0.779	0.902	0.779	0.398	0.07	14.41
B3	0.610	0.915	0.610	0.362	0.36	Innovator

a; If N is 0.45 or less, the release mechanism follows Fickian diffusion,
b; f1 difference factor should be 0 – 15 for Bioequivalence products

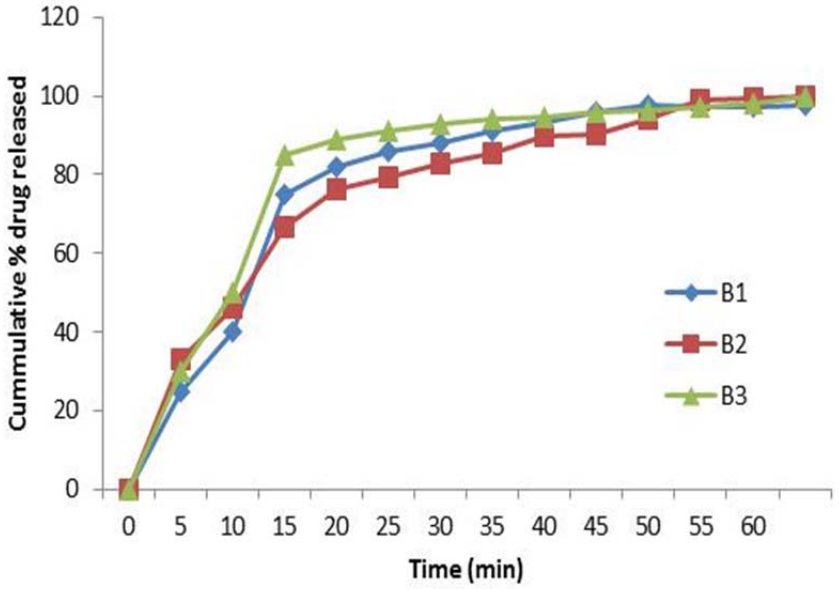

Figure 01:- Dissolution profile of three selected Ciprofloxacin brands

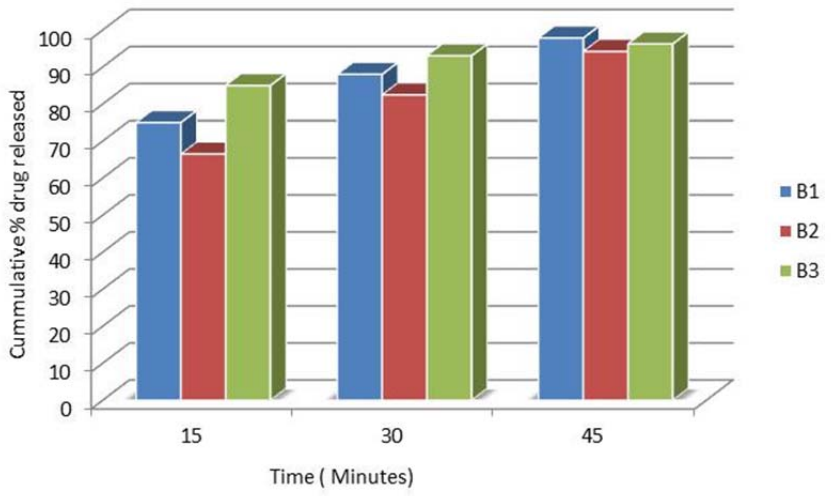

Figure 02:- Dissolution Rate at different 15, 30 and 45 min time intervals

Drug release kinetics and Difference factor

A: Model dependent methods (Drug release kinetics):

The dissolution data for three brands under study were subjected to Zero order, First order, Higuchi and Korsmeyer- Pepas kinetics model and release exponent 'n' was determined which indicates the drug transport mechanisms. The results exposed in Table no- 04 clearly suggest that all three brands had First order rate kinetics due to highest r^2 correlation coefficient value ranged 0.902 – 0.956 , and Fickian was the transport mechanism which is ideal for the immediate release tablets to maintain the effective drug plasma concentration.

B: Model independent methods (Difference factor)

The diference factor f1 is the percentage difference between the two curves at each point and is a measurement of the relative error between the test (generic)and reference(innovator) product. The formulation is said to be bioequivalent when f1 values should be in between 0 to 15. The result of difference factor as given in Table No-04 are within this limit. Therefore the generic version of Ciprofloxacin HCL were bioequivalent with innovator and can be interchangeable.

Antimicrobial study

Table.No:05:- Mean antibacterial activity for marketed and pure drug.

Organism Species	Brand Code : zone of inhibition (mm)			
	B1 (D)	B2 (A)	B3 (C)	Drug – (B) (+ Ve Control)
Escherichia Coli	15	15.5	16.5	15
Staphylococcus aureus	13	14	13	13.5
Mean	14	14.75	14.75	14.25

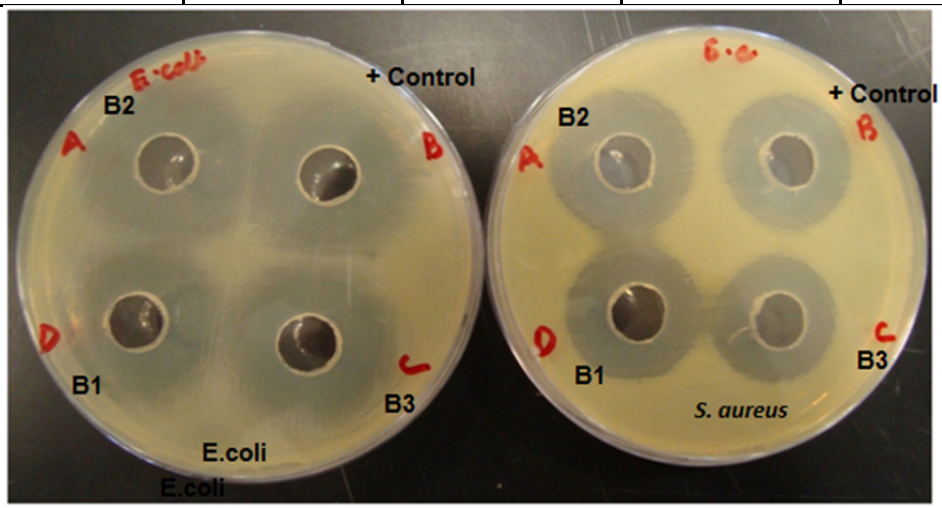

Figure 03:- In –vitro antimicrobial effect of different ciprofloxacin products against two bacterial species.

Anti bacterial activity:

The antibacterial activity was carried out for three brands and Ciprofloxacin HCL pure drug in 50mcg/ml concentration against E.coli and Staphylococcus aureus, the results were given in table no 5 and Fig:3. The mean zone of inhibition was found to be 14 and 14.75 for both brands B1 and B2 respectively which was similar to that of innovator product. Thus the results indicate the generic version was having the same in-vitro antibacterial activity as that of innovator.

CONCLUSION

Ciprofloxacin is an established broad spectrum fluroquinolone antibiotics effective against Gram positive and gram negative bacterial pathogens. The increased use of this drug with vast price difference and multiple brands gives the wide scope to pharmacist to substitute the costly brand with low cost generic versions to assure the complete dosage regimen for effective treatment at low cost. The post marketing surveillance is very crucial in order to restrict the entry of spurious ,fake medicine, this study reveals that the brands evaluated are pharmaceutical and bioequivalent equivalent therefore can be interchangeable. Hence this study will serve as a tool to avoid excess pharmaceutical expenditure in the treatment with ciprofloxacin and to monitor post market quality, safety and efficacy essential drug in the region.

REFERENCES

[1] Adegbolagun OA, Ololade OA, Osamah SE. TJPR. 2007, 6:737-745

[2] Awofisayo OS, Oladoja AA, Nse E, Imo EU. Dissolution Technologies. 2010, 6:20-25.

[3] Esiomone CO, Okoye FBC, Onah BU, Nworu CS, Omeje EO. J.Vector Borne Dis. 2008. 45:60-65.

[4] Ahmed Bendari, Badar Al-Shehi and Alka Ahuja, IJPA.2015 4,2, 9-21.

[5] SÁRKÖZY G. Quinolones (2001) a class of antimicrobial agents. Vet. Med. – Czech, 2001,9–10: 46, 257–274

[6] Hervey SC: Antimicrobial drugs, In: Gennaro AR, Editor, Remington's Pharmaceutical Sciences, Mack Publishing Company, Eston, Pennsylvania 18042, Edition 18, 1991: 1163-1241.

[7] Shahnaz Usman, Aftab Alam, Rahma Suleiman, Khawla Awad, and Isra Abudeek. International Journal of Biopharmaceutics. 2014; 5,1: 65-72.

[8] Chow SJ. J. Drug Information, 1997; 31:1195-1201

[9] Ngwuluka N. C., Lawal K. Olorunfemi1 and N. A. Ochekpe. 2009, 4 ,4, 298-305

[10] Saudi Arabia Pharmaceutical Country Profile, Saudi Food and Drug Authority in collaboration with the World Health Organization, 2012. Available online: http://www.who.int/medicines/areas/coordination/Saudi_ArabiaPSCP_Narrative2 012-04-18_Final.pdf

[11] Saudi Arabia approved list of drug for human use released by SFDA in 2014. www.sfda.gov.sa/en/.../Human_Drug_List_May_2014_V1_Web.xls

[12] The official compendium of standards, The United States Pharmacopoeial Convention, USP30- NF25, 2007.

[13] British Pharmacopoeia.Her Majesty's Stationery Office, London .2003.

[14] United States Pharmacopoeia, Revision 31/NF26, Volume 2, USP Convention lnc.2008.

[15] J. Dredan, R. Istvan, A. Istvan, et al. Int J Pharm, , 1996, 145 ,1,261–64

[16] T. Higuchi. J Pharm Sci, 1963, 52 ,12, 1145–1149

[17] P.L. Ritger, N.A. Peppas ,J Control Release, 1987, 5, 23–36

[18] Narashimhan B., Mallapragada S.K., Peppas N.A, Encyclopedia of Controlled Drug Delivery, John Wiley and Sons, Inc, New York 1999.

[19] Betty A.Forbes., Daniel F.Sahm., Alice S.Weissfeld. Bailey & Scott's Diagnostic Microbiology 11th edition, 229 – 257.1998

[20] Connie R.Mahon., George Manuselis., Saunder's Diagnostic Microbiology 2nd Edition,1985

[21] J.G.Colle., A.G.Faster., B.P.Marmion., A.Simmons. Practical Microbiology, Mackie & Mc Cartney, 14th edition 851 – 852