BCSIR

In vitro quality evaluation of metformin hydrochloride tablets marketed in Addis Ababa

H. Kassahun[1,2], K. Asres[2], A. Ashenef[2]*

[1]*Department of Pharmacy, College of Health Sciences, Wollo University, P.O. Box. 1145 Dessie, Ethiopia*

[1]*Department of Pharmaceutical Chemistry and Pharmacognosy, College of Health Sciences, Addis Ababa University, P.O. Box. 1176, Addis Ababa, Ethiopia*

Abstract

In this study, an attempt was made to assess quality as well as pharmaceutical equivalence of six brands of metformin hydrochloride tablets marketed in Addis Ababa using *in vitro* methods. Friability, disintegration, dissolution and assay for the content of active ingredients were evaluated using the methods described in the United States pharmacopeia (2007). All the brands of metformin hydrochloride tablets complied with the official specification for hardness, friability, disintegration and assay. Five brands of metformin hydrochloride complied with the USP dissolution tolerance limits but Metformin Denk failed to release the stated amount. Statistical comparison for *in vitro* drug release indicates that some of the products of metformin hydrochloride tablets showed significant difference (P<0.05), indicating difference in their *in vitro* drug release that might affect the *in vivo* bioavailability and the bioequivalence of the products.

Key words: Metformin hydrochloride; Physicochemical bioequivalence; Drug release; Drug quality

Introduction

Diabetes mellitus (DM) is a group of metabolic disorders characterized by hyperglycemia, altered metabolism of carbohydrates, fats and proteins with an increased risk of complication of vascular diseases. It results from defects in insulin secretion, insulin sensitivity, or both (Barbara *et al.,* 2009). The increasing prevalence of DM in the world and also in developing countries, the emergence of diabetes complications as a cause of early morbidity and mortality and the enormous and mounting burden on health care systems make diabetes a priority health concern (Khatib, 2006). Long-term complications of diabetes include retinopathy, nephropathy, peripheral neuropathy, amputations and sexual dysfunction (Bastaki, 2005).

Pharmaceuticals are used primarily to save life and to prevent long-term diabetic complications. There has been a global increase in the prevalence of Type 2 DM due to life style changes such as poor diet, decreased physical activity and stress (Wild *et al.*, 2004). This type of DM requires the use of oral hypoglycemic agents when dietary control and exercise have proved inadequate (Katzung *et al.*, 2012). Oral hypoglycemic agents include biguanides (metformin), sulphonylureas (tolbutamide, glibenclamide) and thiazolidinediones (glitazones) (Bastaki, 2005).

Metformin belongs to the biguanide class of oral hypoglycemic agents and is a widely used antidiabetic drug for the management of type II DM (Sahra *et al.*, 2010). Chemically it is N, N-dimethyl imidodicarbonimidic diamide hydrochloride ($C_4H_{11}N_5$, HCl) with a molecular weight of 165.6 (Najib *et al.*, 2002). Metformin hydrochloride decreases intestinal absorption of glucose, suppresses glucose production, especially hepatic gluconeogenesis and improves peripheral tissue insulin sensitivity by increasing peripheral glucose uptake and utilization (Poretsky, 2010).

*Corresponding author e-mail: ayenew.ashenef@aau.edu.et

Many generics of metformin hydrochloride tablets are available within the drug supply system globally after the expiration of patent on the innovator brand. Different reports on comparative *in vitro* quality evaluation of generics of metformin hydrochloride tablets of different countries have been published. Olusola *et al*. (2012) evaluated eight brands of metformin hydrochloride 500 mg tablets available in Lagos, Nigeria and showed that only four brands could be regarded as being biopharmaceutically and chemically equivalent. In addition, Zakeri-Milani *et al*. (2012) evaluated eight generic metformin hydrochloride tablets which are available in Iran market and reported that all except one generic product were bioequivalent with the innovator brand. Moreover, Bhavanam *et al*. (2010) evaluated four brands of metformin hydrochloride tablets available in India and found out that all the products met the requirements as per general specifications of Indian Pharmacopoeia. Preliminary physicochemical assessment of drug products has a paramount importance in ensuring the quality of drug products. Generic drug products must satisfy the same standards of bioavailability or bioequivalence studies which may involve both *in vivo* and *in vitro* studies (Chereson, 1996). Assessment of bioequivalence of the different generic products available in the market is very important to ensure that generic drugs being sold can be used interchangeably with the branded products (Fahmy and Gharbieh, 2014).

generic substitution. Oral metformin are widely used in Ethiopia with several new brands introduced into the Ethiopian market in recent years. Variety of drugs in circulation often put clinicians and pharmacists into difficult situation of choice and the possibility of interchangeability among brands (Olusola *et al*., 2012). Use of substandard products may lead to poor blood glucose control and life threatening complications. Despite widespread presence of NIDDM in Ethiopia and extensive use of metformin, there are no reports on the bioavailability and bioequivalence of the various brands in the country. Hence, the present study was carried out to assess the quality and pharmaceutical equivalence of metformin tablets available in the Ethiopian market.

Materials and methods

Materials and reagents

The chemicals and reagents used to perform the experiments were the following: 500 mg metformin hydrochloride tablets, monobasic ammonium phosphate (FARMITALIA CAROERBA, Italy), sodium hydroxide (BDH limited, Poole, England), potassium phosphate monobasic (Fisher Scientific, USA), and distilled water. Different brands of 500 mg metformin hydrochloride tablets were bought from various pharmacy retail outlets in Addis Ababa. All the brands used were within their shelf life at the time of study. The detailed

Table I. Product description of metformin hydrochloride tablets

Brand	Manufacturer	Batch Number	Mfg. date	Exp. date
Bigomet	ARISTO Pharmaceuticals Pvt. Ltd., (India)	M101E011E	05/2011	04/2014
Brot	Medscheme Ltd, (Cyprus)	A6F099	06/2012	06/2017
Diabetamin	HOVID Bhd., (Malaysia)	BB08422	08/2011	08/2014
Glucomet	Y.S.P Industries SDN. BHD., (Malaysia)	VJ012	10/2011	10/2014
Metformin Denk	DENK PHARMA GMBH & CO.KG., (Germany)	80B	02/2013	01/2018
Neomid	AEGIS LTD., (Cyprus)	12176	08/2011	07/2014

The introduction of generic drug product from multiple sources into the health care delivery system of many developing countries has been accompanied by a variety of problems of which the most critical is the widespread distribution of fake and substandard drug products (Bano *et al*., 2011). The increasing use of metformin hydrochloride tablets in clinical practice creates the need to monitor and ascertain the quality of the various brands available in the drug market for quality control assessment and for purpose of

descriptions of these products are presented in Table I. Standard metformin hydrochloride was obtained from EFMHACA and is of USP reference standard. All chemicals used were analytical grade.

Equipment

The following *equipment* were used for the experiment: analytical balance (Mettler Toledo, Switzerland), hardness tester (Schleuniger, 2E/205, Switzerland), friability tester

(ERWEKA, TAR 20, Germany), disintegration apparatus (CALEVA, G.B. Caleva Ltd., UK), dissolution apparatus (ERWEKA, DT600, Germany), UV-Visible Spectrophotometer (Single beam Spectrophotometer, CM2203, Belarus), filter paper (diameter 110, lot ER0692-1, Schleicher and Schuell, Germany) and PH meter (Mettler Toledo, Switzerland).

Methods

Drug quality assessment experiment was done using pharmacopeial procedures described in the USP/NF XXIV, USP (USP/NF 25, 2007).

Hardness test

The hardness of each tablet was determined by selecting six tablets randomly using a hardness tester. Each tablet was placed between two anvils and force was applied to the anvils, and the crushing strength that causes the tablet to break was recorded. Crushing strength of average of six tablets was recorded.

Uniformity of dosage units

The dosage uniformity of metformin hydrochloride tablets was evaluated by weight variation, where twenty tablets from each of the six brands were selected by chance, weighed individually with an analytical balance. The average weights for each brand as well as the percentage deviation from the mean value were calculated.

Friability test

Ten tablets from each brand was dedusted and weighed on the analytical balance. Tablets were placed in the drum of the friability tester rotated at 25 revolutions per minute (rpm) for four minutes (100 times). Then, tablets were weighed and were compared with their initial weights and percentage friability was calculated.

Disintegration time

Six tablets were placed in a disintegration tester filled with distilled water at 37±0.5°C.The tablets were considered completely disintegrated when all the particles are passed through the wire mesh and time was recorded.

Chemical assay

Assay of metformin hydrochloride is carried out according to USP/NF (2007) specification. Standard preparation: metformin hydrochloride standard was dissolved in distilled water to obtain 0.01 mg/ml concentration of the standard solution. From the stock solution, serial dilutions were made to obtain calibration concentrations of 0.007 mg/ml, 0.008 mg/ml, 0.009 mg/ml, 0.01mg/ml and 0.012 mg/ml.

Sample preparation: twenty tablets of each brand were crushed separately and finely powdered. An accurately weighed portion of the powder was transferred, equivalent to about 100 mg of metformin hydrochloride, to a 100 ml volumetric flask. Water (70 ml) was added, shaken by mechanical means for 15 min, diluted with water to volume, and filtered, discarding the first 20 ml of the filtrate. The filtrate (10 ml) was diluted with water to 100 ml and 10 ml of the resulting solution was further diluted with water to 100 mlto obtain 0.01 mg/ml sample solution. The active pharmaceutical ingredient content of sample solutions was determined by measuring their absorbance against the reagent blank at 232 nm using an Ultraviolet (UV) visible Spectrophotometer.

Dissolution test

The dissolution of metformin hydrochloride was done using dissolution apparatus type II (paddle apparatus) with the rate of 50 rpm at 37±0.5°C on six tablets of each brand. The dissolution medium was 900 ml phosphate buffer (pH=6.8). 10 ml sample was withdrawn at 10, 20, 30, 45, and 60 min and an equivalent amount of fresh dissolution medium, maintained at equal temperature, was replaced. Filtered samples were then appropriately diluted (100 fold dilutions) and absorbance readings were taken with UV/Visible Spectrophotometer at wavelength of 232 nm. Solutions of metformin working standard was also prepared using dissolution medium and absorbance was measured. Phosphate buffer was used as a blank. The concentration of each sample was determined from calibration curve and the percent of drug release at each time was calculated.

Data analysis

Data obtained was treated using ORIGIN[®] graphing and scientific analysis software program, Microsoft Excel 2007 and Windows SPSS Version 20. Comparison and statistical significance was determined by one-way analysis of variance (ANOVA). All data were analyzed at a 95% confidence interval ($P < 0.05$).

Results and discussion

Uniformity of dosage forms

The result of weight uniformity test is shown in Table II. All the brands complied with the USP (2007) specification for uniformity of weight as none had percentage deviation in weight greater than 5 %.

Table II. Weight variation of different brands of metformin hydrochloride tablets

Products	Met. Denk	Brot	Neomid	Bigomet	Glucomet	Diabetamin
Weight (mg)±SD	668.76±6.0	680.92±4.8	599.05±4.1	687.32±7.5	561.88±4.5	564.1±12.3
% Deviation (Range)	(-1.07, 1.53)	(-1.03, 1.3)	(-1.48,0.81)	(-1.66,1.71)	(-1.26,1.21)	(-3.81,4.04)
% RSD	0.90	0.71	0.68	1.09	0.80	2.18

Weight uniformity test is required to ensure that the drug content in each unit dose is distributed in a narrow range around the label strength (USP, 2007). Uniformity of weight serves as a pointer to good manufacturing practices as well as amount of the API contained in the formulation (Oishi *et al*.,2011) and it is an important parameter because high weight variation indicates variation in amount of active ingredients and/or chemical additives. Variation of active ingredients may lead to toxicity, ineffectiveness or unpredictability of action of the product while variability of additives may affect other physicochemical characteristics of the product and ultimately alter the bioavailability of the drug (Ogah and Kadejo, 2013).

Hardness and friability test

The mean hardness values of metformin hydrochloride tablets are shown in Table III. The results showed that the brands had mean hardness value within the range of 156.5±7.86-199.5±0.836 N for metformin hydrochloride tablets. For metformin hydrochloride tablets studied, Bigomet had the highest hardness value (199.5±0.836 N) while Neomid had the lowest value (156.5±7.86 N).

A force of about 40 N is the minimum requirement for satisfactory tablet hardness (Oishi *et al*., 2011). Hence, the tablets of all brands of metformin hydrochloride were satisfactory for hardness. Similarly, the weight loss of the tablets after friability test expressed as percent friability is indicated in Table III. The lowest and highest percent friability for metformin hydrochloride tablets has been obtained for Bigomet (0.036) and Neomid (0.127), respectively.

The USP (2007) states that the friability value of tablets should be less than 1% and the results showed that all the brands of metformin hydrochloride tablets had friability values ranging from 0.036-0.1 27% and thus, all brands

passed the friability specification. Brands of metformin hydrochloride tablets with higher crushing strength showed low friability value. Generally, all the studied metformin hydrochloride tablets passed hardness and friability test.

Hardness or crushing strength of tablets is an important parameter which helps to assess the resistance of the tablet to breakage under condition of storage, transportation and handling (Odeniyi *et al*., 2003; Bano *et al*., 2011). Therefore, it can influence friability, disintegration and dissolution. Excessive hardness of tablets would prolong disintegration time, thereby affecting dissolution and absorption rates, bioavailability and onset of action of the drug. Soft tablets, on the other hand, are unable to withstand conditions of storage, transportation and handling without breaking or chipping. It is, therefore, important that tablets are of optimum hardness. Factors affecting the strength of tablets include the amount of binders used in granulation and the pressure applied during compression of the tablets (Oishi *et al*., 2011; Ogah and Kadejo, 2013). Friability test is closely related to tablet hardness and is designed to evaluate the ability of the tablet to withstand abrasion in coating, packaging, handling and transporting and other manufacturing processes (Kishore and Amareshwar, 2012). Generally, adequate tablet hardness as well as reasonable friability is required for consumer acceptance (Hailu *et al*., 2011).

Disintegration test

The mean disintegration times of the different brands of metformin hydrochloride tablets are shown in Table IV. The results showed that all the brands passed the disintegration test according to USP (2007), which specifies 30 min for uncoated and film coated tablets.

As shown in Table IV, the disintegration times for metformin hydrochloride tablets had fallen within the acceptable range. Brot (6.44±1.64) and Diabetamin (6.17±0.86) with low values are possibly attributed to the presence of large amounts of disintegrants (Muaz *et al*., 2009). These, coupled

Table III. Hardness and friability tests of different brands of metformin hydrochloride tablets

Drug product	Brand	Hardness (N) ±SD	Friability (%)
Metformin 500 mg	Bigomet	199.5±0.836	0.036
	Brot	195.5±4.8	0.046
	Diabetamin	197.83±1.6	0.039
	Glucomet	170.66±6.15	0.116
	Metformin Denk	168.66±4.72	0.117
	Neomid	156.5±7.86	0.127

Table IV. Disintegration tests and percentage drug content of different brands of metformin hydrochloride tablets

Drug product	Brand	Disintegration time ±SD	Assay (%W/W ±SD)
Metformin HCl 500 mg	Bigomet	12.65±0.99 in Minutes	101.64 ±4.14
	Brot	6.44±1.64	97.18±2.2
	Diabetamin	6.17±0.86	100.166±2.88
	Glucomet	14.34±0.43	103.78±.06
	Metformin Denk	15.69±0.83	103.85±0.12
	Neomid	10.16±0.43	97.28±2.249

with the excellent crushing strength observed suggest that there is a good balance between mechanical strength and release properties. Metformin Denk (15.69±0.83) and Glucomet (14.34±0.43) had relatively highest disintegration time.

Tablet disintegration is prerequisite to dissolution and subsequent absorption of a drug from the dosage form. A drug incorporated in a tablet is released rapidly as the tablet disintegrates because the rate of disintegration affects the dissolution and subsequently the therapeutic efficacy of the medicine. Different formulation factors are known to affect results of disintegration test. The type and amount of excipients used in tablet formulation as well as the manufacturing process are all known to affect both the disintegration and dissolution parameters (Muaz *et al.*, 2009).

Chemical assay

The results for actual content of different brands of metformin hydrochloride tablets are depicted in Table IV. The USP states that metformin hydrochloride tablets should contain not less than 95.0% and not more than 105.0% of the stated amount (USP, 2007). All products of metformin hydrochloride tablets passed as per the USP specification. The highest and lowest drug content was obtained for Metformin Denk (104.85%) and Brot (97.18), respectively.

Assay for the content of active ingredients is a critical test of quality, as all the physical properties tested are meant to optimize release of the drug from the product. So, no matter how perfect a product may be in terms of physical

parameters, failure to meet the standard for content of active ingredients will result in poor quality with adverse consequences (Ogah and Kadejo, 2013).

Pair-wise comparisons of products of metformin hydrochloride tablets were performed by one way analysis of variance (ANOVA) multiple comparisons. Statistical comparison for mean difference of drug content with 95% confidence interval indicated that there is no significance difference in the drug content of Diabetamin and Bigomet with other products of metformin hydrochloride tablets (P> 0.05). Similarly, Metformin Denk was not significantly different from Glucomet (P< 0.05). However, Metformin Denk and Glucomet products were significantly different in the drug content from Neomid and Brot (P<0.05).Such differences in drug content could raise doubts on the general equivalence of the brands.

Dissolution test

The dissolution profiles of the six brands of metformin hydrochloride tablets are illustrated in Figure 1. According to USP (2007), the amount of metformin hydrochloride released within 30 min should not be less than 80% of the stated amount. From the dissolution test results shown in Table V, all the brands of metformin hydrochloride tablets studied released more than 80% within 30 min except Metformin Denk which has released only 68.39 (±0.068). Hence, five of the products complied with USP dissolution tolerance limits but Metformin Denk failed to release the stated amount.

Dissolution of drugs can be influenced by the physicochemical proper ties of the drug substance, the dosage form design, the manufacturing process, and the testing conditions (i.e., apparatus, agitation, medium, etc).

A good *in vitro-in vivo* correlation can allow the use of *in vitro* dissolution studies for prediction of product *in vivo* performance and, therefore, *in vitro* dissolution profiles can be utilized as a surrogate for *in vivo* bioequivalence or bioavailability studies.

Table V. Time dependent drug release of products of metformin hydrochloride tablets

Sampling time (min)	Percent of drug release(w/w) ±RSD					
	Neomid	Bigomet	Met. Denk	Brot	Diabetamin	Glucomet
10	38.05± 0.02	24.2±0.037	24.53±0.05	35.03± 0.02	43.32±0.09	31.32± 0.08
20	76.49± 0.07	52.97±0.051	47.20±0.04	64.47± 0.05	72.43± 0.1	61.97 ±0.05
30	88.60 ±0.02	81.62±0.039	68.39±0.07	85.48 ±0.01	81.88 ±0.03	80.23± 0.01
45	95 ±0.004	89.51±0.011	79.31 0.044	96.86± 0.01	90.81± 0.006	95.75 ±0.0
60	98.02±0.005	92.23±0.01	87.96 0.035	97.86±0.01	91.68 ±0.009	97.3± 0.01

It was observed that Brot with the second smaller disintegration time (6.44 min), showed fast percentage drug release and Metformin Denk with the highest disintegration time (15.69 min), showed low percentage of drug release within 30 min which agrees with the general concept that fast disintegrating tablets release their drugs easily and vice versa. The higher rate of disintegration of tablet dosage forms indicates faster break down of a tablet into smaller particles and thus, enhanced the dissolution of the medicaments into the blood circulation, increasing bioavailability (Chandrasekaran *et al*., 2011).

Statistical analysis was conducted for the pharamacopoeially specified time, 30 min, using Tukey's one-way ANOVA. The statistical comparison of the release profile of the different products of metformin hydrochloride tablets indicated that at 95% confidence interval, there is significance difference in the drug release of Metformin Denk with other products of metformin hydrochloride tablets ($P< 0.05$). In addition, the percent drug releases for Bigomet, Diabetamin and Glucomet at 30 min were significantly different from Neomid ($P< 0.05$). Similarly, Bigomet was significantly different in the drug release from Glucomet ($P< 0.05$). However, the percent drug releases for Brot, Bigomet and Glucomet were not significantly different from Diabetamin ($P>0.05$).

Statistically, with 95 % confidence interval, some of the products of metformin hydrochloride tablets showed significant difference ($P<0.05$), indicating differences in their *in vitro* drug release that might affect the *in vivo* bioavailability and the bioequivalence of the products. Thus, the differences in dissolution profiles are likely to reflect potential differences in clinical performance of the products.
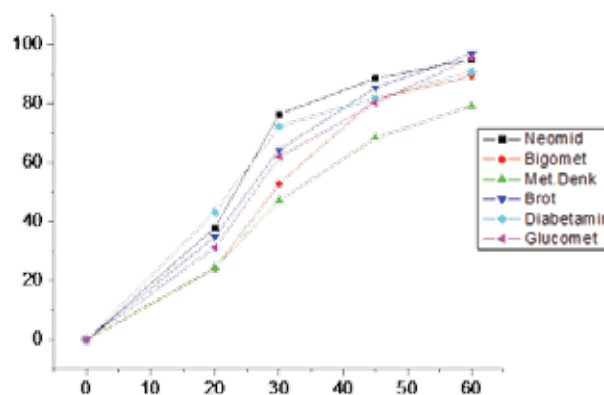

Fig. 1. Dissolution profiles of products of metformin hydrochloride tablets

Comparison of *in vitro* dissolution profiles of drug products may be accomplished by using a model independent or a model-dependent (curve fitting) approach. In the model-independent approach, the data are described by sample times (e.g.$t_{50\%}$, $t_{90\%}$, mean dissolution time, similarity factor (*f2*), or a dissimilarity factor (*f1*).

$t_{50\%}$ and $t_{90\%}$ were used as dissolution parameters to compare dissolution profiles of the different brands of metformin hydrochloride tablets. The $t_{50\%}$ and $t_{90\%}$ are the dissolution parameters that can be utilized to analyze dissolution profile of different pharmaceutical products. The $t_{50\%}$ and $t_{90\%}$ are the times taken for 50% and 90%of the drug to be released respectively. The $t_{50\%}$ and $t_{90\%}$ of the different products of metformin hydrochloride tablets analyzed are shown in Table VI. The results showed that, 50% and 90% release have been achieved within relatively short period of time for Brot

Table VI. $t_{50\%}$ and $t_{90\%}$ values of products of metformin hydrochloride tablets

Brand	Dissolution parameters	
	$t_{50\%}$(min)	$t_{90\%}$ (min)
Bigomet	14.623	48.577
Diabetamin	18	59.8
Brot	9.39	31.2
Met. Denk	18.886	62.74
Neomid	10.376	34.469
Glucomet	9.987	33.178

($t_{50\%}$=9.39 min, $t_{90\%}$=31.2 min), Glucomet ($t_{50\%}$=9.987 min, $t_{90\%}$=33.178 min) and Neomid ($t_{50\%}$=10.376 min, $t_{90\%}$=34.469 min) and hence, they are expected to be absorbed and become bio available within a short period of time. Relatively longer $t_{50\%}$(18.886) and $t_{90\%}$(62.74) values have been obtained for Metformin Denk and hence, the product may manifest lower rate and extent of bioavailability in the body.

Conclusions

This study was aimed to assess quality as well as physicochemical bioequivalence of six brands of metformin hydrochloride tablets marketed in Addis Ababa using *in vitro* methods. The study confirmed that brands of metformin hydrochloride tablets complied with the official specification for hardness, friability, assay and disintegration. Five brands of metformin hydrochloride complied with the USP dissolution tolerance limits but Metformin Denk failed to release the stated amount.

Statistical comparison for *in vitro* drug release showed that some of the products of metformin hydrochloride tablets have significant difference (P<0.05), indicating difference in their *in vitro* drug release that might affect the *in vivo* bioavailability and the bioequivalence of the products.

Acknowledgments

References

Bano R, Gauhar S, Naqvi SBS and Mahmood S (2011), Pharmaceutical evaluation of different brands of levofloxacin tablets (250mg) available in local market of Karachi (Pakistan), *International Journal of Current Pharmaceutical Research* **3**: 15-22.

Barbara G, Joseph T, Terry L and Cecily V (2009), Pharmacotherapy Handbook, 7th Ed. Mc Graw Hill, New York, USA, pp 210-2011.

Bastaki S (2005), Diabetes mellitus and its treatment, *International Journal of Diabetes and Metabolism* **13:**111-134.

Bhavanam PR, Surender G, Subhaskar KV and Reddy KV (2010), Comparative *in vitro* evaluation of commercial metformin hydrochloride tablets, *Journal of Innovative Trends in Pharmaceutical Science* **1**: 152–157.

Chandrasekaran AR, Han CY, Chung ACY, Cheang LW and Ping LS (2011), Post market *in vitro* equivalency evaluation of paracetamol tablets in Kedah, Malaysia, *International Journal of Pharmaceutical Science and Nanotechnology* **4**: 1403-1407.

Chereson R (1996), Basic pharmacokinetics: bioavailability, bioequivalence and drug selection, available from: http://www.scribd.com/doc/496701/basic-pharmacoki netics bioavaiabilty y #scribd [Accessed15/01/2013].

Fahmy S and Gharbieh EA (2014), *In vitro* dissolution and *in vivo* bioavailability of six brands of ciprofloxacin tablets administered in rabbits and their pharmacokinetic modeling, *BioMed Research International* **1**:1-8. DOI:org/10.1155/2014/590848

Hailu GS, Gutema GB, Asfaw AA, Hussen DA and Hadera MG (2011), Comparative assessment of the physicochemical and *in-vitro* bioavailability equivalence of co-trimoxazole tablets marketed in Tigray, Ethiopia, *International Journal of Pharmaceutical Sciences and Research* **2**: 3210-3218.

Katzung BG, Masters SB and Trevor AJ (2012), Basic and clinical pharmacology, 12th Ed., Mc Graw-Hill, USA, pp 737-747.

Khatib O (2006), Guidelines for the prevention, management and care of diabetes mellitus,World Health Organization Regional office for Eastern Mediterranean, EMRO Technical Publications Series 32, Cairo, available from: www.emro.who.int/dsaf/dsa664.pdf. [Accessed15/04/2013].

Kishore KA and Amareshwar P (2012), Quality evaluation and comparative study on tablet formulations of different pharmaceutical companies, *Journal of Current Chemical and Pharmaceutical Sciences* **2**: 24-31.

Muaz J, Gazali K, Sadiq GQ and Tom GM (2009), Comparative *in vitro* evaluation of the pharmaceutical and chemical equivalence of multi-source generic ciprofloxacin HCl tablets around Maiduguri metropolitan area, *Nigerian Journal of Pharmaceutical Sciences* **8**: 102-106.

Najib N, Idkaidek N, Beshtawi M, Bader M, Admour I, Alam S, Zaman Q and Dham R (2002), Bioequivalence evaluation of two brands of metformin 500 mg tablets (dialon & glucophage) in healthy human volunteers, *Journal of Biopharmaceutics and Drug Disposition* **23**: 301-306. DOI:org/10.1002/bdd.326

Odeniyi MA, Adegoke OAA, Adereti RB, Odeku OA and Itiola OA (2003), Comparative analysis of eight brands of sulfadoxine pyrimethamine tablets, *Tropical Journal of Pharmaceutical Research* **2**: 161-167.

Ogah CO and Kadejo FF (2013), Analysis of brands of glibenclamide tablets in Lagos Market, *Journal of Innovative Research in Engineering and Sciences* **4**: 466-471.

Oishi TS, Haque A, Dewan Iand Ashraful I (2011), Comparative *in vitro* dissolution study of some ciprofloxacin generic tablets under biowaiver conditions by RP-HPLC, *International Journal of Pharmaceutical Sciences and Research* **2**: 3129-3135.

Oishi TS, Nimmi I and Islam SM (2011), Comparative *in vitro* bioequivalence analysis of some generic tablets of atorvastatin, a BCS class II compound, *Bangladesh Pharmaceutical Journal* **14**: 61-66.

Olusola AM Adekoya AI and Olanrewaju OJ (2012), Comparative evaluation of physicochemical properties of some commercially available brands of metformin hydrochloride tablets in Lagos, Nigeria, *Journal of Applied Pharmaceutical Science* **2**: 41-44.

Poretsky L (2010), Principles of diabetes mellitus, 2nd Ed. Springer Science and Business Media, USA, pp 630-745.

Sahra IB, Marchand-Brustel YL, Tanti JF and Bost F (2010), Metformin in Cancer Therapy: A New Perspective for an old Antidiabetic Drug, *Molecular Cancer Therapeutics* **9**: 1092-1099. DOI: 10.1158/1535-7163.MCT-09-1186

USP (United States Pharmacopoeia) National Formulary, USP 30/NF 25 (2007), United States Pharmacopoeial Convention Inc., Rockville, Vol. I, MD, USA.

Wild S, Roglic G, Green A and Sicree R (2004), Global prevalence diabetes: Estimates for the year 2000 and projection 2030, *Diabetes Care* **27**: 1047-1053.

Zakeri-Milani P, Nayyeri-Maleki P, Ghanbarzadeh S, Nemati M and Valizadeh H (2012), *In vitro* bioequivalence study of eight brands of metformin tablets in Iran market, *Journal of Applied Pharmaceutical Science* **02**: 194-197.