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Comparative *in vitro* equivalence evaluation of some local Gliclazide brands of Bangladesh

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Abstract
The presence of numerous generic brands of gliclazide in the local drug market makes the situation difficult for health professionals and patients to choose the appropriate product. This study was intended to evaluate the bioequivalence of six marketed brands of gliclazide (80 mg) tablets from different manufacturers using *in vitro* dissolution study in order to minimize health risk factors. Drug releases were compared with that of a reference product. The dissolution profiles showed intra brand and inter brand variability. All the brands achieved 85% dissolution within 45 minutes. Test results were subjected to statistical analysis to compare the dissolution profile. Limit of detection (LOD) and limit of quantification (LOQ) were also calculated. Model independent approaches of difference factor (f_1), similarity factor (f_2) and dissolution efficiency (%DE) were employed. Using a validated UV spectrophotometric method, active ingredients were assayed. Assay value was recorded within 97.75% to 109.5%. Other general quality parameters of these tablets like diameter, thickness, hardness, friability, weight variation, disintegration time were also evaluated according to the established protocols and test results were within the limit.

Keywords: Bangladesh, Gliclazide, difference factor (f_1), similarity factor (f_2), dissolution efficiency (%DE), dissolution test

1. Introduction
Monitoring of post market medicines has been employed to judge the quality, therapeutic efficacy and safety of medicine [1]. Information obtained from such monitoring could be used for product development and improvement of existing regulations [2]. In this research physical parameters of commercially available Gliclazide tablets were evaluated.

Gliclazide (GLK), chemically a 1-(3-azabicyclo (3.3.0) oct-3-yl)-3-p-tolysulphonylurea is a second-generation sulfonylurea derivative, which is profoundly used for the treatment of type II diabetes mellitus and mostly available as oral tablets (30 and 80 mg strength) with the recommended dosage between 40 and 320 mg/day [3-4]. GLK was also shown to protect human pancreatic beta-cells from hyperglycemia-induced apoptosis [5].

Diabetes mellitus is contemplated as one of the five leading causes of death in the world, which is becoming the third most lethal disease of mankind [6]. As of 2013, 382 million people were suffering from diabetes, which is going to be 592 million by 2035 [7]. In 2013, Bangladesh, a developing country in South East Asia, was home to more than 5 million (prevalence adjusted to the national population – 5.5%) diabetic patient, which will rise to more than 10 million (prevalence adjusted to the national population – 8.2%) by 2035 [7-9]. However, for the treatment of diabetes according to 2010-2012 statistics from the U.S. Centers for Disease Control and Prevention (CDC) depicts that about 56.9% adult diabetic patient take oral medications only, 14.7% take both insulin and oral medications, 14.4% do not take either insulin or oral medications and 14% take insulin only [10]. Among oral medications sulfonylureas are the predominant class of oral antidiabetic drug used in Bangladeshi population followed by biguanides and thiazolidenediones[11].

According to the Biopharmaceutical Classification System (BCS) drug substances are classified into four classes upon their solubility and permeability [12-15]. GLK falls under the BCS Class II drug, which is poorly soluble and highly permeable [16-17]. For such drugs the challenge of enhancing their absorption in the gastrointestinal tract is to improve the dissolution profile. Therefore, constant surveillance on marketed GLK tablets by the government, manufactures and independent research groups is essential to ensure availability of quality medicines. Side by side there is a common psychology that high cost drug products

manufactured by top pharmaceutical companies are better in comparison with the low cost products manufactured by small scale companies. Moreover, no such recent evaluation of widely used BCS Class-II drug, gliclazide of the local market is available. These facts directed our interest to assess the quality of some commercially available GLK brands in the Bangladeshi market with special emphasis on disintegration and dissolution study due to their enormous prominence in predicting bioavailability and product quality. Six units from each brand were tested for dissolution. Other general quality parameters of these tablets like diameter, thickness, hardness, friability, weight variation, disintegration time were also determined according to the established protocols. Test results were subjected to statistical analysis to compare the dissolution profile. Model independent approaches of difference factor (f_1), similarity factor (f_2) and dissolution efficiency (%DE) were also employed.

2. Materials and Methods

2.1 Materials

2.1.1 Drug

Standard of gliclazide was a gift from Incepta Pharmaceuticals Ltd, Bangladesh.

2.1.2 Dosage form

Gliclazide tablets (80 mg) from six different brands and reference product were purchased from the local drug store of Dhanmondi, Dhaka city. The samples were properly checked for their manufacturing license numbers, batch numbers, production and expiry dates. They were coded as A, B, C, D, E, F where brand A, B, C, E represents IMS-Health reported top and brand D, F belongs to small scale companies [18].

2.1.3 Solvents and reagents

Potassium dihydrogen phosphate (Lot No: P21010D, Daejung Chemicals & Metals Co. Ltd.) and sodium hydroxide (Batch No: PA344CB01, Qualikems Fine Chem Pvt. Ltd.) were of analytical-reagent grade and obtained from South Korea and India respectively. Distilled water was used during the study.

2.2 Methods

2.2.1 Determination of diameter and thickness

20 tablets from 6 brands were taken and both the diameter and thickness of the tablets were measured with an electronic digital caliper (MEGA Digital Clipper) in order to determine the average diameter and thickness.

2.2.2 Hardness test

The crushing strength (KgF) was determined with an Automatic Tablet Hardness Tester (8M, DrSchleuniger, Switzerland). The force applied to the edge of the tablet was gradually increased by moving the screw knob forward until the tablet was broken. Ten tablets were randomly selected from each brand and the pressure at which each tablet crushed was recorded.

2.2.3 Friability test

Ten tablets from each brand were weighed and subjected to abrasion by employing a Veego friabilator (VFT-2, India), operated at 25 RPM for 4 minutes. The friabilator was divided into two plastic chambers. During each revolution the tablets were made to fall from a distance of six inches to undergo shock. After 100 revolutions the tablets were weighed again. The loss in weight indicated the friability.

2.2.4 Determination of uniformity of weight

20 tablets from each of the 6 brands were weighed individually with an analytical weighing balance (AY-200, Shimadzu, Japan). The average weight for each brand was determined as well as the percentage deviation from the mean value were calculated using the formula given by Banker and Anderson [19].

2.2.5 Disintegration test

Six tablets from each brand were employed for the test in distilled water at 37 °C using a Tablet Disintegration Tester (Model: VDT-2, Veego, India). As stated by Alderborn, the disintegration time (DT) was taken as the time when no particle remained in the basket of the system [20].

2.2.6 Dissolution test

The dissolution test was undertaken using Tablet Dissolution Tester (TDT-08L, Electrolab, India) in 6 replicates for each brand involving USP apparatus-II (paddle) at 100 RPM. The dissolution medium was 900 ml of phosphate buffer (P^H 7.4) which was maintained at 37 ± 0.5 °C. In all the experiments, 10 ml of dissolution sample was withdrawn at 0, 15, 30 and 45 min and replaced with an equal volume to maintain an ideal sink condition. Samples were filtered and from the filtrate 1 ml solution was taken and diluted with 6 ml phosphate buffer to make the final volume of 7 ml. The solution was then assayed by UV-VIS spectrophotometer (UV-1700, Shimadzu, Japan) at 226 nm. The concentration of each sample was determined from a ten point calibration curve (Fig. 1), which was obtained from standard curve of gliclazide. Drug lost by per withdrawn from the vessel was considered during the determination of concentration.

2.2.7 Assay

Tablets from each brand were weighed and finely powdered. The powder equivalent to 10 mg of gliclazide was taken and transferred to 100 ml of volumetric flask. Then, the volume was made up to 100 ml with phosphate buffer (P^H 7.4). Flasks were subjected to sonication to dissolve the powdered material. Then the solution was filtered**.** 1 ml of the filtrate and 4 ml phosphate buffer was taken into the test tube; added and mixed. After that absorbance values were measured at the maximum wavelength (λ_{max}) of these concentrations using a UV-VIS spectrophotometer (UV-1700, Shimadzu, Japan). Maximum wavelength (λ_{max}) was obtained by scanning samples from 200 to 400 nm and it was found 226 nm.

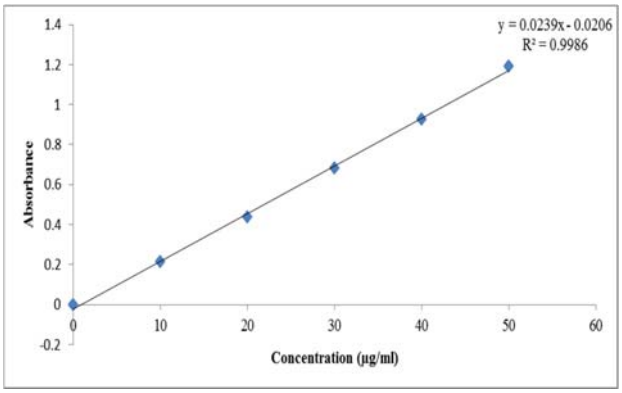

Fig 1: Standard Curve of Gliclazide

2.2.8 Limit of detection (LOD) and limit of quantification (LOQ)

Limit of detection (LOD) and quantification (LOQ) were

calculated directly from the calibration plot. LOD and LOQ were calculated as 3.3σ/S and 10σ/S, respectively, where σ is the standard deviation of intercept and S is the slope of the calibration plot [21-24].

2.2.9 Data analysis
The uniformity of weight was analyzed with simple statistics while the dissolution profiles were analyzed by difference factor (f_1), similarity factor (f_2) and dissolution efficiency (%DE).

3. Result and Discussion
3.1. Diameter test
By monitoring the diameter and thickness of the tablets at regular intervals, potential problems relating to tablet weight and hence content uniformity can be detected at an early stage [25]. From the data mentioned in Table 1, it has been found that among six brands, brand-E had the highest average diameter (9.24 mm) whereas brand-B had lowest average diameter (8.02 mm).

3.2 Thickness test
With an increasing thickness, there is a decrease in hardness due to compression force and vice versa. The average thickness of Brand A, B, C, D, E, F were found 3.07 mm, 2.87 mm, 3.27 mm, 3.06 mm, 4.21 mm and 2.92 mm respectively as shown in Table 1. The individual thickness of each tablet from the respective brand was found satisfactory as compared to the average thickness.

Table 1: A summary of the quality control tests undertaken on different brands of GLK tablets.

Brand code	Diameter (mm)*	Thickness (mm)*	Hardness (KgF)*	Friability (%)	Weight deviation (mg)	DT (min)*	% Drug content
A	8.09 ± 0.01	3.07 ± 0.02	0.35 ± 0.19	0.32	169.52 ± 3.59	2.23 ± 0.63	103.25
B	8.02 ± 0.02	2.87 ± 0.02	1.95 ± 0.30	0.23	175.51 ± 2.52	2.94 ± 0.52	105.75
C	8.10 ± 0.02	3.27 ± 0.03	0.40 ± 0.28	0.30	198.9 ± 10.40	0.35 ± 0.05	100.75
D	8.07 ± 0.02	3.06 ± 0.02	0.30 ± 0.12	0.22	184.79 ± 4.33	2.39 ± 0.58	109.50
E	9.24 ± 0.03	4.21 ± 0.03	0.45 ± 0.38	0.38	265.59 ± 2.19	0.49 ± 0.33	99.50
F	8.07 ± 0.02	2.92 ± 0.01	1.42 ± 1.20	0.11	177.85 ± 3.96	3.87 ± 1.08	97.75

*Values are expressed as mean ± SD

Table 2: Dissolution profile of six brands of GLK tablets (values are expressed as mean ± SD).

Time (min)	% Drug release					
	Brand A	Brand B	Brand C	Brand D	Brand E	Brand F
0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
15	77.77 ± 2.53	84.13 ± 3.74	75.34 ± 4.35	74.55 ± 5.52	60.51 ± 3.72	56.7 ± 10.98
30	93.00 ± 1.57	94.52 ± 2.52	82.47 ± 0.87	82.33 ± 1.24	70.63 ± 3.76	60.22 ± 1.58
45	95.08 ± 1.22	100.28±1.37	86.66 ± 1.84	87.18 ± 1.39	85.45 ± 1.84	85.42 ± 5.55

3.3 Hardness test
Hardness has an impact on disintegration. If the tablet is hard then it cannot disintegrate within the specified time and if the tablet is soft, then it becomes hard to withstand the handling during coating or packaging. Therefore, adequate tablet hardness and resistance to powdering and friability are necessary requisites for producing quality tablets [26]. Oral tablets normally have a hardness of 4 to 8 or 10 kg. In general, if the tablet hardness is too high, disintegration test is performed before rejecting the batch. And if the disintegration is within limits, the batch is generally accepted [25]. According to Table 1, brand-B had a maximum hardness of 1.95 kgF whereas brand-D had the lowest hardness of 0.3 kgF among the six brands. Here, no brands were within the range, but since the hardness test is an unofficial test [27] and later their disintegration time (DT) was found satisfactory, the batches were considered as of good quality.

3.4 Friability test
Friability assessment reveals good mechanical strength of the tablets [28]. The compendium specification for friability is not more than 1% [29]. Friability test is influenced by internal factors like the moisture content of tablet granules and finished tablets. Moisture at low and acceptable level acts as a binder. As the hardness of the tablets is increased gradually there is a notable decrease in the percentage friability in all formulations. The possible reason for this result may be that at high compression force the granules are packed strongly together and there is a low degree of crumbling during friability. So harder the tablets less will be the percentage friability and vice versa [30]. As shown in Table 1, all the brands had percent friability below 1%, which indicates good mechanical resistance of the tablets. Among six brands, brand-E had maximum friability (0.38%) whereas brand-F had minimum friability (0.11%).

3.5 Test of uniformity of weight
Weight variation does serve as a pointer to good manufacturing practices (GMP) maintained by the manufacturers as well as the amount of active pharmaceutical ingredient (API) contained in the formulation [29]. The weight variation for all the tablets used in this study showed compliance with the official specifications of USP. Since all the brands have an average weight between 130 mg to 324 mg. Therefore, not more than 2 tablets should differ from the average weight by more than 7.5% and none will deviate by 15% of average weight. Here, as depicted in Table 1, brand C showed the highest deviation, two tablets crossed the limits, but none of them crossed the double limit of 15%. And brand E showed least deviation among all six brands.

3.6 Disintegration test
As disintegration plays an important role in a tablet's dissolution before the active drug substance is finally released from the tablet's structure into the body. Therefore, type, concentration, and the efficiency of disintegrates to a large extent affects the dissolution [31]. BP specifies that uncoated tablets should disintegrate within 15 minutes, which is 30

minutes in case of USP [27]. Table 1 shows all the brands met the official criteria. Here, brand F took maximum time of 3.87 minute and brand C took the minimum time of 0.35 minutes to disintegrate.

3.7 Dissolution test

The drug gliclazide is not included in USP yet. But by comparing with the USP specification of another brand, glipizide (dissolution limit: not less than 80% in 45 min) we can say that dissolution profile (Table 2) of all the six brands was within the limit as all the brands achieved 85% dissolution within 45 minutes. Intra-brand (within a brand) dissolution profile in Fig. 2 and inter-brand (brand to brand) dissolution profile in Fig. 3 reveals that brand B showed maximum % of drug release (100.28%) whereas brand F showed minimum % of drug release (85.42%) in 45 minutes. Therefore, dissolution profile of all the brands was satisfactory and almost similar regardless of top and small scale companies.

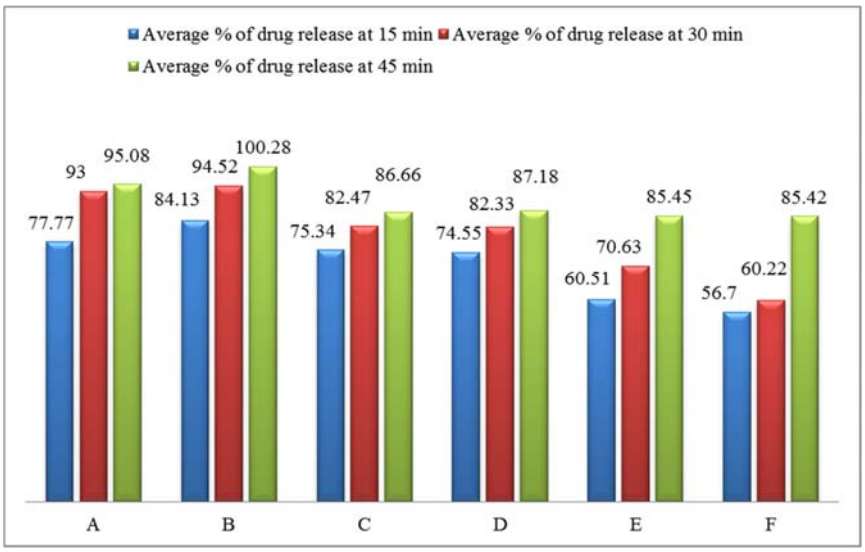

Fig 2: Intra brand Dissolution Profile of Six Brands of Gliclazide Tablets

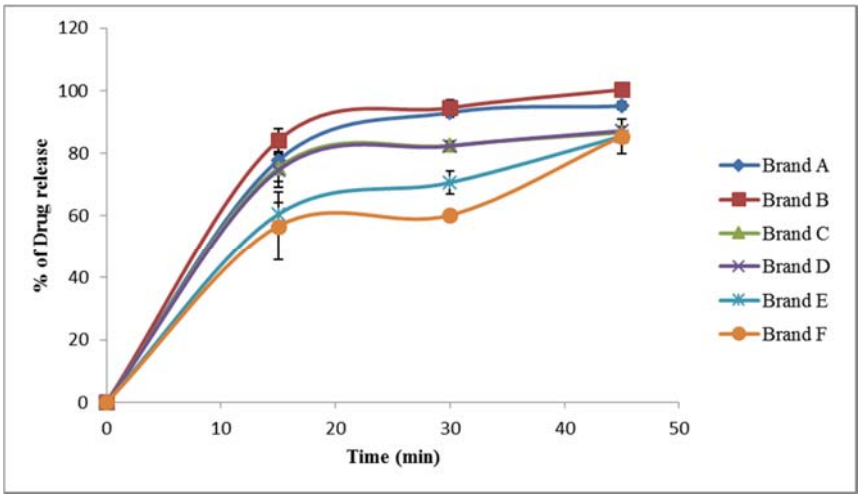

Fig 3: Inter brand Dissolution Profile of Six Brands of Gliclazide Tablets. Vertical Bars Represent Mean ± SD

3.8. Comparison of dissolution data

Difference factor (f_1), similarity factor (f_2) and dissolution efficiency (%DE) were calculated to compare the dissolution profile. Difference factor (f_1) is the percentage difference between the two curves at each point and is a measurement of the relative error between the two curves. The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves [32-33]. The following equations were used to calculate difference factor (f_1) and similarity factor (f_2):

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} X100$$

$$f_2 = 50 \log \left\{ \left(1 + \frac{1}{n} \sum_{i=1}^{n} (R_t - T_t)^2 \right)^{-0.5} X100 \right\}$$

Where n is the number of time points, R_t is the dissolution value of the reference product at time t and T_t is the dissolution value for the test product at time t. Similarity

factor (f_2) has been adopted by FDA and the European Agency for the Evaluation of Medicinal Products [34] by the Committee for Proprietary Medicinal Products (CPMP) to compare the dissolution profile. Two dissolution profiles are considered similar and bioequivalent, if f_1 is between 0 and 15 and f_2 is between 50 and 100 [27, 35]. Table 3 shows the f_1 and f_2 values of different brands in respect of the reference brand. It reveals only for brand A, B, C and D, f_2 value were more than 50 and f_1 were less than 15. So, their dissolution profile is similar to that of the reference product and can be used interchangeably.

Table 3: Calculated values of f_1, f_2 and %DE for test and reference products.

Brand	Difference Factor(f_1)	Similarity Factor(f_2)	Dissolution Efficiency (% DE)
A	2.75	73.75	76.54
B	3.41	69.81	76.05
C	9.4	50.93	77.37
D	9.55	51.18	76.65
E	19.73	37.32	67.82
F	25.01	31.47	62.29
Reference Product	-	-	72.99

Dissolution efficiency (%DE) was also employed to compare the drug release from various brands. Dissolution efficiency is the area under the dissolution curve within a time range (t_1 - t_2). DE was calculated by using the following equation:

$$AUC = \sum_{i=1}^{i=n} \frac{(t_i - t_{i-1})\,(y_{i-1} + y_i)}{2}$$

Where *y* is the percentage dissolved at time *t*. Table 3 shows the dissolution efficiency of different brands along with the reference product. The reference and the test product can be said to be equivalent if the difference between their dissolution efficiencies is within appropriate limits (± 10%, which is often used) [33]. According to Table 3, brand A, B, C and D are equivalent to reference product as difference of % DE (test product – reference product) is less than 10. However, the rest of the brands were away from the limit (± 10%). So, they are not similar with reference product and cannot be considered as interchangeable.

3.9 Assay

Analysis of drug potency in tablets indicates the presence of drug in dosage form and their stability [36]. Since no specific limit regarding the potency of gliclazide has been found in USP, the general potency limit of tablet dosage form as mentioned in USP was considered. Here, Table 1 depicts that the active content of all the brands was in between 97.75% (brand-F) and 109.50% (brand-D). The result indicates there was no significant variation in content of the active moiety in their dosage form among the six companies and all are within the USP specification of 100 ± 10%.

3.10 Limit of detection (LOD) and limit of quantification (LOQ)

The limit of detection (LOD) is the lowest concentration of an analyte that an analytical process can reliably differentiate from background levels. The limit of quantification (LOQ) is the lowest concentration of the standard curve that can be measured with acceptable accuracy, precision and variability. The LOD and LOQ were found to be 2.645 µg/ml and 8.014 µg/ml, respectively.

4. Conclusion

In the current industrial practice, to compare with the multi brand generic molecules and to provide enough therapeutic activity of the dosage form, *in-vitro* tests play an important role. This investigation reveals no noteworthy difference in quality parameters of the investigated products manufactured by IMS-Health reported top and small scale companies. The presented data demonstrate that although six brands of GLK tablets included in this study seem to have good overall quality with sufficient dissolution rate and adequate potency, two brands failed to meet the equivalence criteria. This study emphasized that chemical equivalence may not always indicate bioequivalence. It also states the need for constant surveillance of the marketed drugs in order to ascertain quality medicines. However, *in vivo* testing may be required for final comments regarding the quality of marketed brands of gliclazide.

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6. References

1. Hailu GS, Gutema GB, Hishe HZ, Ali YS, Asfaw AA. Comparative *In vitro* Bioeqivalence Evaluation of Different Brands of Amoxicillin Capsules Marketed in Tigray, Ethiopia. Int J Pharm Sci Nanotech 2013; 6(1):1966-1971.
2. Chandrasekaran AR, Han CY, Chung ACY, Cheang LW, Ping LS. Post-marketing *in vitro* equivalency evaluation of paracetamol tablets in Kedah, Malaysia. Int J Pharm Sci Nanotech 2011; 4(2):1403-1407.
3. Grbic S, Parojcic J, Ibric S, Djuric Z. *In vitro – In vivo* Correlation for Gliclazide Immediate Release Tablets Based on Mechanistic Absorption Simulation. AAPS PharmSciTech 2011; 12(1):165-171.
4. Varshosaz J, Tavakoli N, Enteshary S. Enhancement of Anti-Diabetic Effects of Gliclazide Using Immediate Release Tablets in Streptozotocin-Induced Diabetic and Normal Rats. Farmacia 2013; 61(4):820-836.
5. Del Guerra S, Grupillo M, Masini M, Lupi R, Bugliani M, Torri S *et al*. Gliclazide protects human islet beta-cells fromapoptosis induced by intermittent high glucose. Diabetes Metab Res Rev 2007; 23(3):234-238.
6. Joseph B, Jini D. Antidiabetic effects of Momordica charantia (bitter melon) and its medicinal potency. Asian Pac J of Trop Dis 2013; 3(2):93-102.

7. Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projection for 2035. Diabetes Res Clin Pract 2014; 103(2):137-149.
8. Kadir MF, Karmoker JR, Alam MR, Jahan SR, Mahbub S, Mia MMK. Ethnopharmacological Survey of Medicinal Plants Used by Traditional Healers and Indigenous People in Chittagong Hill Tracts, Bangladesh, for the Treatment of Snakebite**.** Evidence-based Complementary and Alternative Medicine, 2015.
9. Ramachandran A, Snehalatha C, Wan-Ma RC. Diabetes in Sounth-East Asia: An Update. Diabetes Res Clin Pract 2014; 103(2):231-237.
10. Centers for Disease Control and Prevention (CDC). National Diabetes Statistics Report: Estimates of Diabetes and its Burden in the United States, 2014. Atlanta, GA: U.S. Department of Health and Human Services, 2014. Available at: cdc.gov/diabetes/pubs/statsreport14/national-diabetesreport-web.pdf. [Visited on 01 November, 2015].
11. Latif ZA, Jain A, Rahman MM. Evaluation of management, control, complications and psychosocial aspects of diabetes in Bangladesh: DiabCare Bangladesh 2008. Bangladesh Med Res Counc Bull 2011; 37(1):11-16.
12. Khadka P, Ro J, Kim H, Kim I, Kim JT, Kim H *et al*. Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability. Asian J Pharm Sci 2014; 9(6):304-316.
13. Dahan A, Miller JM, Amidon GL. Prediction of Solubility and Permeability Class Membership: Provisional BCS Classification of the World's Top Oral Drugs. AAPS J 2009; 11(4):740-746.
14. Yasir M, Asif M, Kumar A, Aggarval A. Biopharmaceutical Classification System: An Account. Int J PharmTech Res 2010; 2(3):1681-1690.
15. Yu LX, Amidon GL, Polli JE, Zhao H, Mehta MU, Conner DP *et al*. Biopharmaceutics classification system: the scientific basis for biowaiver extensions. Pharm Res 2002; 19(7):921-925.
16. Vijayaraj S, Anoop S, Sampathkumar KP. Synthesis and characterization of novel amino acid prodrug of gliclazide. Int J Biol Pharm Res 2015; 6:723-730.
17. Lakka NS, Goswami N. Solubility and dissolution profile studies of gliclazide in pharmaceutical formulations by RP-HPLC. Int Res J Pharm 2012; 3(6):126-129.
18. EBL Securities Ltd. Pharmaceutical sector overview, 2015. Available at: http://www.eblsecurities.com/report/9fec95fc34f0649c4a5f5575ead478ed.pdf. [Visited on 01 November, 2015].
19. Banker GS, Anderson NR. The Theory and Practice of Industrial Pharmacy. Edn 3, Lea & Febiger Verghese publishing house, Philadelphia, 1986, 293-303.
20. Alderborn G. The Design and Manufacture of Medicines. Edn 1, Churchill livingstone: Elsevier, Hungary, 1988, 441-481.
21. Friedrich RB, Ravanello A, Cichota LC, Rolim CM, Beck RC. Validation of a simple and rapid UV spectrophotometric method for dexamethasone assay in tablets. Química Nova 2009; 32(4):1052-1054.
22. Wankhede SB, Lad KA, Chitlange SS. Development and validation of UV-spectrophotometric methods for simultaneous estimation of cetirizine hydrochloride and phenylephrine hydrochloride in tablets. Int J Pharma Sci Drug Res 2012; 4(3):222-226.
23. Jamadar SA, Mulye SP, Karekar PS, Pore YV, Burade KB. Development and validation of UV spectrophotometric method for the determination of Gliclazide in tablet dosage form. Der Pharma Chemica 2011; 3(4):338-343.
24. Sahoo SK, Giri RK, Patil SV, Behera AR, Mohapatra R. Development of ultraviolet spectrophotometric method for analysis of lornoxicam in solid dosage forms. Trop J Pharm Res 2012; 11(2):269-273.
25. Bano R, Gauhar S, Naqvi SBS, Mahmood S. Pharmaceutical evaluation of different brands of Levofloxacin tablets (250 mg) available in local market of Karachi (Pakistan). Int J Curr Pharm Res 2011; 3(1):15-22.
26. Saleem M, Shahin M, Srinivas B, Begum A. Evaluation of tablets by friability apparatus. Int J Res Pharm Chem 2014; 4(4):837-840.
27. Oishi TS, Nimmi I, Islam SMA. Comparative *in vitro* Bioequivalence Analysis of Some Generic Tablets of Atorvastatin, a BCS Class II Compound. Bangladesh Pharm J 2011; 14(1):61-66.
28. Kumar P, Ganure AL, Subudhi BB, Shukla S, Upadhyay P. Design and comparative *in-vitro* and *in-vivo* evaluation of starch–acrylate graft copolymer based salbutamol sulphate sustained releasetablets. Asian J Pharm Sci 2015; 10(3):239-246.
29. Nayak AK, Pal D. Comparative *in vitro* Bioequivalence Analysis of Some Ciprofloxacin HCl Generic Tablets. Int J Pharm Sci Res 2010; 1(8):51-57.
30. Karmoker JR, Joydhar P, Sarkar S, Rahman M. Comparative *in vitro* Evaluation of Various Commercial Brands of Amlodipine Besylate Tablets Marketed in Bangladesh. Asian J Pharm Hea Sci 2016; 6(1):1384-1389.
31. Mangal M, Thakral S, Goswami M, Thakur N. Comparison study between various reported disintegration methods for fast dissolving tablets. African J Basic & Appl Sci 2012; 4(4):106-109.
32. Islam SMA, Islam S, Shahriar M, Dewan I. Comparative *in vitro* dissolution study of Aceclofenac Marketed Tablets in Two Different Dissolution Media by Validated Analytical Method. J Appl Pharm Sci 2011; 1(9):87-92.
33. Popy FA, Dewan I, Parvin MN, Islam SMA. Evaluation of *In vitro* Equivalence for Tablets Containing the Poorly Water-Soluble Compound Atrovastatin. Dissolut Technol 2012; 19(4):30-33.
34. The European Agency for the Evaluation of Medicinal Products (EMEA), Note for guidance on the investigation of bioavailability and bioequivalence, 2000. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003519.pdf. [Visited on 22 June, 2016].
35. Karmoker JR, Sarkar S, Joydhar P, Chowdhury SF. Comparative *in vitro* equivalence evaluation of some Aceclofenac generic tablets marketed in Bangladesh. Pharma Innovation J 2016; 5(3):03-07.
36. Abbirami V, Sainithya P, Shobana A, Devi DR, Hari BNV. Review on In-vitro Bioeqivalence Studies and its Methodologies. Int J Chem Tech Res 2013; 5(5):2295-2302.