In-vitro Quality Assessment of Some Quetiapine Fumarate 25mg Tablet Brands Commercially Accessible in Bangladesh

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Abstract

Background: Quetiapine fumarate (QF) is a drug frequently prescribed to treat various psychotic conditions such as bipolar disorder and SCZ (schizophrenia). More than 50 companies in Bangladesh manufacture this generic.

Aim: The use of substandard or counterfeit medicines may worsen the disease condition and significantly reduce patient quality of life. As there is a vast opportunity to use low-cost generic products, we aimed this project to evaluate whether these QF brands meet the in-vitro quality control parameters for ensuring pharmacopoeial criteria.

Methods: Nine brands of QF 25mg tablets were purchased from a local model pharmacy in Kushtia, Bangladesh, and were serially named QF1 to QF9. All the quality control parameters, i.e., weight variation, friability, hardness, assay, disintegration, and dissolution profiles, were studied and compared according to pharmacopoeial specifications. We used two different medium types, pure water (DW) and 0.1N HCl, for both dissolution and disintegration studies.

Results: According to the results, all the QF brands passed the tests and met the USP/BP specifications. The highest and the lowest weight variation from the average limit was 2.86% and -4.23% for brands QF3 and QF7, respectively. The friability and hardness results varied between 0.01 to 0.17% and 4 to 8.09 Kgf for all tested tablets. The disintegration time for all the tablets ranged from 0.51-8.22 and 0.35-6.44 minutes in 0.1N HCl and distilled water, respectively. In terms of dissolution study, within 60 minutes, brand QF6 released the maximum 97.56% of its content, and QF9 released the lowest 88.33% in DW, while it was 99.28% (QF4) and 59.77% (QF5) in 0.1N HCl, respectively. The drug assay showed all brands contained 95.50% -103.87% of active QF.

Conclusion: Based on our findings, the brands complied with pharmacopoeia standards and specifications, with a few exceptions. So, the study concluded that the brands of QF were sufficiently safe and could be used to achieve the desired therapeutic outcome; however, further in-vivo studies are required to declare pharmacological equivalents.

Keywords: Quetiapine fumarate, Tablets, Pharmacopoeia, In-vitro, Quality control, Bangladesh

Introduction

Today, the pharmaceutical industry is the fastest-growing sector in Bangladesh. At present, there are about 300 drug manufacturing companies in Bangladesh. Almost 97% of the marketed products are produced by these local manufacturers, and the remaining 3% are imported. It is possible because of the quality of the product [1]. According to the International Organization for Standardization (ISO), "quality is a totality of features and characteristics of a product or service that bears its ability to satisfy stated or desired needs." A drug's quality must be considered during the product and process planning. It is affected by the manufacturing facility's physical layout and factors like air, space, cleanliness, and hygienic conditions. Research and development are the first step in the product and process design process, which takes preformulation, physicochemical, therapeutic, and toxicological considerations into account. It focuses on the control of process, raw materials (both active and excipients) and product itself. In the products along with its specific stability measures, liberty from microbial adulteration, packaging, containers & closures, labelling, appropriate storage, to ensure functional protection against factors like as humidity, volatility, air, light, and interaction (both drug and/or package interaction) [2-3]. So, quality is a crucial part of a pharmaceutical company. The collection of attributes that enable the products to satisfy particular pharmacopeial requirements is known as its quality. Patients might not have the specific information necessary to determine whether the product they are taking is of high quality or not. WHO said in 2017 that developing countries have a higher frequency of fake medications due to weak law enforcement, a lack of supplies of important medications, an unregulated market, and high prices. Post-market quality assessments are essential because these circumstances make it impossible to ensure the quality, efficacy, and safety of pharmaceutical goods, especially in developing nations [4]. GMPs are manufacturing processes that guarantee worker safety by taking the required precautions and producing high-quality final products. GMP covers two aspects: production and quality control (QC). As part of GMP, QC specialists assess the quality of all production-related factors in order to eliminate errors at every level of production. [5-7]. Quetiapine Fumarate (QF) is a 2nd generation atypical antipsychotic drug that was developed by AstraZeneca in 1985 and approved by the US FDA in 1997 [8-9]. Over 50 pharmaceutical companies manufacture this generic, and it is available in different strengths throughout Bangladesh under different brand names. Thus, this study aimed to assess some QF tablet brands to determine whether or not these products will meet Pharmacopeia's standard requirements. It will briefly explain weight variation, friability, hardness, drug content, disintegration, and dissolution test profiles of QF tablets available in the market. It may help consumers alter their brand in emergencies and needs if these quality parameters are comparable, satisfying the official specifications.

Materials and Methods

Materials

We procured hydrochloric acid (HCl) from MERCK, Germany. Distilled water (DW) used throughout the study was generated locally at the Laboratory of the Applied Chemistry and Chemical Engineering department, Islamic University, Kushtia. All the remaining chemicals and reagents used were laboratory-rated.

Sample collection, physical examination and labelling

We purchased QF 25mg tablets from nine companies manufactured in Bangladesh from a model pharmacy in Kushtia City, Bangladesh. We carefully noted the batch number, manufacturing date, and expiry date of each product and gave them a unique identification number: QF1, QF2, QF3, QF4, QF5, QF6, QF7, QF8, and QF9 (Table 1). Finally, we conducted a visual inspection to assess their appearance, shape, colour, break line, cracked edges, and deformities.

TABLE 1: Physical identification and naming of QF 25mg tablets used in this study.

Serial number	Company batch number	Color	Shape	Any defects	Code name
1	3282102	Blue	Round	No	QF1
2	H5	Pink	Round	No	QF2
3	2100938	Yellow	Round	No	QF3
4	KE091	Light green	Oblong	No	QF4
5	TKA061	Granola	Round	No	QF5
6	22012	White	Round	No	QF6
7	XF200	Pink	Round	No	QF7
8	GRD0218A	Yellow	Round	No	QF8
9	T162029	Orange	Round	No	QF9

Weight Variation (WV) Test

20 tablets of each QF brand were removed from the sheet and placed in an analytical balance (UNILAB, U.S.A) to measure their weight. Then, the average weight of each brand was calculated. The percentage of WV was calculated using the formula stated below [10]. Limits for acceptable variances in tablet weights were supplied by the pharmacopoeias (BP, USP) and were given as a percentage of the sample's average weight. A batch of tablets complies with the specification if the weight of no more than two tablets out of twenty tablets falls outside the acceptable range of variation [11].

$$\%\, WV = \frac{Individual\ weight\ weight - Average\ weight}{Average\ weight} \times 100$$

Hardness (HD) Test

The load necessary to crush the tablet when it is put on its edge is known as the HD of the tablet. Ten tablets were used to evaluate their HD. One tablet was placed in the HD tester (Harrison Pharma MPL, India) at a time, and the amount of force needed to shatter or crack the tablet was noted. Individual and average HD of different QF brands' were computed and compared [12].

Friability (FT) Test

Friability, a tablet's ability to powder, chip, or fragment, can impact the tablet's aesthetic, appearance, and reliability. It can also intensify the tablet's weight variation or content homogeneity issue. Ten tablets of each brand were weighed and placed into the FT tester (Electronics, India). Tablets were subjected to rolling and continuous vibrations for 4 minutes and 100 cycles, and every time, they fell 6 inches distance. The tablets were removed from the apparatus, brushed to eliminate any particles, and weighed again. The following equation was used to calculate the %FT [4]:

$$\%\, FT = \frac{Weight\ of\ tablets\ before\ testing - Weight\ of\ tablets\ after\ testing}{Weight\ of\ tablets\ before\ testing} \times 100$$

Disintegration (DT) Test

Six tablets from each batch were used in the test. We used two types of medium, 0.1N HCl and DW, for the DT study. The tablets were placed in the disintegration apparatus (Model-901, Electronics India), which was operated at a frequency of 28 to 32 cycles per minute, and the medium temperature was maintained at 37±2˚C. A device is placed at the top of each tablet to prevent floating. The time was recorded when the tablet disintegrated completely, leaving no palpable bulk in the device [13-14].

Assay

This test was done to verify the claimed drug content. Each QF tablet equivalent to 25mg of QF was transferred into a conical flask containing 0.1N HCl to make a final concentration of 1000 µg/ml. After filtering the solution, appropriate dilution was made, and the absorbance was recorded at 248 nm. Then, the sample absorbance at 248 nm was recorded, and this was used to determine the amount of drug present. Finally, the amount of drug present was calculated with the help of a standard curve [15]. The standard curve (Figure 1) was created using different known QF concentrations (10, 20, 30, 40, 50, 60, 70, and 100 µg/ml). The correlation coefficient value (R^2) was used for model fitting. Each test was performed in triplicate.

Dissolution (DS) Test

DS represents the availability of an active ingredient and allows for the timing of the material's full release from the dosage form. Using the paddle method and USP apparatus II, the DS was conducted. The dissolution media were the same as the DT test. In brief, 500 ml of medium was taken in the dissolving vessel, and a sample equal to 25 mg of QF was added. The paddle's speed and temperature applied were 50 rpm and 37±5˚C, respectively. At 0, 5, 15, 30, 45, 60, 90, and 120 minutes, an aliquot (5 ml each) samples were taken, and the sink condition was maintained by replacing them with an equivalent volume of fresh dissolution medium. The samples were filtered and diluted suitably to determine the concentration with the help of a standard curve. Each sample's absorbance in 0.1N HCland DW were measured at 248nm and 254nm using a UV spectrophotometer (Apel, Japan) [16-17]. Each test was performed in triplicate.

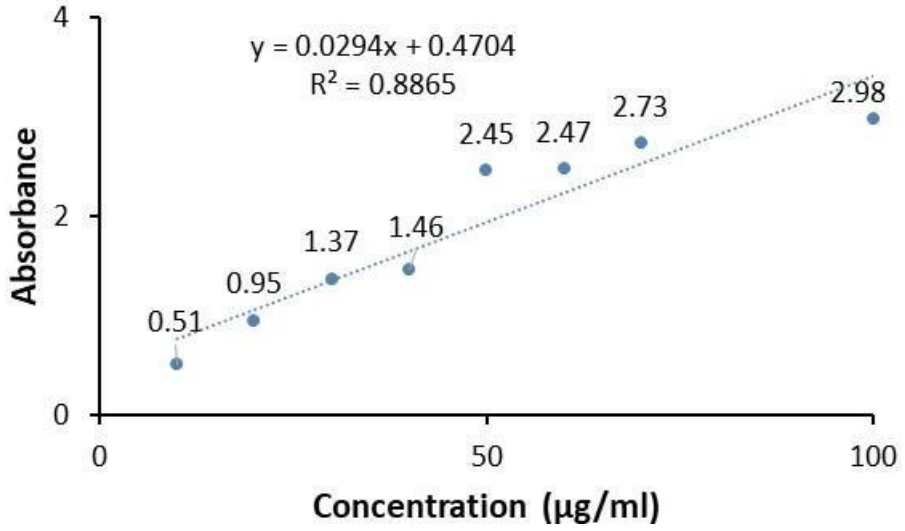

FIGURE 1: Standard curve for assay and % drug release determination of QF.

Statistical Analysis

We presented the data as mean± SD (standard deviation). Microsoft Office Excel 2016 was used to analyze the data and construct the graph. We considered the values statistically significant if "p" was equal to or less than 0.5.

Results

WV test results

The results obtained from WV tests are summarized in Table 2. The WV ranged between -4.23±1.75 to 2.86±2.05 percent. From the data, it was evident that the highest WV was in the order of QF3>QF4>QF1>QF7>QF8>QF2>QF9>QF6>QF5, while the lowest variation was QF7<QF3<QF8<QF1<QF2< QF4<QF9<QF5<QF6.

TABLE 2: Summary of WV, HD, FT, DT, and assay study of QF25mg tablets brands in Bangladesh.

Sample	WV (%)		HD (Kgf)	FT (%)	DT (minutes)		Assay (%)
	Maximum	Minimum			0.1N HCl	DW	
QF1	2.30±1.45	-2.92±1.45	4.48±0.30	0.01	4.09 ± 0.82	2.84±0.20	98.04±2.50
QF2	1.66±1.30	-2.43±1.30	4.00±0.72	0.17	2.69 ± 0.61	1.88±0.27	95.50±1.50
QF3	2.86±2.05	-3.63±2.05	6.64±0.79	0.01	5.59 ± 2.03	4.36±0.31	102.69±2.80
QF4	2.52±1.31	-2.33±1.31	8.09±1.58	0.02	6.06 ± 0.32	3.35±0.50	97.50±1.50
QF5	0.89±0.68	-1.38±0.68	4.62±0.44	0.02	0.51 ± 0.26	0.61±0.11	96.00±2.85
QF6	1.39±0.74	-1.00±0.74	5.10±0.63	0.01	8.22 ± 1.93	6.44±0.74	103.87±1.97
QF7	2.25±1.75	-4.23±1.75	5.92±0.53	0.05	0.62 ± 0.26	0.35±0.08	99.50±3.60
QF8	2.05±1.35	-3.35±1.35	4.39±0.53	0.13	7.82 ± 2.19	3.90±0.40	102.40±1.58
QF9	1.56±0.92	-1.63±0.92	7.74±1.52	0.09	6.73 ± 2.05	5.83±1.92	102.20±1.50

HD test results

Table 2 depicts the value average value of each QF brand. We found that the QF4 brand showed the maximum strength for breaking the tablets. The lowest HD was obtained from the QF2 brand. Overall, the HD values were in the range of 4.00±0.72 to 8.09±1.58 Kgf. The order of HD increment is found as QF2<QF8<QF1<QF5<QF6< QF7<QF3<QF9<QF4.

FT Test results

The average FT of the selected brands of QF tablets varied from 0.01% to 0.17%, stating that the lowest FT was 0.01%, showed by QF1, QF3, and QF6 (Table 2). The remaining brands produced FT in increasing order as QF4, QF5<QF7<QF9<QF8<QF2.

DT test results

The DT results obtained from two different media are summarized in Table 2. In 0.1N HCl, the maximum and the minimum time required for complete disintegration was 8.22 ± 1.93 and 0.51 ± 0.26 minutes. The highest time required for DT was for QF6 followed by QF8, QF9, QF4, QF3, QF1, QF2, QF7, and QF5. On the contrary, in DW media, it was between 6.44±0.74 and 0.35±0.08 minutes with the decreased order of QF6>QF9>QF3>QF8>QF4> QF1>QF2>QF5>QF7.

Assay results

The amount of active drug present within the QF tablet dosage form ranged between 95.5% and 103.87% (Table 2). The uppermost drug content was present in QF6, while the lowest was in QF2.

DS rest results

The percentage of drug release in 0.1N HCl from the studied QF tablets is depicted in Figure 2. Among these brands, QF4 (99.28±3.57) showed the highest drug DS. The remaining brands produced drug release as QF2 (98.45± 2.78) >QF9 (81.41± 3.44) >QF6 (78.65± 4.16) >QF8 (75.29± 2.65) >QF7 (70.24± 1.28) > QF1 (63.58± 3.17) >QF3 (60.64± 2.98) >QF5 (59.77± 2.42).

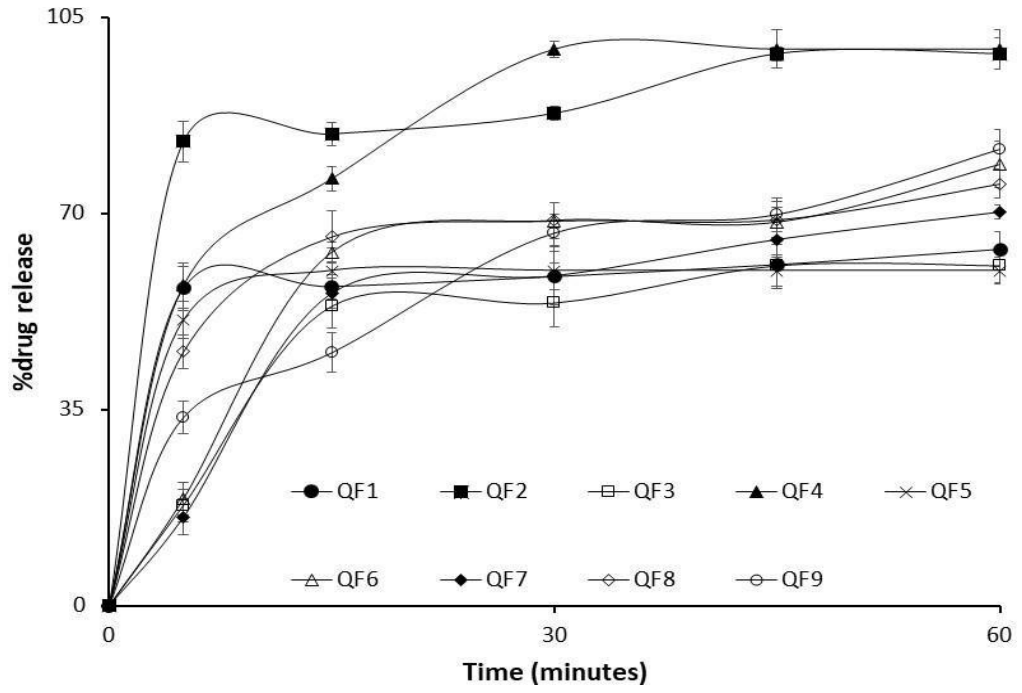

FIGURE 2: Cumulative drug release (%) from marketed QF tablets in 0.1N HCl.

On the other hand, in DW (Figure 3) the uppermost drug release was from QF6 (97.56±2.60) followed by QF1 (97.04± 4.83) >QF3 (95.82± 1.99) >QF2 (93.73± 2.18) >QF7 (91.99± 2.00) >QF4 (90.94± 2.84) >

QF5 (90.07± 3.34) >QF9 (88.33± 3.69).

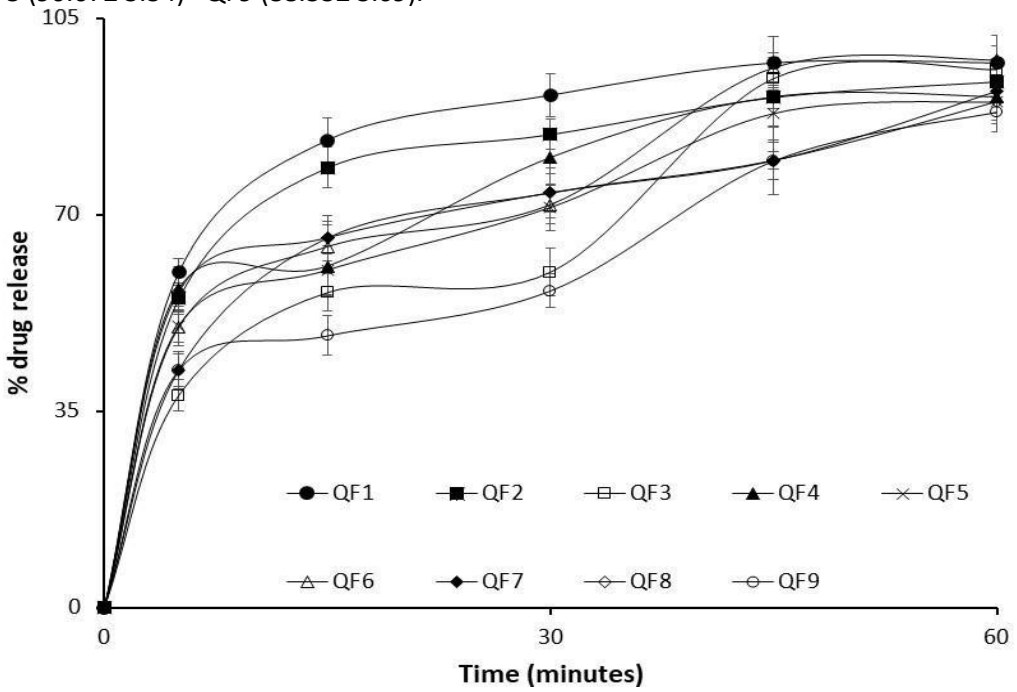

FIGURE 3: Cumulative drug release (%) from marketed QF tablets in DW.

Discussion

To limit the availability of low-quality or adulterated medicines in the pharma market, evaluating the excellence of commercial products is crucial. The WV test is a way to determine whether tablets contain a uniform quantity of claimed active moiety. This test indicates whether the manufacturer follows good manufacturing practices (GMP). The average weight of our studied brands ranged between 98-205 mg. The weight variation for all the tablets used in this study was within the official specifications, as the WV obtained was within -4.23% to 2.86%. This result is verified with the USP specifications, as they stated the limit of WV as ±10% and ±7.5% for tablets weighing 130-324 mg and <130 mg, respectively. Our results also satisfy the BP criteria as it allows ±7.5% WV for the tablet weighed between 80-250 mg [1,4, 18-19].

HD test is another essential criterion for assessing the tablets' ability to endure external forces during handling, packaging, and transportation. As well as it ensures the tablets' disintegration upon oral administration. If the HD falls below the normal limit, it will be easily fragile during production, processing, and storage. In contrast, if it is above the range, it will not disintegrate in the body and will produce less or no effect. Except for one brand QF4 (8.09 Kgf), the study indicated that the average HD of the tablets was within the permitted range (4.0- 8.0 Kgf) defined by USP [2].

For all QF tablet brands, the FT values satisfactorily meet the USP requirement as no brand loses > 1% of its parent weight [4]. This result shows good mechanical resistance of the tablet throughout its shelf life. Moreover, these tablets will maintain a good physical appearance and sufficient strength to survive from product manufacturing until patient consumption. Therefore, they will give ultimate patient compliance regarding all aspects of good products [20-21].

DT is an important condition for oral drug dissolution, rapid absorption, and subsequent therapeutic response [22]. If the DT becomes too high, it will take longer for the drug to dissolve, and consequently, the pharmacological response will follow a time-consuming process after oral administration. Hence, the result must be within the pharmacopeial reference. All of our studied QF tablets satisfied USP specifications, which stated that tablets should be fully disintegrated within 30 minutes [18]. The comparative results of this study suggest that the DT medium influences the DT time of QF tablets. The QF tablets were more quickly disintegrated in DW rather than 0.1N HCl because the fumarate salt of quetiapine is a more water-soluble form of the drug than the other salts, emphasizing QF is more likely to dissolve in DW, which can help speed up the tablet's DT time.

The assay of an active drug in a specified dosage form is a vital quality control aspect. If the values fall below the stated amount of the drug, the drug will not produce the expected outcomes. All of our study samples passed the standard criteria of assay results, as all of the samples fell within ±5% value [1].

Dissolution is a key idea in all physical and chemical studies, including biopharmaceutical and pharmacokinetic issues related to the distribution of any medicinal drug. A drug's dissolving behaviour significantly impacts its oral bioavailability, which is the rate-limiting stage in drug absorption from the gastrointestinal system [1]. This study's results showed marked variations in the dissolution rate of Bangladeshi brands of QF 25mg tablets. However, all the brands satisfy the standard guidelines of QF drug release as 30% of the drug dissolution required 0.6 to 6.4 hours at different pH [17, 23].

The correlation coefficient value (R^2) was used to categorize the model that best suited the data. The proportion of drug release is determined using the developed regression equation, $y = 0.0294x + 0.4704$, where y is the absorbance and x is the correlation. The correlation coefficient $R^2 = 0.8865$ (Figure 1) indicates a linear relationship between the concentration of the samples and absorbance.

As well as the study also has some limitations as particular batches of tablets were studied. Additionally, the study did not assess the in-vivo bioavailability of the tablets.

Conclusion

The findings of our study revealed that the tested QF tablets met the pharmacopoeial standards and were also comparable to the reference value. These results prove that the QF tablets marketed in Bangladesh are of good quality for assuring the patients that those who take these tablets will receive the expected therapeutic benefit. Therefore, this type of study should be conducted regularly to alert the manufacturers and drug control authorities to ensure the consistent production of high-quality products and monitoring alongside in-vivo evaluation.

Acknowledgment

We, the authors, acknowledge the Department of Pharmacy, Islamic University, Kushtia-7003, Bangladesh, for providing all sorts of instrumental support to complete this study as part of conferring the B.Pharm. (Hons.) degree.

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