doi.org/10.36721/PJPS.2019.32.6.REG.2709-2715.1

Pharmaceutical quality evaluation of different glimepiride brands marketed in Karachi (Pakistan): In pursuance to global issue of availability and affordability of quality medicines

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Abstract: Availability of economical quality medicines is always required for chronic disease management. Price differences among multiple brands of a product do not essentially displays low quality for the more affordable brand, however in a few occurrences it appears. Glimepiride, an oral anti-diabetic drug, is produced by several national and multinational industries in Pakistan with considerable cost variation. The study aimed to evaluate the quality and economy of various Glimepiride brands available in Karachi, specifically of public sector hospitals. For this, eight glimepiride brands were collected and analyzed for the pharmaceutical quality using physical parameters, disintegration test, dissolution profile, spectrophotometric assay and content uniformity. Pharmacoeconomic assessment was also carried out such as availability, affordability and price variation. A profound discrepancy was observed among the prices of selected brands. All of the products found to be equivalent to the reference product except G5, the most inexpensive and highest consumed product of a public sector hospital. Study concludes that products with higher quality and lesser price can be used as a substitute to the costly brands while availability of a substandard product looks for consideration of pertinent authorities to assure the distribution of quality medicines.

Keywords: Pharmacoeconomics, pharmaceutical quality, glimepiride.

INTRODUCTION

Product quality is an indicator to its adequacy and efficiency. Quality parameters are the accepted specifications that expect to focus on the desired attributes of the product (Salgueiro *et al.,* 2010). Such quality procedures are valuable tools for drug consistency and are fundamental to perform for each drug product. Drugs with multiple generic products stand in need for their chemical and biopharmaceutical equivalency (Chandrasekaran *et al.,* 2011). Pharmacoeconomics deals with the monetary assessment of pharmaceuticals to which expenses and impacts of substitution treatment are correlated. Cost-benefit assessment is a sort of economic analysis which bargains costs with outcomes in fiscal terms (Drummond, 2006).

Affordability is the way to availability. In advancing the healthcare framework of developing countries, less expensive medications and economical health services can bring incredible impacts (Mazumdar-Shaw, 2018). In the modern world, one of the greatest challenges is to add quality with relaxation in cost for healthcare services (Batalden *et al.,* 1996). In spite of the fact that the motivation behind presenting multi-source generics was to advance the common health services of financially underdeveloped nations, it has been trailed by the extended circulation of incompetent and substandard items (Adegbolagun *et al.,* 2007). An investigation in Italy compared the bio-equivalency of two marketed amoxicillin products and results uncovered that a generic product did not meet the acknowledgment criteria of pharmacokinetic appraisal (Del Tacca *et al.,* 2009). With a specific end goal to deliver safe and quality drugs to patients at a sensible price, it is especially basic to test distinctive products that are accessible in a region (Fatima *et al.,* 2013). Remembering, appropriate use of medicines contributes to the public health while inadequate use results in endangering the health and wasting resources, including scarce utilization of safe generic products, availability of substandard medicinal products in government sector health facilities and counterfeit products in the market (Wagner *et al.,* 2014).

Diabetes Mellitus, a metabolic disease, has become a serious threat to populace's health universally and its management cost is to a great extent expanding. The costly diabetes care puts financial load on the patients especially in immature countries where dominant part of the general population are surviving the neediness limit. For every diabetic person in Pakistan, the yearly average direct cost is likely to be 11,580 PKR and a major portion of immediate cost i.e. 46% is accounted by pharmaceuticals. It is, therefore, important to lead cost effective studies to limit the monetary weight and expand the medical advantages (Khowaja *et al.,* 2007).

Glimepiride is a widely used sulfonylurea derivative, incorporated in the regimen of type 2 diabetes therapy. It is the main decision among different sulfonylureas in view of its benign profile (Onuma *et al.,* 2014). It brings

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down blood glucose levels by energizing pancreas to discharge insulin. Glimepiride enjoys complete GI absorption, has distribution throughout the body and extensively binds to plasma protein. It undergoes oxidative metabolism in liver and 60% is eliminated through urine while remaining in feces (Dwivedi *et al.*, 2013). Because of its low solubility and high permeability, glimepiride is specified under class II of biopharmaceutical classification system (Nagpal *et al.*, 2012). On account of its provoke beginning of activity and extended span of glucose level lessening, glimepiride is the preferred medication among other traditional sulfonylureas (Klepzig *et al.*, 1999).

A study detailed that in Pakistan, generic products are promptly accessible in the public sector hospitals while the availability of expensive pioneer brands in private divisions is altogether higher (Mendis *et al.*, 2007). Globally, several researches have been conducted in the same perspective of quality versus price comparison. Quality evaluation of pharmaceutical products marketed with fluctuating prices, in Pakistan, was carried out by, Hussain *et al* on twelve ciprofloxacin brands (Hussain *et al.*, 2013), Israr *et al* on four cefuroxime axetil tablets (Israr *et al.*, 2016), while Hettiarachchi *et al* compared different Metformin HCl marketed brands in Sri Lanka (Hettiarachchi *et al.*, 2015).

The best substitute for costly lead brands are the generic drug products, not only in terms of low price but also quality, efficacy, and safety (El-Dahiyat, 2017). As glimepiride being manufactured by more than 60 pharmaceutical companies across Pakistan with variable prices, there might be the possibility of availability of substandard products. The purpose of this study was to evaluate different glimepiride (2mg) brands available in public and private sector hospitals, as well as local pharmacies of Karachi (Pakistan). The collected test products were then compared with the expensive and quality reference product using physicochemical parameters such as weight variation, thickness, diameter, hardness, friability, disintegration test, dissolution profile comparison, assay and content uniformity. Pharmacoeconomic features were also addressed such as availability and affordability of products, and price variation among different brands.

MATERIALS AND METHODS

Materials and equipment

Reference glimepiride sample was gifted by Sanofi Aventis Pakistan Limited. Eight different glimepiride brand products were purchased from some retail pharmacies and renowned public as well as private sector hospitals of Karachi (Pakistan). Sodium hydroxide (Merck, Germany), potassium dihydrogen phosphate (Merck, Germany) and distilled water (freshly prepared) were used for the analysis.

For the chemical analysis of glimepiride content, UV-Visible spectrophotometer (Shimadzu, Japan) was used. Other equipment included electronic balance (Sartorius, Germany), friabilator (Co-D2800, Germany), disintegration basket rack assembly (Erweka ZT2, Germany), Vernier caliper (Seiko Brand), hardness tester (Campbell electronics), pH meter (Sartorius, Germany) and importantly dissolution paddle apparatus (Erweka DT 600, Germany).

Pharmacoeconomic evaluation

Price of pharmaceuticals is an affair of interest for people who cannot manage the cost of expensive products. In Pakistan, medicines are manufactured either by national or multinational companies and their product cost vary respectively. A humble survey was led for this examination to investigate the availability of glimepiride brands in public hospitals, private health centers and retail drug stores of various areas in Karachi. After the review, eight glimepiride brand products with fluctuating prices were chosen and analyzed. The products were granted specific codes from G1 to G8 (G1 assigned for reference brand).

Pharmaceutical evaluation

Physical parameters

Weight variation is an important pharmaceutical test related to the constancy of the drug substance. Twenty tablets from each selected brand were weighed singly in order to determine any variation in the tablet weight.

Thickness and diameter of a tablet are those parameters which are generally connected with the packing operation and their deviation highlights packaging issues. A digital Vernier caliper, initially set to zero, was employed in order to determine the dimensions of twenty tablets from individual brand. Reading was noted after placing the tablet between two jaws of caliper.

Crushing strength of tablets is usually assessed by exposing the tablets to a diametrical failure test. Tablet hardness leads to its slow disintegration. For the test, ten tablets from each brand were selected, subjected to hardness tester and the tablet breaking point was noted.

Mean and standard deviation of above mentioned physical parameters were calculated with the help of MS Excel 2010.

The potential of tablets to combat abrasion during packaging, transportation and handling is determined by the friability test. Ten tablets from each formulation were weighed accurately and placed in the friabilator chamber, rotated for 4 minutes at 25 rpm for 100 revolutions. After four minutes, tablets were weighed again and their initial and final weights were compared. Pharmacopeia specifies percent friability less than 1% as the acceptable criteria for tablet friability test (B.P., 2013).

Table 1: Price variation among different glimepiride brands (2mg)

S. No.	Brand	Lot No.	Mfg. Date	Exp. Date	Manufacturer	Unit Price (PKR)	Price variation with innovator
1	G1	WE008	Feb 2015	Jan 2018	Multinational	15.53	innovator
2	G2	311T11	Dec 2015	Dec 2018	National	8.3	46.50%
3	G3	6A078	Jan 2016	Jan 2018	National	8.3	46.50%
4	G4	5002	Apr 2015	Apr 2018	National	4.95	68.10%
5	G5	6452	Nov 2013	Nov 2016	National	4.5	71%
6	G6	27	Apr 2016	Apr 2018	National	7.25	53.30%
7	G7	A9259	May 2016	May 2019	National	5	67.80%
8	G8	P03848	Nov 2015	Nov 2018	National	8.3	46.50%

Table 2: Availability and unit consumption/day of glimepiride brands

Brand	Procured from	Unit Consumption/Day
G1	Private sector hospital tertiary care	70-120
G2	Public sector hospital tertiary care	200-300
G3	Public sector hospital tertiary care	80-90
G4	Public sector hospital tertiary care	100-150
G5	Public sector hospital tertiary care	400-500
G6	Retail pharmacy in West Karachi	60-80
G7	Public sector hospital tertiary care	400-500
G8	Retail pharmacies in Central and East Karachi	40-50

Table 3: Statistical Analysis of physical parameters of eight glimepiride (2mg) brands

Brand code	Average weight mg ± S.D	Thickness mm ± S.D	Diameter mm ± S.D	Hardness kg ± S.D
G1	170.24±2.19	2.93±0.03	10.21±0.03	6.44±0.24
G2	174.24±1.65	2.77±0.04	10.22±0.02	5.53±0.20
G3	99.91±2.22	2.63±0.05	8.70±0.03	6.37±0.34
G4	200.66±4.10	2.49±0.04	9.04±0.02	7.33±0.31
G5	103.25±2.46	2.79±0.04	5.93±0.02	7.79±1.31
G6	197.48±4.11	2.56±0.03	10.05±0.02	6.98±0.55
G7	171.96±3.46	2.85±0.06	9.96±0.06	4.99±0.13
G8	158.96±4.77	2.96±0.05	8.09±0.05	5.93±0.47

Table 4: Analytical parameters for glimepiride estimation

λmax	211 nm
Molar absorptivity (ϵ)	70.443 M–1 cm–1
Linearity	
• Range	0.00313-0.05 mg/ml
• Correlation coefficient	1
• Slope	70.443
• Intercept	0.0051
• SE[1]of intercept	0.004622
• SD[2] of intercept	0.010335
Recovery range (%)	98.09-99.82
Accuracy (%) ± SD	98.69±0.74
Precision	0.75495
LOD (mg/ml)[3]	0.000484
LOQ (mg/ml)[4]	0.001467

[1] SE = standard error, [2] SD = standard deviation, [3] LOD = (Limit of Detection), [4] LOQ = (Limit of Quantification)

Table 5: Similarity Factor of different glimepiride brands

Brands	f2 value	Is f2 ε[50,100] between Mean Reference and Mean Test	Similarity of Reference and Test
G1	Reference		
G2	84.62	Yes	Accept
G3	88.06	Yes	Accept
G4	76.86	Yes	Accept
G5	31.63	No	Reject
G6	67.70	Yes	Accept
G7	65.44	Yes	Accept
G8	79.64	Yes	Accept

Disintegration test

It is an imperative testing that verifies time in which a tablet breaks up into fragments under experimental set-up. The test was conducted on randomly selected six tablets using distilled water as a medium, maintained at 37±2°C. The disintegration time was recorded for all the tablets. The test was repeated for each glimepiride brand.

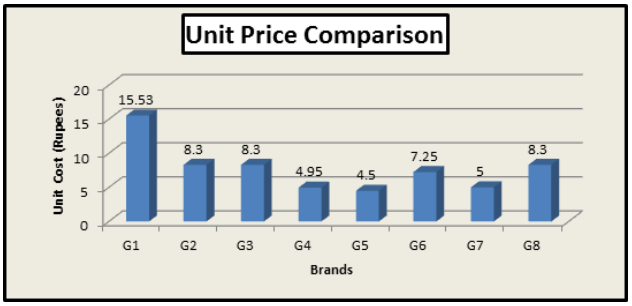

Fig. 1: Unit price comparison of different glimepiride (2mg) brands

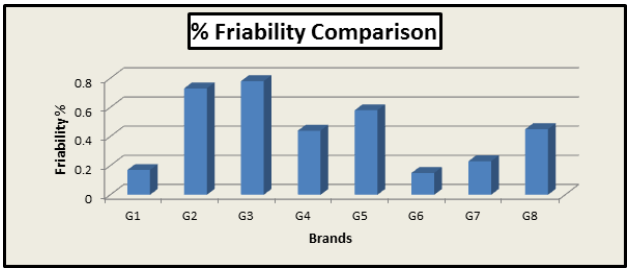

Fig. 2: Percent friability comparison of different glimepiride (2mg) brands

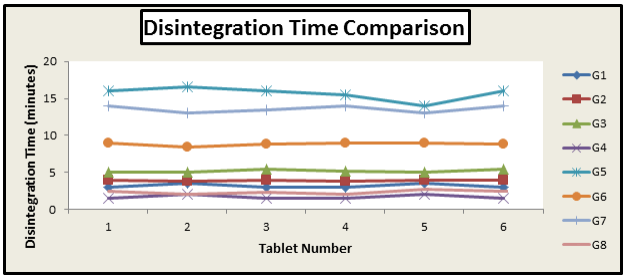

Fig. 3: comparison of disintegration time of different glimepiride (2mg) brands

Assay and content uniformity

Assay of tablets is carried out to examine if the tablets have a similar measure of active ingredient as indicated by specifications. Test for uniformity of content assures the consistency of dosage units within a batch.

Validation of analytical method

For the assay of glimepiride tablets, a developed reported spectrophotometric method (Bonfilio *et al.*, 2011) was employed, which was validated prior to performing assay. λmax determination, linearity and range, accuracy, precision and sensitivity were the parameters on basis of which analytical method was validated.

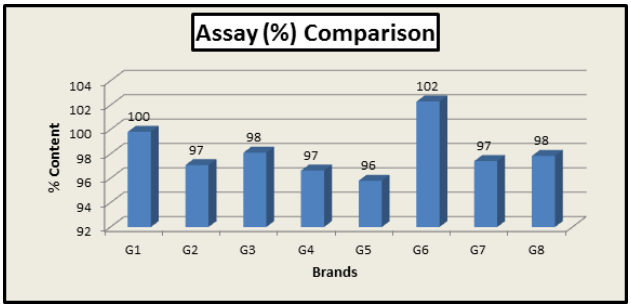

Fig. 4: Assay (%) comparison of different glimepiride brands

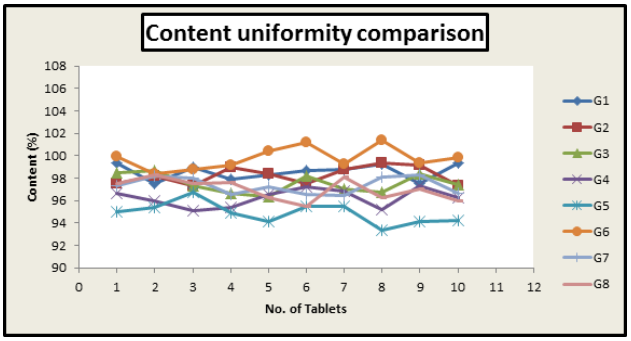

Fig. 5: Content uniformity (%) comparison of glimepiride brands

Standard Preparation

5 mg of glimepiride was dissolved in 100 ml of 0.005M NaOH to prepare stock solution. From this standard solution, further aliquots were made using 0.005M NaOH as diluent.

Sample Solution Preparation

For assay of tablets, twenty glimepiride tablets were weighed and crushed. The average glimepiride tablet

mass having 2 mg of active substance was withdrawn from powder, transferred into a 100 ml volumetric flask and dissolved in 0.005M NaOH solvent. This sample solution of concentration 0.02mg/ml was then filtered before running on spectrophotometer.

In case of content uniformity test, individual glimepiride tablet was crushed to powder and dissolved in solvent i.e. 0.005M NaOH. The remaining procedure was followed in the same manner on 10 tablets from each formulation. According to USP, 10 individual units of a solid dosage form must be analyzed for the content uniformity.

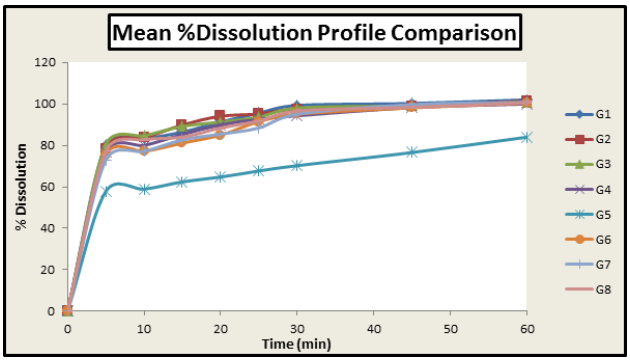

Fig. 6: Dissolution profile comparison of eight glimepiride brands

Dissolution test

Dissolution test is an obligatory test in determining the drug release and bioavailability of an oral solid dosage form. For comparison of different glimepiride brands, multiple point dissolution profile was established using six tablets of each formulation, as per standard. Dissolution paddle apparatus was operated at 75 rpm using 900 ml medium of phosphate buffer pH 7.8 (USP34-NF29, 2010, Revision Bulletin December 1), maintained at 37±0.5^{o}C temperature. 10 ml of the sample was pipette out after spells of 5,10,15,20,25,30,45 and 60 minutes. After each sample withdrawal, fresh medium was introduced to the system. Each sample solution (containing 0.0022mg/ml of active glimepiride) was then filtered, and analyzed using UV spectrophotometer at 211 nm (wavelength obtained after assay method validation) against dissolution medium. The dissolution profiles of eight glimepiride brands were assessed by the comparison of f2 similarity factor using an add-in program DDSolver (Zhang *et al.*, 2010).

Standard preparation

2 mg of standard Glimepiride substance was accurately weighed and dissolved in 100 ml of phosphate buffer pH 7.8 (dissolution medium). 11 ml of this stock solution was diluted to 100 ml with dissolution medium and filtered, producing final standard solution of concentration 0.0022mg/ml.

RESULTS

Pharmacoeconomic evaluation

In this study, quality and price of glimepiride generic products were compared with that of innovator brand (G1) and so interchangeable brands were identified. Table 1 represents the price difference among eight glimepiride (2mg) brands, their label information and nature of the manufacturer. Price variation was calculated using the following formula:

$$\% \text{ Price difference} = \frac{\text{Price of reference brand} - \text{Price of test brand}}{\text{Price of reference brand}} \times 100$$

A more clear illustration of unit price comparison is demonstrated in Fig. 1, indicating vast difference among the prices. Table 2 shows unit consumption (per day) of each brand and from where it was procured.

Pharmaceutical evaluation

Statistical Analysis of physical parameters

Physical parameters such as weight variation, thickness, diameter and hardness were performed according to the specifications, to analyze the pharmaceutical equality among selected brands. The statistical analysis of these physical parameters is mentioned in Table 3.

The percent friability of ten tablets of each glimepiride brand existed within the acceptable limit of less than 1% (fig. 2).

Disintegration test

Disintegration time of six tablets of each of the tested brand is shown in fig. 3.

Assay and content uniformity

After re-validation, the reported analytical method was revealed to be linear, accurate and precise on the basis of analytical findings mentioned in table 4.

The method was, therefore, used to detect the amount of active drug substance present in tablets of glimepiride brand. For glimepiride, USP specifies that 90%-110% of the labeled drug amount must be present in each dose unit (USP34-NF29, 2010). Results of assay and content uniformity are represented in fig. 4 and fig. 5 respectively.

Dissolution test

Multiple-time point sampling was made for the dissolution profiles comparison of test products with that of reference brand. Fig. 6 compares drug release profiles of eight glimepiride tablet brands. Similarity among reference and test products was also determined by calculating f2 value as shown in Table 5.

DISCUSSION

In Pakistan, prevalence of diabetes mellitus has highly increased over the years, and more than 10% of its adult populace is suffering with this chronic disorder. The

majority of Pakistani public lives at or beneath the poverty threshold and consumption of 18% of their total earning on diabetic care brings financial burden on them (Shaikh, 2009). Utilization of less expensive generic medicines marketed by local manufacturers has been monetarily effective in compressing expenses and promoting affordability of drug products in Pakistan (Jamshed *et al.,* 2009).

Accessibility to affordable medicines has become a leading health dispute around the world. The role of a strong regulatory system is crucial in ensuring the circulation of low-priced quality medicines (Piniazhko *et al.,* 2018). Improvement, in this regard, can consequently enhance social health and welfare globally (Campbell and Kaló, 2018).

The present study noticed that the prominent private hospitals in Karachi were dispensing the leading glimepiride brand whereas the generics were available mostly in public healthcare facilities and retail drug outlets. According to results of pharmacoeconomic evaluation, a brand coded G5 was found to have a significant price difference of 71% with innovator (table 1, fig. 1). Among eight brands, G5 was the highly consumed glimepiride product of a tertiary care public sector hospital in Karachi (table 2). Fluctuation in price has been a serious matter related to drug quality in communities where there is lack of regulation. Pharmacoeconomic studies can aid in lowering treatment cost for patients, which would lead to such further studies (Bano *et al.,* 2011).

Tablets of selected brands were also subjected to different pharmaceutical quality testing. Results revealed that average tablet weight of all brands lie within the acceptable limits, where G2 possessed least and G8 owned highest value of standard deviation. Thickness and diameter of all tested brands were maintained within the control limits. Prominent variation in the hardness of G5 tablets was observed as indicated by the highest standard deviation value (Table 3). None of the brand failed in friability test (fig. 2).

It was discovered that the tablets of most of the brands disintegrated within 5-10 minutes but five tablets of brand G5 did not disintegrate in the required time limit of 15 minutes (fig. 3). G5 glimepiride brand was found to have the highest hardness and disintegration time among various brands. Delay in tablet disintegration could profoundly affect *in-vivo* drug release and consequently bioavailability.

It is obvious from the findings that all the glimepiride brands contained more than 90% of the chemical content, according to the results of assay and content uniformity test (figs. 4-5), hence obeyed the pharmacopeial criteria.

Comparison and analysis of dissolution profile can be used to evaluate the in-vitro equivalence among reference and test products. Dissolution profiles of different brands can be analyzed by ANOVA-based, model-dependent and model-independent methods (Khan *et al.,* 2013). For the current study, model independent approach was used, employing similarity factor f2 as an aid to determine the equivalence of various brands. A value of f2 between 50 and 100 reflects similar dissolution profile. It is evident from Table 5 that the majority of the test brands have effectively discover the comparability with the reference product aside from one. Brand coded G5 failed to establish similarity with the reference mark, as its f2 value found below 50. It should be noted that G5 brand was the most inexpensive product of a public sector hospital with the highest consumption, prescribed to type 2 diabetic patients.

Increased prices of patented medicines affect the consumer directly if there is a lack of competitive cheaper generic products. Along with other elements, prescribing generic drugs can improve medicine accessibility and decrease pharmaceutical expenses (Halpenny, 2016). There is a need for quality improvement and accountable regulations in the healthcare sector by implementing exemplary initiatives taken by certain nations (Mainz *et al.*, 2015).

CONCLUSION

This study concludes that most of the tested brands produced by local manufacturers possess fulfilling quality and could be used as a substitute to the costly reference brand(s). Moreover, exceptionally low cost of medicines may influence their quality particularly those endorsed out in public sector hospitals. Such investigations seek attention of relevant authorities to regulate the supply of valuable standard medications with reasonable prices.

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