Analytical appraisement of some commercially available brands of Metformin Hydrochloride Tablet in Dhaka, Bangladesh

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Abstract
Metformin hydrochloride contains metformin500mg, a medicine to treat diabetes. It belongs to a class of oral hypoglycemic agent called biguanide. It is the first-line drug of choice for the treatment of type-2 diabetes, particularly in overweight and obese people (International Diabetes Federation, Akinleye M.2012). There are several of metformin hydrochloride tablets available within the drug delivery system globally including Bangladesh. Availability of numerous brands of metformin tablets in Bangladesh drug market today places health practitioners in a dilemma of generic substitution. The objective of the study was to evaluate the physicochemical equivalence of seven brands of metformin hydrochloride tablets marketed in Bangladesh using in vitro tests. The physicochemical equivalence of seven brands Metformin hydrochloride tablet were assessed through the evaluation of both official and non-official standards such as uniformity of weight, friability, hardness, disintegration, assay and dissolution rate. All the brands complied with the official specifications.

Keywords: Metformin hydrochloride, type-2 diabetes physicochemical equivalence

Introduction
World Health Organization has estimated that about 80% of people with diabetes live in low- and middle-income countries. World Health organization has also estimated that 30%of the medicine on sale for consumption in many countries in Africa and part of Asia and Latin America are counterfeit. (WHO, 2006). Counterfeiting can apply to both branded and generic products and could include products with the correct ingredients or with the wrong ingredients, without active ingredient, with insufficient active ingredient, or with fake packaging (WHO, 1999). While substandard drugs are genuine drug products that upon laboratory testing do not meet the quality specifications claimed by their manufacturers (Taylor et al., 2009). The introduction of generic drug product from multiple sources into the health care delivery system of many developing countries is aimed at improving the overall health delivery systems. However, this has been bedeviled with widespread distribution of fake and substandard drug products. Quality of medicinal drugs in many underdeveloped countries is inadequate. In some cases, use of poor-quality medicines has resulted in treatment failure (Petralanda, 1995). Pharmacists have great responsibilities and they should uphold the highest standards in dispensing medication. Counterfeit medication is extremely dangerous and can cause patients to suffer side effects or even lose their lives (Fake Drugs in Bangladesh, 2013). While Bangladesh's mammoth Pharmaceutical industry exports drugs to as many as 52 countries worldwide, an annual testing of 5000 drug samples this year, the Public Health and Drug Testing Laboratory (PHDTL) detected 300 drugs that are either counterfeit or of very poor quality. Significantly, these include many popular antibiotics and lifesaving drugs. Jolted into action, the health ministry's Drug Administration authorities have launched a drive against illegal and fake drug vendors in the country. Preliminary findings reveal Bangladesh boasts a whopping 80,000 unlicensed drugstores. Smuggled drugs are the biggest threat, as this is a grey area which is totally unmonitored. The rampant growth of contraband drugs is blamed on the poor quality of health services and cut-throat competition between drug manufacturers. Worse, the acute shortage of doctors and clinics in rural areas forces patients to purchase off-the-counter drugs sans a prescription. A large percentage of patients also travel to neighboring country for treatment, returning with prescriptions of foreign drugs. To cater to them, dozens of...
unauthorized pharmaceutical establishments have mushroomed on the Bangladesh border. These units either smuggle in foreign drugs or manufacture fake ones that threaten the lives of thousands of patients. Recently, the Drug Testing Laboratory found that a popular drug used for strokes and brain hemorrhages, was being marketed minus its main chemical ingredients. "The presence of fake and illegal drugs in Bangladesh is itself surprising because we manufacture over 96 per cent of our requirements and even export drugs. The industry comprises over 800 drug-manufacturing companies, 230 of which manufacture allopathic drugs, 255 producing traditional herbal drugs, 300 engaged in the manufacture of modern herbal drugs and 80 homeopathic drug producing outlets. Pharmacists allege that apart from some three dozen leading allopathic drug manufacturers, the rest are involved in the production of fake and low quality drugs (Fake Drugs Flood Bangladesh, 2013). Testing of 5,000 medicine samples this year by the government of Bangladesh revealed that 300 or 6 per cent were either counterfeit or of substandard quality, according to Business Monitor International. The country's Public Health and Drug Testing Laboratory found that many of the fake or low-quality products were antibiotics and other potentially life-saving medicines and therefore pose a risk to public health. The main channels for distribution of the substandard and counterfeit drugs seems to be the country’s huge network of unlicensed pharmacies - which could number as many as 80,000 according to some estimates. It is thought that these counterfeit products are produced in numerous drug factories situated along the Bangladeshi, Indian, Pakistani, Chinese and Thailand borders. (Bangladesh carrying heavy counterfeit, 2012)

The aim of the research that to find out good quality of marketed metformin which are used for the type-2 diabetes. i.e. it is use in Diabetes Mellitus(DM). Which has great role to control the blood sugar alone or combine with other drugs. According to the latest WHO data published in April 2011 Diabetes Mellitus Deaths in Bangladesh reached 19,598 or 2.05% of total deaths. The age adjusted Death Rate is 23.80 per 100,000 of population, ranks for Bangladesh #109 in the world. A research initiative in Bangladesh, which is conducted by the Diabetic Association of Bangladesh and the University of Oslo. According to the IDF Diabetes Atlas, the diabetes cases in Bangladesh will have risen to 7.9 % by the year 2030(Prof. Akhtar Hussain, 2011). Asia is emerging as the epicenter of diabetes epidemic. Like all other develop and developing countries prevalence and incidence of type-2 DM is also increasing in Bangladesh. In 2010, the International Diabetes Federation (IDF) estimated that 5.7 million (6.1%) and 6.7 million (7.1%) of people living in Bangladesh is suffering from diabetes and impaired glucose tolerance (IGT) respectively. By 2030, that number of diabetic population is expected to rise to 11.1 million. Besides lifestyle intervention pharmacological interventions especially using metformin has also been shown to be effective in reducing the onset of diabetes in subjects with impaired glucose tolerance (IGT).Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, Metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects. (Except in special circumstances), and does not cause hyperinsulinemia. With Metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease (Dr. Javed Yousuf, 2006).

Generic drugs are copies of innovator drug products with expired patents. They are promoted for use in practice because they are usually less expensive than the innovator products, thereby improving access to life-saving drugs, especially in developing countries. Regardless of price, generic drug quality should be com-parable to that of the innovator product. Generic drug products can only be interchangeable with innovator products when they are pharmaceutically and therapeutically equivalent. In vivo bioequivalence (BE) studies are commonly used to assess therapeutic equivalence, but these studies are often costly and involve invasive procedures. The Bio Pharmaceutics Classification System (BCS) can be used to reduce in vivo BE requirements. In vitro dissolution tests based on BCS are acceptable surrogates for establishing the bioequivalence of generics with the innovator products. WHO also recommends bio-waiver for Class 2 and 3 drugs that are very rapidly dissolving (Rajesh, 2012 and Samar A, 2012) Metformin hydrochloride is highly soluble with low permeability; it is therefore a BCS Class 3 drug and is eligible for a bio-waiver based on the WHO criteria. According to the WHO bio-waiver testing procedure for Class 3 drugs, a bio-waiver can be considered only if both the generic and the innovator products dissolve very rapidly (i.e., 85%or more dissolved within 15 min in standard dissolution media at pH 1.2, 4.5, and 6.8(Block.L.2007). Dissolution efficiencies variation known as predicted availability equivalent (PAE) is used to predict the likely in vivo bioavailability. The implication of the PAE is to express the relative ease of release and predictive release pattern of the drugs in vivo. In vitro dissolution methods are developed to assess the potential in vivo performance of a solid oral dosage form. The appropriate performance of drugs products is determined through the quality control tests. Recently, understanding of the Physiological environment and processes of absorption, critical deconstruction of the mechanisms of release from formulations and improved computational tools has led to a more sophisticated
discussion of the role of dissolution testing in drug product design and control (Rohini Diwedi, 2012). This study sought to apply the BCS bio-waiver requirements to assess the equivalence of commonly interchanged generic metformin hydrochloride tablets with their respective innovator products (Olubukola O., 2012. Pamula Reddy Bhavanam). Dissolution time is the time required for the tablet to go into solution in the suitable medium, dissolution rate is the rate of which a drug goes into solution, both these are determined in simulated gastric fluid at 37°C by the help of dissolution instrument. After oral administration, a tablet undergoes disintegration on and then the drug goes into the solution. The rate of absorption and bioavailability of the drug are directly related to the dissolution rate of the drug.

**Materials and Methods**

**Sample:**
Metformin hydrochloride, having label strength of 500mg of seven different brands were purchased from local Pharmacy in Dhaka, Bangladesh. Tablets were manufactured by Bangladeshi local and multinational pharmaceutical companies. The brands of metformin tablets which were presented as the code A, B, C, D, E, F and G respectively. All products were manufactured within six months from the date of study.

**Reagents/chemicals:**
All reagents were analytical grade: potassium di-hydrogen orthophosphate, hydrochloric acid, and sodium hydroxide, Methanol and DI water.

**Reference Standards:**
Metformin hydrochloride was obtained from Euro Bangla Chemical Dhaka, Bangladesh.

**Determination of physiochemical equivalence:**

**Uniformity of Weight:**
**Method:** Sample tablets (20) of each brand were weighed together and average weight was determined. Each tablet was weighed individually on electronic analytical balance and the percentage (%) deviation was determined.

**Hardness Test**
**Method:** Sample tablets (20) of each brand were taken, a tablet was placed between the spindle of the hardness tester machine and pressure was applied by turning the knurled knot just sufficiently to hold the tablet in position. The pressure was then increased as uniformly as possible until the tablet breaks and the pressure required to break the tablet was then read off the machine and recorded.

**Thickness Test:**
Tablet thickness is an important quality control test for tablet packaging. Very thick tablet affects packaging either in blister or plastic container. Tablet thickness is determined by the diameter of the tablet.

**Friability Test**
Sample tablets (20) of each brand were taken and weighed, these tablet were then put in the automated Friabilator and this test for the tendency to crumble by allowing it to roll and fall within the rotating apparatus, after 100 revolutions the tablets were weighed and recorded. The friability of the tablets were then calculated using the following expression:

\[
\text{% Friability} = \left( \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \right) \times 100
\]

**Disintegration Test**
The disintegration time of randomly selected six tablet of each of the seven brands was determined at 37°C in distilled water using a Multi-unit disintegration tester (USP) Electro lab® apparatus. The disintegration time was taken to be the time no granule of any tablet was left on the mesh.

**Potency test:**
Dissolve 0.630g of drug (with excipient) in 25 ml of 0.01 M HCl acid previously cooled in iced water and titrate immediately with 0.05 M iodine. Then added 5ml of starch solution and titrate until the blue color of the solution persists for at least 2 minutes.

**Dissolution studies:**
Test was determined by using a 2-compartment dissolution test apparatus (basket type) containing 900ml of phosphate buffer pH 6.8, maintained at 37 ±0.5°C with a fixed speed of 100rpm. A tablet of each was put in each of the compartments and the machine operated at the intervals of 15, 30, and 45 minute. In the experiments of each sample, 5ml of the sample was withdrawn at specified intervals and replaced with a fresh 5ml dissolution medium to maintain the sink conditions. Each of the withdrawn samples was filtered with syringe filter 0.45µm, the filtrate diluted and its absorbance at 233nm was measured using UV-visible spectrophotometer. The concentration of Metformin hydrochloride dissolution medium was calculated According to Beer’s-Lambert’s law. From the concentration percentage (%) drug release was determined at specified time intervals.

**Assay of the Tablets**
According to European pharmacopoeia, dissolve 0.200g in 10 ml of 0.01 M hydrochloric acid previously cooled in iced water and titrate immediately, drop wise, with 0.05 M iodine. Before each addition of 0.05 M iodine dissolve
the precipitate by swirling. At the end of the titration add 2 ml of starch solution and titrate until the blue color of the solution persists for at least 2 minutes temperature of the solution during the titration must not exceed 10° C. (1 ml of 0.05 M iodine is equivalent to 16.67 mg of metformin HCl).

**Data Analysis:**
The dissolution profiles were estimated by plotting the percent drug released versus time and were compared using a model independent approach, similarity factor \(f_2\) as described by FDA guide line for industry and presented in the following equation:

\[
F_2 = 50 \log \left\{ \frac{1}{n} \sum_{i=1}^{n} \left( \frac{R_i - T_i}{2} \right)^2 \right\}^{0.5} \times 100
\]

Where \(R_i\) and \(T_i\) are percent dissolved at each time point for reference and test products respectively. If the \(f_2\) value is greater than or equal to 50 it shows sameness or equivalence of the two dissolution profiles. If \(f_2\) is less than 50, that mean the dissolution profile is different from the innovator product hence not interchangeable (FDA guidance, 1997. Moore and Flanner, 1996)

**Result and discussion**
Seven different brands of Metformin hydrochloride tablets which are commercially available in Dhaka were subjected to a number of quality control tests in order to assess their biopharmaceutical equivalence. The assessments involved the evaluation of uniformity of Weight, friability, hardness, disintegration, potency test and dissolution tests. All the brands used were within their shelf life as at the time of study. The weight uniformity for the six brands of Metformin hydrochloride tablets gave values that comply with the USP specification with a deviation less than 5% from the mean value. Using hardness tester, the strength of the tablets was tested. Seven brand tablets allow this official test according to USP specifications (4-6 kg). Brand E had the maximum hardness. Hardness values of brand E were 6 kg but which was within the USP specification. (Table no. 1) The friability test is mostly important criteria for uncoated tablets (during and after manufacture) to examine that the tablets have a good withstand strength for transportation, packaging, shipping and coating. All the tested brands in this study were film coated tablets. The friability was also tested for these coated tablets for all brands. The friability was less than 1% for all the brands. The values of <1% are considered to be highly satisfactory evaluation characteristics Table 1.

**Table 1: The evaluated physical characteristics of Metformin tablet**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Weight uniformity Deviation (%) ±SEM*</th>
<th>Friability (%)</th>
<th>Thickness Deviation (%) ±SEM</th>
<th>Diameter Deviation (%) ±SEM</th>
<th>Average Hardness (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.42 ± 0.99</td>
<td>0.70</td>
<td>0.76 ± 1.14</td>
<td>0.37 ± 0.32</td>
<td>5.80</td>
</tr>
<tr>
<td>B</td>
<td>4.98 ± 2.13</td>
<td>0.17</td>
<td>3.79 ± 3.42</td>
<td>0.43 ± 0.40</td>
<td>5.40</td>
</tr>
<tr>
<td>C</td>
<td>4.90 ± 1.86</td>
<td>0.76</td>
<td>2.63 ± 1.31</td>
<td>0.91 ± 0.60</td>
<td>5.98</td>
</tr>
<tr>
<td>D</td>
<td>1.74 ± 1.16</td>
<td>0.36</td>
<td>1.42 ± 1.40</td>
<td>0.66 ± 0.57</td>
<td>5.66</td>
</tr>
<tr>
<td>E</td>
<td>6.23 ± 5.56</td>
<td>0.42</td>
<td>6.75 ± 5.10</td>
<td>2.15 ± 1.16</td>
<td>5.34</td>
</tr>
<tr>
<td>F</td>
<td>5.35 ± 3.01</td>
<td>0.91</td>
<td>1.88 ± 0.68</td>
<td>0.60 ± 0.59</td>
<td>6.00</td>
</tr>
<tr>
<td>G</td>
<td>2.61 ± 1.11</td>
<td>0.74</td>
<td>1.72 ± 0.85</td>
<td>0.33 ± 0.08</td>
<td>5.48</td>
</tr>
</tbody>
</table>

*Standard error of mean

**Table 2: The evaluated chemical characteristics of Metformin tablet**

<table>
<thead>
<tr>
<th>Sample Code</th>
<th>Disintegration time (minute)</th>
<th>Drug Released (%) after Assay %</th>
<th>Potency (500mg tablet with excipient)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15min</td>
<td>30min</td>
<td>45min</td>
</tr>
<tr>
<td>A</td>
<td>10</td>
<td>59</td>
<td>77</td>
</tr>
<tr>
<td>B</td>
<td>8</td>
<td>66</td>
<td>80</td>
</tr>
<tr>
<td>C</td>
<td>9</td>
<td>64</td>
<td>86</td>
</tr>
<tr>
<td>D</td>
<td>13</td>
<td>62</td>
<td>84</td>
</tr>
<tr>
<td>E</td>
<td>7</td>
<td>61</td>
<td>77</td>
</tr>
<tr>
<td>F</td>
<td>11</td>
<td>59</td>
<td>79</td>
</tr>
<tr>
<td>G</td>
<td>7</td>
<td>64</td>
<td>75</td>
</tr>
</tbody>
</table>
The results obtained from the assessment, the percentage content of active ingredient of seven brands of Metformin hydrochloride tablets showed values within the monograph specification 95% to 105% of stated amount of Metformin HCL as demonstrated in table 2.

When a drug is administered orally in the form of the tablet, the absorption of the tablet depends upon how fast it goes into solution i.e. absorption of a drug is totally dependent upon the dissolution of the tablet. Dissolution of a tablet is influenced largely by the pH of the absorption site as well as pKa factor of a drug. Some factors directly affect dissolution: A-Physicochemical properties of the drug: Partition coefficient, dissociation constant, particle size, crystal habit and crystal structure, polymorphism, hydration state etc. B-Formulation Factors: Binder, lubricant, compression force and nature of the dissolution medium and also depend on temperature of the medium, intensity of agitation of the drug. The observed disintegration times for all the brands of Metformin hydrochloride was less than the 30-min limit prescribed by the official compendium (Table 2). All tablets of the different brands passed the disintegration test. The fastest disintegrated tablets were of brand E and G while the slowest one was brand D even though their active drug release pattern and potency 96.68%, 483mg, 95.86%.479mg, and 95.86%.479mg, respectively. From above analyzed cleared that all branded samples within the standard but small variation in strength of tablets, it was might be while handling active powders. Dissolution of drug from oral solid dosage forms is an important aspect for drug bioavailability (i.e., the drug must be solubilized in the aqueous environment of the gastrointestinal tract to be absorbed). Accordingly, dissolution testing of solid oral drug products has emerged as one of the most important control tests for assuring product uniformity and batch-to-batch equivalence.

According to the monographs in British Pharmacopoeia, each tablet tested for dissolution, the amount of active ingredient in solution is less than 70% of the prescribed or stated amounts. In the present investigation, the release of Metformin hydrochloride from all tablets was immediate release and the percent of drug released at 30 and 45 mins were more than 70% as shown in Table 2. The results obtained from this study revealed that all the brands passed the USP 32 general specifications standard for dissolution rate test for conventional release tablets. The fastest disintegration samples B, G pattern of drug release 98.35 and 95.86% which were within the range of BP and USP Standard. Dissolution profile curves of all the samples were compared using similarly factor $f_2$, $f_2$ statistical methods all the tested samples values greater than 50 which show that selected branded metformin tablets were standard.

<table>
<thead>
<tr>
<th>Branded sample</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
</tr>
</thead>
<tbody>
<tr>
<td>$F_2$ values</td>
<td>72</td>
<td>67</td>
<td>69</td>
<td>60</td>
<td>57</td>
<td>55</td>
<td>58</td>
</tr>
</tbody>
</table>

Chart of dissolution profile of all the 7 brands
Conclusion

There are several generics of metformin hydrochloride tablets available within the drug delivery system globally including Bangladesh after the expiration of patent on Glucophage, the innovator brand. The increasing level of use of metformin hydrochloride tablets in the 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 generic substitution. All the products have satisfactory results in respect of uniformity of weight, hardness test, friability test, thickness, disintegration and dissolution profiles and potency determinations. Every test related the evaluation of Metformin HCL 500mg tablets BP was successfully finished according to USP and BP. the important quality characteristics of Metformin HCL 500mg tablets BP are well defined and controlled. There are no outstanding quality issues that would have a negative impact on the benefit balance. The efficacy of these tablets were well established which lead to diabetes mellitus patient will get expected therapeutic effects and minimum side effects. Everything was satisfactory and consistent with that for the cross-reference product. The quality of the products were acceptable.so this study revealed that collected samples of metformin 500mg tablet available in Dhaka, Bangladesh manufactured accordingly to cGMP as well as other standard monograph.

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