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Research Article

PHARMACEUTICAL QUALITY ASSESSMENT OF GLIMEPIRIDE TABLETS – COMPARISON OF BRANDS AND NEWLY FORMULATED TABLETS WITH INNOVATOR

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ABSTRACT

Objective: The main objective of the study was to assess the quality attribute of generic brands and newly formulated tablet of glimepiride and compare their drug release profile with innovator brand.

Methods: Different brands were purchased from different markets of UAE. The validated high-performance liquid chromatography method was used to assess the quantitative analysis of glimepiride. The linearity of curve (r^2 = 0.9999) indicated the accuracy and precision of the analytical method. Comparative dissolution of newly formulated and generic tablets was carried out using USP dissolution apparatus II. Study was accomplished in phosphate buffer (pH = 7.8), the paddle speed was adjusted at 75 rpm. F_1 and F_2 factor among the brands and kinetic assessment were done to obtain the order of release.

Results: Dissolution profiles of formulated tablets were almost same as that of innovator, 91.53 and 94.9, respectively, in 15 min. The statistical value between the different brands (F = 3.698) indicated that there were some differences among the few groups of tablets and p-value (0.002154) indicated that it supported H1 hypothesis. First-order and Weibull models described the drug release with r^2 value of 0.9981–0.927210 and 0.9992–0.9835, respectively. Stability of optimized formulated batch was also examined.

Conclusion: It was concluded that the formulated tablets are stable and pharmaceutically as good as the innovators; however, all the selected brands could not be used interchangeably in the clinical practice. It was also concluded that the scrutiny and screening of the drug products, available in the markets, can help to build a better health-care setup.

Keywords: Comparative dissolution behavior, Glimepiride, High-performance liquid chromatography method of analysis, Pharmaceutical quality assessment, Stability study of tablets.

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INTRODUCTION

Glimepiride is useful in the treatment of non-insulin dependent diabetes mellitus [1,2]. It is 1-(p-(2-(3-ethyle-4-methyl-2-oxo-3- pyrroline-1-carboxamido) ethyl) phenyl) sulfonyl)-3-(trans-4-methylcyclohexyl) urea which belongs to third generation of hypoglycemic sulfonylurea. The use of oral antidiabetic drugs is more preferred as compared to other routes for the treatment of disease. The basic objective of these drugs is to control the glycemic condition of patients by controlling and avoiding hypoglycemia and weight gain that helps to decrease the risk of potential micro- and macro-vascular impediments [3].

Glimepiride falls in BCS Class II, it has low solubility and high permeability making it difficult to manufacture tablets with good dissolution rate that consequently affects the systemic availability of drug in the body. In 2007, Adegbolagun *et al*. [4] suggested a need to analyze and evaluate the generic brands available in the market. These drugs should be analyzed for their chemical and biopharmaceutical equivalence, strength, quality, purity, and releasing profile of active ingredient in comparison of innovator drug.

The aim of the present study was to assess the characteristics of different brands and newly formulated immediate release tablets [5] and compares their dissolution profile with innovator brands. The focus of the study was to verify and optimize the new formulation as well as to evaluate the quality of generic brands available in different market of UAE (Ras Al Khaimah, Dubai, and Abu Dhabi). These brands of glimepiride were manufactured by different pharmaceutical companies, including UAE, Saudi Arabia, Pakistan, Jordan, and India. The study was also concentrated on the suitability of the newly formulated tablets which was estimated by accelerated stability studies. Consequently, the study was performed to provide the guideline to the physicians and pharmacists on the basis of which they can select the appropriate brands for their patients.

METHODS

Glimepiride reference powder (purity 99.61%) was obtained as a gift sample from Julphar, Ras Al Khaimah, UAE. Brands of glimepiride tablets purchased from UAE (Ras Al Khaimah, Dubai, and Abu Dhabi), Lactose monohydrate (VWR International, Germany), Microcrystalline cellulose (Fluka–Biochemika, Germany), Polyvinyl Pyrrolidone K-30 (PanReac–AppliChem, Italy), Sodium Starch Glycolate (Gift sample from Julphar), Mg stearate (Sigma Aldrich, Germany), and all other chemicals and solvents such as methanol, acetonitrile, and phosphate buffer used were of analytical reagent grade.

Method of analysis

To achieve the consistent, reliable, and accurate data for the analysis of drug in dosage form, reported high-performance liquid chromatography (HPLC) [6] analytical method was first validated as per ICH guideline [7] and was then used to estimate glimepiride in marketed as well as in newly formulated tablets [5].

Mobile phase preparation

Accurately, weighed 0.5 g of monobasic sodium phosphate was taken and dissolved in 500 ml of double distill water. It was thoroughly mixed and the pH was adjusted at 2.4 with 10% orthophosphoric acid.

Acetonitrile with phosphate buffer in the ratio of 1:1 was added, mixed, and filtered through 0.45 µm Millipore filter paper.

Calibration curve and estimation of glimepiride

A series of dilutions was prepared in the diluent mixture (ACN: H_2O; 9:1) according to the study design [5]. The concentrations of these solutions were 2.5, 5, 7.5, 10, and 12.5 µg/ml, respectively. Absorbance of the solutions was measured at λ = 228 nm.

Experimental Design

In vitro pharmaceutical quality of different brands of glimepiride tablets was estimated to establish the *in vitro* bioequivalence among the different generic brands. The preliminary information of different brands was used to construct the basic design and formula for new tablets [5] and then to compare this newly formulated tablets with different brands to verify and confirm the *in vitro* equivalency of it.

Optimized formula for new tablets

Using the basic idea of formulation from innovator tablet (Glim-A; 2 mg), new tablets of glimepiride were prepared by Slurry method [5]. Total ten formulations were designed using different composition of polyvinyl pyrrolidone K-30, Crospovidone, tween 80, and sodium starch glycolate. The following composition was selected as finally optimized Batch/check point batch (G10) with dissolution rate of more than 90% in 15 min (Table 1).

Pharmaceutical evaluation of marketed and newly formulated tablets

Different brands of glimepiride are available in the market of UAE. Out of them, eight brands were selected and evaluated for weight variation, hardness, disintegration, wetting time, and content assay. The release profile of drug from their tablets was estimated and compared by different statistics.

Drug release kinetics studies

The dissolution tests were carried out using the Type-II apparatus (paddle), at 75 rpm. Dissolution was done in phosphate buffer (pH 7.8) with multipoint sampling at different time intervals of 5, 10, 15, 20, 30, and 45 min and analyzed by HPLC method at λ_{max} = 228 nm.

The dissolution data of prototype tablets (G10) were analyzed with various kinetic equations in comparison to generic (Glim-B - H) and Innovator tablets (Glim-A), to understand the kinetic release and ability of the tablets [8,9].

Stability studies

One of the most important pharmaceutical parameters to assess the quality of any newly designed formulation is the stability of the drug in its dosage form. After the quality assessment of tablets, G10 was kept for stability for 3 months (0, 1, 2, and 3 months) under accelerated conditions, 40±2°C; 75±5% R.H, as per the ICH guidelines [10].

RESULTS AND DISCUSSION

Glimepiride is used to reduce both fasting and postprandial blood glucose. These reductions are dose dependent over a range of 1–8 mg daily [11]. On the other hand, it is a poorly soluble drug that makes it difficult to maintain the consistency of quality and performance. The performance of solid tablets depends on the release of the drug from their dosage form. *In vitro* dissolution or drug release is supposed to work as a powerful tool in the measurement of quality attributes of new formulation as well as for the assessment of generic products.

In 2018, Ministry of Health and Prevention issued a circular on withdrawal of diabetic medicine from the UAE market [12]. Under these situations, time to time review of post marketed generic drug products is expected to not only improve the overall health delivery systems [4] but also to reduce the cost of treatment, especially for the low-income developing countries [13]. Moreover, the distribution of these generic brands may be associated with many problems due to fake, counterfeit, and substandard quality of drug products that are main triggers for morbidity and mortality [14, 15].

In 2011, the International Diabetes Federation (IDF) estimated 366.2 million adult populations with diabetes, which is estimated to grow by 51%–551.8 million by 2030 [16]. Glimepiride is widely used as monotherapy or in combination with insulin for diabetes mellitus type II [17]. However, UK Prospective Diabetes Study (UKPDS), American Diabetes Association (ADA), and UK National Institute for Health and Clinical Excellence (NICE) incorporated the findings of some research that sulfonylureas can increase risks of hypoglycemia, weight gain, and cardiovascular issues [18, 19].

Different studies revealed that the generic products with the same amount and salt of active ingredient display differences in their therapeutic responses. Lot of generic products that are not interchangeable with their reference or some time even with each other, have been reported [16, 17, 20, 21] that makes it important to conduct the post-market evaluation of products to reduce the chances of error in the selection of good one for the patients.

For the accurate and precise analysis, it is important to validate the analytical method as per the availability and feasibility of the equipment before starting the estimation [5]. Calibration curve for glimepiride was constructed in the concentration range of 2.5–12.5 µg/ml and was found to be linear with the regression analysis (R^2) of 0.9999 (Fig. 1).

The series of tests defined by the pharmacopeias were conducted on different brands to evaluate their pharmaceutical characteristics and were compared with innovator to check and verify the quality attributes of tablets.

The weight variation of different tablets was calculated with their standard deviation, that is, between 141.15±1.80 and 200.95±1.61, whereas the newly formulated tablets showed more consistency in their weight with less SD 170.45±1.04. In 1993, Gupta [22] investigated that hardness depends on the nature and quantity of excipients. The results of study showed that the proportion of selected excipients for

Table 1: Optimized formula for new tablets (G10)

Materials	Formulation G10 (mg/tablet)
Glimepiride (API)	2
Lactose monohydrate	136
Microcrystalline cellulose	20
Polyvinyl Pyrrolidone K-30	1
Tween 80	2
Sodium Starch Glycolate	8
Mg stearate	1
Total weight	170

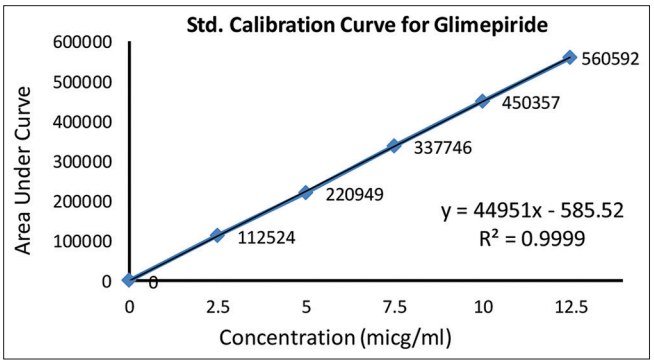

Fig. 1: Calibration curve (linearity)

Table 2: Pharmaceutical evaluations of G10 and marketed tablets

Brand Name	Weight variation±SD	Hardness (Kp)±SD	Friability (%w/w)±SD	Wetting time (Sec)±SD	Disintegration time (Sec)±SD	Drug content (%)±SD
Glim-A (Innovator)	170.2±1.43	3.98±0.106	0.20±0.002	90.00±0.92	77.50±0.11	102.3±0.75
G10 (Formulated)	170.45±1.04	4.35±0.104	0.11±0.014	94.00±1.55	96.8±1.22	100.34±0.66
Glim-B	141.15±1.80	3.95±0.097	0.21±0.01	4.80±1.73	3.00±0.07	102.01±0.11
Glim-C	170.5±1.85	4.3±0.100	0.12±0.003	72.00±2.23	93.75±0.78	99.93±0.45
Glim-D	169.5±1.83	2.73±0.110	0.26±0.023	64.00±3.11	236.5±0.88	98.76±0.32
Glim-E	169.75±1.80	4.38±0.097	0.14±0.006	118.00±3.15	88.75±0.75	100.9±1.10
Glim-F	168.65±1.98	4.05±0.092	0.17±0.012	30.00±1.66	44.50±0.63	104.3±0.99
Glim-G	141.35±1.95	3.43±0.080	0.18±0.004	45.00±3.43	44.00±0.33	100.3±1.33
Glim-H	200.95±1.61	4.08±0.100	0.30±0.014	78.00±3.87	190.75±0.17	97.9±0.65

SD: Standard deviation

new tablets (G10) was appropriate as the hardness was 4.35±0.104 which was more than innovator tablets (Table 2).

The results of disintegration test presented that Glim-D was disintegrated in 236.5±0.88 sec (3 min and 57.5 s), which was the highest time and Glim-B was within 3.0±0.07 s. Disintegration time of G10 is 96.8±1.22 s (1 min and 36.8 s) which is extremely near to that of innovator, that is, 77.50±0.11 s (1 min and 17.5 s). In case of glimepiride, dissolution rate is considered as the rate limiting step for the drug absorption. In the illustration of formulated tablets [5], the targeted time for disintegration was kept <5 min (300 s), the concept was to facilitate faster disintegration to improve overall dissolution and solubility of drug (Table 2).

All the eight brands have no statistically significant difference in drug content (97.9–104.3%). The percentage content of G10 was 100.34±0.66 that indicated the uniformity of powder blend. Wetting time was performed with three units of each marketed brand and the results were in the range of 4.80±1.73–118.00±3.15 s whereas G10 has 94.00±1.55 s showing a good relationship with disintegration time (Table 2). Robustness and strength of tablets were checked by friability test. Veego Friability Apparatus was used to test the friability according to the USP and NF as shown in Table 2. The friability of G10 was found 0.11±0.014, which indicated the durability and potential of tablets required for their transit.

***In vitro* drug release**

Ninety percent of drugs are administered through oral route, so if the dissolution of the drug is slow, it leads to subsequently incomplete absorption and low bioavailability. The dissolution rate was estimated by validated HPLC method. This analysis was carried out to estimate whether the generic brands and newly formulated tablets had capability to release the drug as that of their innovator. G10, Glim-A, B, C, E, and F showed more than 85% in 15-min, Glim-G and Glim-H showed more than 85% in 30 min whereas the Glim-D released <85% even after 45 min (Fig. 2).

To confirm the releasing pattern of drug from these brands, ANOVA was also applied to estimate the variation among the brands [23]. The statistical value (F=3.698) indicated that it is not in the p<0.05 critical value accepted range: (−∞: 2.1521), so there were some differences among the few groups of tablets (Table 3). P-value is also smaller (0.002154) which indicates that it supports H_1 hypothesis (Fig. 3).

In addition, the similarity and difference factor (F_1 and F_2) among the brands was also evaluated using Glim-A (innovator) as reference standard [24]. The results indicated that Glim-D did not comply with the F_1 factor having 32.66% of difference. Whereas, three brands (Glim-C = 48.62; Glim-D = 26.98, and Glim-H = 44.08) did not comply with the F_2 factor (Table 4). At the same time, newly formulated tablets were also compared with innovator to estimate the f_1 and f_2 factors which were 7.02 and 56.77, respectively.

The dissolution data were also analyzed with various kinetic equations in comparison to Innovator (Glim-A). These kinetic models were estimated using DD solver (version 1.0). The Table 5 shows that the batches of formulations failed to obey the zero-order and Higuchi

Table 3: Single factors analysis of variance (ANOVA) for % dissolution of marketed brands+G10

Source of variation	SS	df	MS	F	p-value
Between Groups	5191.03	8	648.88	3.698	0.002154
Within Groups	7896.96	45	175.49		
Total	13087.99	53	246.94		

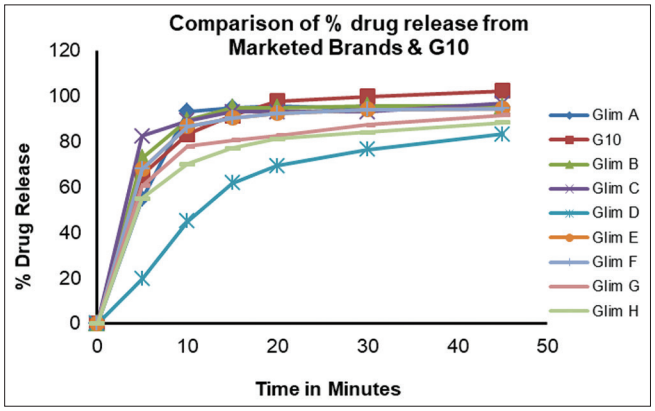

Fig. 2: Comparative graphical presentation of % dissolution profile of marketed brands and formulated tablets (G10)

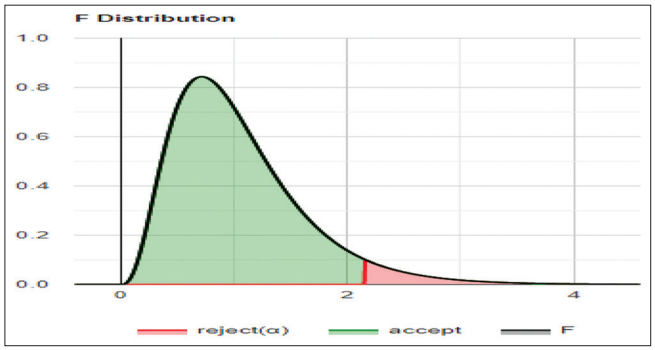

Fig. 3: Graphical presentation of F value

kinetics. Whereas, first-order and Weibull models describe the drug release with R^2 value of G10 = 0.9905 and 0.9991, which is very similar to Glim-A for both model, that is, 0.9396 and 0.9992. The generics brands also obey the first-order kinetics and Weibull models with R^2 = 0.9981–0.9272 and 0.9975–0.9835, respectively. The first-order model helps to describe the relationship between pharmaceutical dosage form and the release pattern of drug from it. Glim-C, D, G, and H along with G10 showed good commitment with Hixson-Crowell Model as compared to the Glim-A, B, E, and F that confirmed the size distribution study indicated most of the particle fell in the same size range.

Table 4: Similarity and difference factor (F1 and F2) among the brands+G10

Parameters	G10	Glim-B	Glim-C	Glim-D	Glim-E	Glim-F	Glim-G	Glim-H
f_1 value	7.02	4.68	7.33	32.66	5.26	5.26	11.07	13.65
f_2 Value	56.77	57.58	48.62	26.98	61.18	61.18	50.01	44.08

Table 5: Kinetics study of drug release for marketed and formulated tablets

Parameter	Glim-A	G10	Glim-B	Glim-C	Glim-D	Glim-E	Glim-F	Glim-G	Glim-H
Zero-order – model									
k_0	2.383	3.264	2.404	2.409	1.912	2.358	2.358	2.226	2.139
R^2	0.4871	0.7917	0.5949	0.8097	0.8280	0.6593	0.6593	0.8258	0.8231
First-order – model									
k1	0.189	0.194	0.245	0.310	0.053	0.206	0.206	0.140	0.111
R^2	0.9396	0.9905	0.9981	0.9272	0.9696	0.9964	0.9964	0.9752	0.9966
Higuchi model									
kH	18.928	19.366	16.994	17.046	12.752	16.602	16.602	15.499	14.841
R^2	0.6486	0.8758	0.7024	0.8807	0.9051	0.7599	0.7599	0.8974	0.9001
Hixson-Crowell model									
kHC	0.033	0.034	0.026	0.026	0.015	0.026	0.026	0.024	0.023
R^2	0.8484	0.9815	0.8693	0.9492	0.9642	0.9074	0.9074	0.9657	0.9862
Weibull model									
α	0.382	93.432	0.531	0.624	3.439	0.638	0.638	1.065	1.326
β	0.040	1.713	0.150	0.186	0.486	0.170	0.170	0.244	0.274
Ti	5.000	-9.626	4.913	3.448	4.471	4.847	4.847	4.021	3.775
R^2	0.9992	0.9991	0.9892	0.9835	0.9940	0.9975	0.9975	0.9945	0.9975

Table 6: Stability study of optimized prototype formulated tablets (G10)

Test	Open			Blister			Amber		
Duration	**1st Month**	**2nd Month**	**3ed Month**	**1st Month**	**2nd Month**	**3ed Month**	**1st Month**	**2nd Month**	**3ed Month**
Weight variation (mg)	174.25±0.024	172.4±0.014	173.6±0.021	178.7±0.05	178.2±0.046	178.1±0.045	172.5±0.015	174.7±0.027	174±0.023
% Drug release (After 15 min)	86.26±0.45	98.48±0.37	100.13±0.44	85.85±0.50	94.77±0.49	92.07±0.62	90.85±0.61	97.09±0.41	94.42±0.62
Hardness (Kp)	2.75±0.313	2.50±0.375	2.125±0.469	3.75±0.062	3.50±0.125	3.50±0.125	3.50±0.125	3.50±0.125	3.25±0.188
Friability % w/w	0.33	0.11	0.37	0.22	0.19	0.21	0.36	0.34	0.41
Disintegration time (sec)	101±0.11	89.0±1.31	99±1.34	87±2.02	100±1.97	105±1.27	111±0.83	67±0.92	88±1.99

The model dependent method, Weibull is considered as a good model in determination of differences among various formulations. No significant variations were found among all β values. The Weibull model provided the best adjustment curve for all the eight generic brands plus G10, with the higher determination coefficients R^2, that is, 0.9835–0.9992. These curves suggested the similarity in dissolution profile of all brands along with formulated tablets which help to estimate the amount of drug dissolved as a function of time (Table 5).

Stability studies of prototype formulated tablets

After the pharmaceutical analysis of G10 tablets, they were exposed to stability studies [25]. Tablets were kept at accelerated stability conditions (40±2°C and 75±5% RH) under the three conditions such as Alu/Alu blister, amber, and an opened container along with refrigerator for comparison with standard condition. After 3 months of storage, it was observed that the formulated tablets (G10) were not very much different from innovator tablets in terms of both drug content and dissolution profile. No significant variation was experiential that evidenced the stability of formulation at accelerated conditions (Table 6).

CONCLUSION

The validated HPLC method was used for the evaluation of glimepiride tablets. The comparison of dissolution profiles concluded that the release of drug from the generic tablets as well as from the selected prototype formulated tablets was same as that of innovator tablets. Based on the results, it was concluded that the newly formulated glimepiride tablets are as good in quality as innovator. It was also concluded that the approach used to prepare new prototype formula was found better in term of rapid disintegration and maximum dissolution. The results of study also concluded that time to time screening of marketed products gave the idea about the level of the therapeutic efficacy of different generics of same API. Based on the finding, it was suggested, the quality of brand must be considered before using them as interchangeable medicine.

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AUTHOR'S CONTRIBUTIONS

Each author has made great contributions to the work reported in the manuscript.

CONFLICTS OF INTEREST

There are no conflicts of interest between the authors for article contents

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