Original Research Article

Quality Assessment of Hydroxychloroquine Tablet: A Comparative Evaluation of Drug Produced by Different Pharmaceutical Companies in Bangladesh

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Abstract: Hydroxychloroquine is the most commonly prescribed antimalarial extensively used to treat rheumatoid arthritis. It is extensively utilized as a repurposing drug, as well, in many countries worldwide to treat COVID-19. The pharmaceutical sector of Bangladesh is much enriched, and different pharmaceutical companies in Bangladesh produce this drug. Since the drug quality might vary significantly among different brands, assuring the quality

of medicine is absolutely necessary considering the health issues, particularly therapeutic efficacy and safety. Therefore, this study examined the quality of hydroxychloroquine produced by Bangladeshi pharmaceutical companies, concentrating on quality control parameters: the assay, dissolution, disintegration, hardness, friability, and weight fluctuation. All the brands of hydroxychloroquine tablets contained the stated amount of API between the range of 96.41±0.62 and 100.61±0.71 that met USP specification (100±5%). All brands met the pharmacopeial limit for the percentage of weight fluctuation, hardness test, friability, and disintegration time. Weight variation was between 0.31±0.01% and 0.46±0.02%, hardness was between 4.31 ± 0.88 and 7.36 ± 0.74 kgf, friability was less than 1%, and disintegration time was 5.42± 0.11 and 5.42± 0.11 min. In the dissolution test, all the samples attained more than 70% dissolution after 30 minutes. The mean percentage of hydroxychloroquine released in phosphate buffer was between 95.44±0.55 (Brand B) and 98.19±0.39 (Brand C) after 60 min. No significant difference was among the tested drugs from different companies, and all quality assessment parameters were within USP specifications. Therefore, hydroxychloroquine from the Bangladesh market is safe and effective.

Keywords: Hydroxychloroquine; dissolution; disintegration; hardness; Bangladesh

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1. Introduction

The pharmaceutical industry in Bangladesh has grown tremendously over the past few decades and has become one of the most vital sectors of the country's economy. This is one of the largest sectors in South Asia, with a market size of around USD 3 billion. According to industry experts, this sector is projected to continue its upward trajectory, and the market size is expected to exceed USD 6 billion by 2025[1]. There are 231 active and licensed pharmaceutical companies available in Bangladesh[2]. These pharmaceutical companies meet about 97% of the country's total demand[3]. Thus, ensuring the quality, therapeutic efficacy, and safety of drugs has become a fundamental issue in the post-marketing monitoring of the drug. This type of monitoring can play a leading role in ensuring quality products[4].

The support from the pharmaceutical industries was remarkable during COVID-19 pandemic. Various precautious programs and strategies were undertaken to stop the spread of SARS-CoV-02 throughout the world, e.g., in South Africa, Australia, Malaysia, etc.[5–10], as well as a unique strategy like establishing artificial intelligence to provide advice and inquiries about COVID-19, was done by Spain[11]. An exception, although a lockdown has been implemented to decelerate the transmission of COVID-19, the number of deaths in the United Kingdom was still rising rapidly[12].

Repurposing a medicine refers to using existing pharmaceuticals for new therapeutic possibilities rather than their primary uses[13]. From the early phase of the COVID-19 pandemic, several investigations towards repurposing drugs for COVID-19 have been performed, and clinical trials on several drugs are still being conducted[14]. Hydroxychloroquine has been widely used in different countries worldwide as a repurposed drug to overcome the COVID-19 pandemic[13]. Hydroxychloroquine has been recommended for the last 60 years as a safer analog of chloroquine and is also the most commonly prescribed antimalarial drug[15]. This drug is broadly used as a therapeutic agent against Systemic Lupus Erythematosus and Rheumatoid Arthritis[16–17].

It has become a challenging issue for physicians to choose the right drug as these drugs are readily available in different brand names. So, assessing the quality of medicine has become more critical. Since effective and safe treatment is vital for everyone, such research plays a significant role in this case. The primary goal of this research is to compare the efficacy of hydroxychloroquine (200 mg) generic drug (tablet) produced by different pharmaceutical companies in Bangladesh and to decrease health risks by ensuring drug safety.

2. Materials and Methods

2.1. Collection of Standard

API powder of hydroxychloroquine was supplied Pharmaceutical Sciences Research Division, Bangladesh Council of Scientific and Industrial Research (BCSIR), Dhaka, Bangladesh, as a gift for conducting the research.

2.2. Collection of Sample

Five different brands of Hydroxychloroquine (200 mg) tablets respectively were bought from the resident drug shop of Dhaka Metropolitan City. All the samples were precisely examined during purchase for their physical appearance, manufacturing license numbers, batch numbers, manufacturer name, DAR numbers, manufacturing date, expiry dates, and maximum retail price. The samples were arbitrarily coded as A, B, C, D, and E. Samples were kept by maintaining standard storage conditions (humidity: 45–60% and temperature: 25±2°C).

2.3. Solvents and Reagents

This study used purified water, sodium hydroxide, analytical grade of Di-sodium hydrogen phosphate, and Sodium dihydrogen phosphate.

2.4. Weight Variation Test

Twenty-five tablets from each of the 5 (five) different brands of hydroxychloroquine were taken and weighed individually with the help of an analytical weighing balance (AND EK-600i; Electronic Precision Balance). Then the mean weight for each brand was calculated, and the weight variation from the actual value was calculated using the following equation[18].

$$\% \text{ Weight variation} = \frac{Individual\ Weight - Average\ Weight}{Average\ Weight} \times 100$$

2.5. Hardness Test

To resist friability and remove mechanical shocks during packaging and shipping, tablets need a definite amount of strength or hardness[19]. A Monsanto-type (Vinsyst Technologies, India) hardness tester was used to perform this test. Ten tablets were arbitrarily chosen from each brand of hydroxychloroquine. The tested tablet was placed vertically between the spindle and the anvil. Each tablet was subjected to pressure in a clockwise direction, and the amount of pressure required to break each tablet was noted[20].

2.6. Friability Test

A friability test can be done to evaluate the ability of tablets to withstand abrasion, transporting, and handling. Friabilator is made of a plastic chamber with two parts and revolves at 25 rpm. Ten tablets from each brand of hydroxychloroquine were taken and weighed together. Then the machine was fixed at 25 rpm for 5 minutes, and all the tablets (10 tablets) were placed on the Roche Friabilator. After 125 revolutions, the tablets were removed from the machine and weighted together again. The loss in weight indicated friability[21]. The following equation was used to determine the percentage of friability:

$$\% \text{ Friability (f)} = \frac{Initial\ Weight - Final\ Weight}{Initial\ Weight} \times 100$$

2.7. Disintegration Test

The process by which a tablet breaks down into smaller pieces is called disintegration[22]. At first, the vessel (1000 mL) of Tablet Disintegration Tester (disintegration test apparatus, single unit; CAT No. 2249) was filled with 900 ml distilled water, and the temperature was set to 37±0.5°C. Six tablets from each brand of hydroxychloroquine were taken and placed in the disintegration chamber basket and the disk

appropriately, respectively. The machine was started, and the disintegration time (DT) was noted when no particles were in the system basket[23].

2.8. Assay Preparation

Twenty tablets from each of the brands of hydroxychloroquine were taken and finely pulverized. The powdered samples were accurately weighted. Powdered samples were taken in a 200 mL volumetric flask equivalent to 200 mg of Hydroxychloroquine sulfate, and 150 mL phosphate buffer (pH 6.8) was added to make the solution cooled at room temperature and filtered. 5 mL of filtered solution were transferred to a 100 mL volumetric flask and diluted using phosphate buffer. Absorbance was measured at 343 nm wavelength (λmax) using a UV-VIS spectrophotometer (T60 U, PG Instruments Limited, UK).

2.9. Preparation of Standard Curve

In a 100 mL volumetric flask, 100 mg hydroxychloroquine sulfate was dissolved with the help of 100 mL phosphate buffer to make a concentration of 1000 μg/mL. From this standard solution, 10 mL of the solution was transferred to a 100 mL volumetric flask, and up to 100 mL of phosphate buffer was added to make the concentration 100 μg/mL. The serial dilution (2.5, 10, 10, 15, 20 μg/mL) was made using the above method. The absorbance of the following concentration was measured using a UV-VIS spectrophotometer (T60 U, PG Instruments Limited, UK) at 254 nm wavelength. Phosphate buffer was used as a blank. A standard curve was obtained by plotting the measured absorbance against the corresponding concentration (Figure 1).

2.10. Dissolution Test

Dissolution tests are typically conducted to identify the drug release pattern over time. The dissolution study of five different brands of hydroxychloroquine was performed with USP apparatus type II (Paddle; RC-8; Minhua Pharmaceutical Machinery Co., Ltd, China) at 50 RPM. As dissolving media, 900 ml of phosphate buffer (pH 6.8) was utilized, and the temperature was always maintained at $37 \pm 0.5°C$. In the entire procedure, 10 mL of sample were taken out at 10, 20, 30, 40, 50, and 60 minutes, respectively, and substituted with phosphate buffers of equal volume. Samples were kept dark and then examined by UV-VIS Spectrophotometer (T60 U, PG Instruments Limited, UK) at 343 nm. Utilizing the standard curve of API (The data shown in the result section) of generic hydroxychloroquine drugs, the concentration of the sample was calculated from the equation $Y = mX + C$.

3. Result and Discussion

All the results were represented as mean ± SD, and the obtained data were then analyzed using nonlinear regression with the help of GraphPad Prism software (version 8.1). To evaluate quality parameters, various tests were performed for all the tablets of different brands of hydroxychloroquine obtained at Dhaka city's local market. The weight variation test is an effective method for assessing the uniformity of the API present in the dosage form. Keeping the weight variation accurate serves as an indicator of GMP compliance for every manufacturing organization. For tablets weighing 130 mg or less, the weight difference deviation range is ±10%, ±7.5% for tablets weighing more than 130 mg to 324 mg, and ±5% for tablets weighing more than 324 mg. If not more than two tablets cross the percentage limit, the sample passes the USP test, and if no tablet does not cross two times the percentage limit[24]. When the weight variation is within the pharmacopeial specifications, the active ingredient in the tablets is suspected to be uniform, providing the desired therapeutic response[22]. The weight variation of all the tablets of the same brand tested in this study met the USP specifications (Table 1).

The hardness test determines how resistant a tablet is to pressure or stress during manufacture, packaging, handling, and transportation[25]. It affects disintegration and dissolution, thus affecting bioavailability. A tablet may not disintegrate in the required amount of time if it is too hard, and if it is too soft, it may not resist handling. It has been observed that several factors may influence a tablet's hardness, including drug concentration, particle size and density, binder type, lubricant type and concentration, compression force, etc.[26–28]. The acceptable range of the hardness of an oral tablet is usually 4–8 kgf [25]. The hardness of five brands of hydroxychloroquine was between 4.31 ± 0.88 to 7.36 ± 0.74 kgf, which is within the USP specification (Table 1).

Another mechanical property of a tablet is friability. Friability is a surface deformation, whereas hardness is a bulk deformation[29]. According to the USP guidelines, the percentage of ideal friability should be more than 1%[30]. In this study, all of the evaluated brands of hydroxychloroquine tablets had a percentage of friability of less than 1%; hence they all met the specification of pharmacopeia. As a result, the five brands of hydroxychloroquine tablets available in Bangladesh tested in this study had good strength and could withstand shocks during handling and transportation.

Disintegration is the initial stage of dissolution and involves breaking down a tablet into smaller pieces[31]. The fact that a drug has a fast disintegration time does not necessarily mean it will be quickly available for the body to absorb. Other factors are also linked to the

drug's bioavailability[32]. A longer disintegration time indicates that the tablet is probably too tightly compressed. When the disintegration time is irregular, a lack of batch consistency will likely present[21]. The rate of dissolution is directly proportional to the disintegration rate. Disintegration time also affects the absorption and efficacy of a drug[25]. According to USP guidelines, uncoated and film-coated tablets need 5–30 minutes to disintegrate[30]. The disintegration time of five brands of hydroxychloroquine tablets meets the USP specification (Table 1).

Pharmaceutical product assay is a crucial quality characteristic needed to check that the stated quantity of API is present in a specific dosage form; failing to achieve the standard specifications will result in substandard quality medications. An insufficient amount of API may result in poor-quality treatment, whereas an excessive amount of API may create adverse drug reactions[21]. The assay result of all five brands of hydroxychloroquine met the USP standardization, which lies between 96.41±0.62 to 100.61±0.71 (Table 1).

The dissolution test determines the percentage of medications that dissolve in a specific time under controlled in vitro conditions. The dissolution rate determines the rate and extent of drug absorption and the subsequent therapeutic result of medicine. Dissolution has been used to demonstrate bioequivalence and is considered the most essential tool for predicting *in vivo* bioavailability. The dissolution test of solid oral medicinal formulations has evolved into an important quality control test for ensuring product homogeneity and batch-to-batch consistency[25]. The percentage of drug release of five brands of hydroxychloroquine at different time intervals is shown in Figure 2. The mean percentage of hydroxychloroquine released in the phosphate buffer was found to be between 95.44±0.55 (Brand B) and 98.19±0.39 (Brand C) after 60 min. Following the USP specification, the percentage of hydroxychloroquine dissolved should not be less than 70% after 60 min[33]. The dissolution test results showed that each brand passed the USP-instructed dissolution standards that ensure the quality of this medication produced in Bangladesh.

Table 1. Weight Variation, Hardness, Friability, Disintegration Time, and Assay Results of various brands of hydroxychloroquine (200 mg) tablets.

Brand Code	Weight Variation (%)	Hardness (kgf)	Friability %	DT (min)	Drug Content (%)
A	0.45±0.01	7.36 ± 0.74	0.44	5.79 ± 0.46	98.28±0.89
B	0.46±0.02	4.31 ± 0.88	0.45	6.46 ± 0.29	96.70±0.45
C	0.31±0.01	6.39 ± 0.43	0.65	8.52 ± 0.05	99.82±0.91
D	0.32±0.01	5.62 ± 1.03	0.63	5.42± 0.11	96.41±0.62
E	0.39±0.01	5.71 ± 0.44	0.91	7.23 ± 0.14	100.61±0.71
USP specification	± 5% to ± 7.5%	4–8 kgf	Less than 1%	5–30 min	95–105%

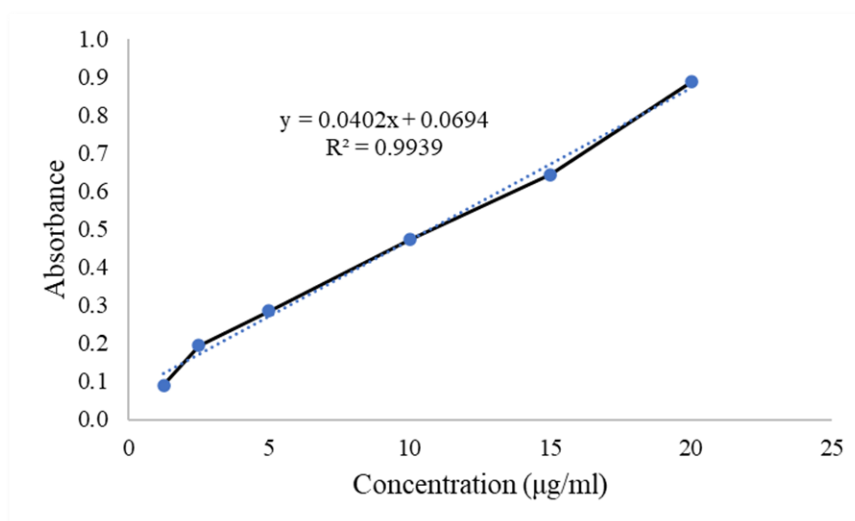Values are expressed as mean ± SD (n=5)

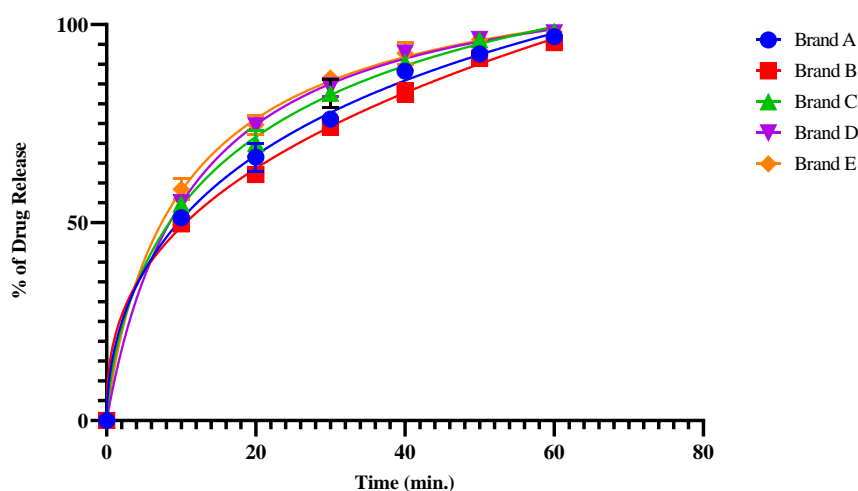**Figure 1.** Standard curve of hydroxychloroquine.

Figure 2. Intra-brand Dissolution Profile of Hydroxychloroquine. Data represents as the Mean±SD (n=5).

4. Conclusion

In vitro trials play an essential role in ongoing industrial practice because comparing different brands of the same generic drug makes it easy. At the same time, such exercises play a beneficial role in manufacturing an effective dosage form. Hydroxychloroquine is a widely used antimalarial drug but has been used to repurpose therapeutics for treating COVID-19. In this study, we evaluated *in vitro* comparison of five brands of hydroxychloroquine available in Bangladesh. The results obtained from this research have met the pharmacopeial specification. These findings conclude that the hydroxychloroquine tablets of these five brands sold in Bangladesh satisfy the therapeutic efficacy quality requirement.

Every brand, including lower-ranked ones, has shown that their products meet official standards for quality. This research may help the drug regulatory authority and the general public overall idea regarding the quality of commercialized hydroxychloroquine tablets in Bangladesh. Since a small number of pharmaceutical companies were selected for this research, it is necessary to conduct further research involving many manufacturing companies to understand the overall scenario. High throughput analytical techniques like High-Performance Liquid Chromatography (HPLC) are highly recommended for quantifying hydroxychloroquine since it has high sensitivity and can separate and identify impurities or closely related compounds.

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