

Evaluation of Critical Quality Attributes of Immediate Release Ciprofloxacin Tablets of Different Pharmaceutical Companies in Bangladesh

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<http://dx.doi.org/10.13005/bbra/2883>

(Received: 30 November 2020; accepted: 09 January 2020)

Critical Quality Attributes (CQAs) is an important factor in Pharmaceutical development as it determines the strength, release of the API from SDFs, and stability of a pharmaceutical dosage form. Moreover, substandard and counterfeit drugs have been a major concern in recent days. Ciprofloxacin is a second-generation fluoroquinolone derivative that exerts its effects by inhibiting bacterial DNA gyrase (Topoisomerase II). It is used for the treatment of bacterial gastroenteritis, respiratory tract infections, controlling bronchitis and pneumonia caused by Gram negative bacteria. Ciprofloxacin has been listed in the World Health Organization (WHO) Model list of Essential Medicines. In recent decades, the pharmaceutical industry has been experiencing excellent growth in both local and international market. In our present study, we have analyzed the Critical Quality Attributes (CQAs) including length, thickness, friability, weight variation, hardness test and disintegration time of Ciprofloxacin tablet to study whether the ciprofloxacin immediate release tablets of different pharmaceutical companies available in the Bangladeshi market to assess whether they are compliant to BP or USP guidelines in respect of physical parameters. We have also performed statistical analysis and found that that all the tablets from different brands are within the BP or USP requirements. So, from the study, we reached the conclusion that the critical quality attributes for ciprofloxacin immediate release tablets of different pharmaceutical companies in Bangladesh ensure the appropriateness of their strength, purity, release of the API from SDFs, and stability.

Keywords: Ciprofloxacin, immediate release, critical quality attributes, Drug release, stability, strength.

Critical Quality Attributes (CQAs) refers to a physical, chemical, biological, or microbiological feature of a product that must be within an appropriate range, or limit, or distribution to confirm the expected quality.^{1,2} CQAs are

generally related to the active pharmaceutical ingredients (API), excipients, intermediates (in-process materials), and drug product. For solid dosage forms (SDFs) like tablets or capsules that are taken orally, CQAs are generally the aspects

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that determine the strength, purity, release of the API from SDFs, and stability. For other types of dosage forms, CQAs include additional aspects specific to that dosage form, for instance, sterility for parenteral products, aerodynamic features for metered dose inhalers (MDIs), and adhesion for transdermal patches. CQAs is an important factor in Pharmaceutical development.³ The recently developed approach of drug development, 'Quality By Design' (QBD) include design involving the parameter ranges for all CQAs to ensure the product complies the quality target product profile (QTPP).²

Substandard and counterfeit drugs have been a major concern in recent days. There are a number of instances that account for substandard and fraudulent medications in the global market. Substandard pharmaceutical products do not follow the specifications and are ineffective and even hazardous to the patients^{4,5}. A study in 2017 showed that globally, about 10% of the pharmaceutical dosage forms were claimed to be counterfeit products, but this number increased to 25% for developed countries, and surpassed 50% in some countries, as reported by World Health Organization (WHO). The FDA reports that up to 25% of medications in developing states are not standard or fraudulent. In 2016, the volume of global trade in fraudulent pharmaceutical products was up to USD 4.4 billion, as per the OECD/EUIPO (2019) report which constitutes 0.84% of the estimated pharmaceutical goods imported worldwide⁶.

By contributing more than 90 percent of the available drugs on the market, local pharmaceutical manufacturers have recently emerged as a game-changer. Bangladesh Pharmaceutical Market Future Opportunity Outlook 2025, a recent report published in 2020, has demonstrated that Bangladesh Pharmaceutical Market has marketing prospects of more than US\$ 6 Billion by 2025 with an absolute growth of 114% from 2019 levels and exports opportunity of more than US\$ 450 Million by 2025. For the achievement of this goal, Bangladesh, like other countries, has to maintain the quality of the drugs and dosage forms by maintaining the critical quality attributes suggested by FDA.⁷

Ciprofloxacin tablets Ciprofloxacin is an antibiotic of fluoroquinolone group. It is used

for the treatment of certain kinds of bacterial infections⁸. It exerts its effects by inhibiting DNA replication². The enzyme inhibits the bacterial DNA gyrase (Topoisomerase II). This enzyme helps to inhibit relaxation of supercoiled DNA and consequently leads to breakage of dsDNA.⁹⁻¹¹

The range of various brands of the same drug puts several prescribers in a challenging situation of choosing of an 'ideal' brand. In vitro research or drug quality control allows understanding in vivo dissolution pattern and bioavailability. Ciprofloxacin is quickly and well absorbed from the gastrointestinal tract when given orally in tablet form.^{8,10} The absolute bioavailability is about 70 percent with no significant loss by first-pass metabolism. The half-life is about 3.5-4.5 hours for Ciprofloxacin. In 1987, Ciprofloxacin was approved by the Food and Drug Administration (FDA) to be used in the United States as the first oral broad-spectrum antibiotic. It is amongst the most necessary medicines required for the basic health care system and is present in the World Health Organisation (WHO) Model list of essential medicines.¹² In our current study, we have analyzed the critical quality attributes of ciprofloxacin tablets of different pharmaceutical industries of Bangladesh to study whether the companies provide the necessary quality attributes so that the drug can be dissolved properly in vivo and give required bioavailability. Six brands of immediate release Ciprofloxacin HCl 500 mg were randomly collected from Bangladeshi market and uniformity of weight, thickness, length, hardness, friability, and disintegration tests were carried out with the aim to assess their physical quality.¹³⁻¹⁶

MATERIALS AND METHODS

Materials

Hydrochloric acid (HCl) was taken from Merck, Germany and Ciprofloxacin VETRANAL analytical standard (Sigma Aldrich) was used as standard.^{17,18} Distilled water used throughout the work. Six different brands of Ciprofloxacin 500 mg tablets were purchased from the retail pharmacy and were called as Brand-A, Brand-B, Brand-C, Brand-D, Brand-E and Brand-F respectively. The labeled shelf life was three years from the date of manufacturing and the tablets were evaluated two years before the labeled expiry date.

Different Physical Test Methods^{10,19,20}**Thickness and Length**

Table thickness and length was measured by slide calipers. Tablet thickness and length should be in variation within $\pm 5\%$ of standard value according to USP guidelines.^{13,21,16}

Weight variation test

The aim of this test is to check the weight uniformity of manufactured batches, which essentially represents the uniformity of the

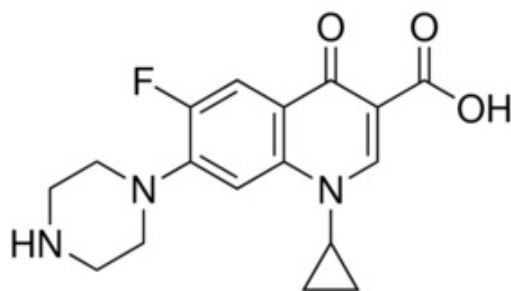


Fig. 1. Ciprofloxacin

presence of the active pharmaceutical ingredient. 20 tablets were arbitrarily taken and individually measured, and the mean was also evaluated. The difference between mean and individual tablet was calculated.^{13,16,22,23} If not more than two tablets fall below the percentage range and if no tablet varies by more than 2 times the percentage limit, the tablet batch passes the USP (United States Pharmacopeia) test.¹⁶⁻¹⁹ The weight variation test was done for six different brands according to the Official USP guidelines.

Friability

Friability test was done using Roche friabilator. The friability test was done according to USP guidelines.^{22,24-26} The tablets are vulnerable to abrasion in the friability test. Thereby it is helpful to evaluate the strength of the tablet by this test.

Hardness

Tablet hardness of tablets of six brands was measured using Monsanto tablet hardness tester. Ten tablets were arbitrarily taken from

Table 1. Brands of Ciprofloxacin

Code	Dosage form	Tablet strength (mg)	Manufacturing date	Expiry date
A	Tablet	500	May, 2018	Mar, 2021
B	Tablet	500	Jan, 2018	Jan, 2021
C	Tablet	500	May, 2018	May, 2021
D	Tablet	500	May, 2018	Apr, 2021
E	Tablet	500	Mar, 2018	Jul, 2021
F	Tablet	500	Mar, 2018	Mar, 2021

Table 2. Thickness studies for six brands

Sl no	Thickness (mm)					
	Brand A	Brand B	Brand C	Brand D	Brand E	Brand F
1	4.85	6.44	5.66	6.51	4.94	5.42
2	4.86	6.47	5.63	6.51	4.95	5.42
3	4.86	6.46	5.63	6.50	4.94	5.41
4	4.89	6.47	5.63	6.50	4.88	5.40
5	4.81	6.44	5.64	6.51	4.96	5.38
6	4.93	6.46	5.57	6.50	4.94	5.42
7	4.90	6.51	5.45	6.50	4.94	5.42
8	4.86	6.44	5.60	6.50	4.94	5.41
9	4.90	6.51	5.64	6.50	4.94	5.42
10	4.93	6.43	5.61	6.50	4.94	5.42
Mean	4.879	6.463	5.606	6.503	4.937	5.412
Standard Deviation	0.038	0.028	0.060	0.005	0.021	0.013

Table 3. Length studies for six brands

Sl no	Length (mm)					
	Brand A	Brand B	Brand C	Brand D	Brand E	Brand F
1	19.26	20.72	19.32	18.18	18.28	17.86
2	19.27	20.72	19.32	18.17	18.28	17.87
3	19.27	20.71	19.34	18.17	18.30	17.84
4	19.27	20.72	19.37	18.18	18.30	17.86
5	19.27	20.72	19.32	18.17	18.28	17.86
6	19.27	20.71	19.31	18.18	18.30	17.86
7	19.26	20.72	19.33	18.18	18.28	17.86
8	19.25	20.71	19.33	18.17	18.28	17.85
9	19.27	20.71	19.32	18.17	18.30	17.86
10	19.26	20.72	19.32	18.17	18.30	17.86
Mean	19.265	20.716	19.328	18.174	18.29	17.858
Standard Deviation	0.007	0.005	0.017	0.005	0.010	0.008

Table 4. Weight variation studies for six brands

Sl no	Individual Weight Variations (gm)					
	Brand A	Brand B	Brand C	Brand D	Brand E	Brand F
1	0.71	0.85	0.83	0.79	0.73	0.70
2	0.71	0.87	0.83	0.79	0.73	0.71
3	0.71	0.88	0.83	0.78	0.74	0.71
4	0.70	0.86	0.85	0.79	0.74	0.68
5	0.72	0.85	0.81	0.79	0.71	0.69
6	0.72	0.85	0.82	0.78	0.71	0.68
7	0.73	0.85	0.83	0.79	0.73	0.71
8	0.71	0.85	0.83	0.78	0.73	0.69
9	0.73	0.86	0.81	0.79	0.73	0.70
10	0.70	0.87	0.81	0.79	0.72	0.69
Mean	0.714	0.859	0.825	0.787	0.727	0.696
Standard Deviation	0.011	0.011	0.013	0.005	0.010	0.012

Table 5. Hardness studies for six brands

Sl no	Hardness (kg/cm ²)					
	Brand A	Brand B	Brand C	Brand D	Brand E	Brand F
1	3	3.5	6	4	6	6.5
2	3	3.5	5.5	4	6	6
3	3	3.5	6	4	5.5	6.5
4	3	3.5	6.5	3.5	6	6
5	3	3.5	4	4	6	5
6	3.5	3.5	6.5	4	6	5.5
7	3	4	6.5	4	6	6
8	3	4	4	4	6	6
9	3.5	4	6	4	6	5.5
10	3	4.5	6	3.5	6	5.5
Mean	3.10	3.75	5.7	3.9	5.95	5.85
Standard Deviation	0.211	0.354	0.949	0.211	0.158	0.474

each brand and then the pressure was given. The pressure point at which the tablet crushed was recorded. This is the hardness value for the specific tablet.^{16,23,27} The average hardness value was calculated and compared.

Disintegration

The disintegration test was performed using Disintegration apparatus (Copley). 0.1 N HCl at 37° C was used for disintegration test. The test was performed according to USP guidelines.^{10,19,28}

Sample collection

Six different brands of Ciprofloxacin tablet available in Bangladesh were randomly selected. They were collected from retail pharmacies. For confidentiality purposes, they were designated as A, B, C, D, E and F.

RESULTS AND DISCUSSION

Thickness Test

Table 2 shows that thickness of all brands of ciprofloxacin tablets is acceptable according to

USP/BP specification.

Length Test

Length of tablets can be dimensionally described and controlled. Tablet length should be within $\pm 5\%$ of standard value according to USP/BP specification. Table 3 shows that, the length of brand-B shows less deviation compared to the brand-C, brand-A, brand-E, brand-D and brand-F. But all brands are acceptable according to USP/BP specification.

Weight variation test

All the brands conformed to the USP guidelines of weight variation test as Table 4 shows. Weight of two tablets should not differ from the average weight not more than 5%. Table 4 shows that the weight of brand-B and brand-C shows less deviation compared to the brand-A, brand-D, brand-E, brand-F. But all brands were found to pass according to USP/BP specification.

Hardness Test

The capacity of tablets to survive handling without cracking or chipping is represent

Table 6. Friability studies for six brands

Sl no	Brands	Average Weight of tablet before test (gm)	Average Weight of tablet after test (gm)	Loss due to friability	Friability (%)	USP/BP Specification	Deviation from BP/USP
1	A	8.24	8.23	0.01	0.140	Not more than 1%	Pass the requirements according to USP/BP
2	B	7.88	7.88	0	0		
3	C	7.24	7.23	0.01	0.121		
4	D	6.94	6.94	0	0		
5	E	7.24	7.24	0	0		
6	F	6.94	6.94	0	0		

Table 7. Disintegration test results

Sl. No.	Individual tablet DT(Min:Sec)					
	A	B	C	D	E	F
1	2:40	2:24	10:38	1:53	5:00	2:25
2	2:46	2:31	12:00	1:54	6:12	2:30
3	2:56	2:50	11:00	1:50	6:34	2:06
4	2:27	2:57	12:24	1:57	4:17	2:13
5	2:35	2:44	11:55	1:44	6:46	2:19
6	3:04	2:39	10:45	1:53	5:56	2:36
Average Dissolution Time (Min:sec)	2:44	2:46	11:27	1:51	5:47	2:35
BP/USP specification	For uncoated or Film coated tablet Within 15 min					
Comments	Pass the requirements according to USP/BP					

by the hardness. It may influence friability and disintegration as well. The harder the tablet, the more time it takes to disintegrate. Table 5 shows that brand A and B had less hardness while brands C, D, E, F could not be broken at 5 kg/cm². So, brand C, D, E, F is preferable according to USP/BP specification but brand A, B show less deviation.

Friability Test

The USP and BP specification for friability is not more than 1%. Friability for all the brands was below 1%.

Disintegration test

Disintegration could be directly related to dissolution and subsequent bioavailability of a drug. All the brands complied with compendia specifications for disintegration. The BP specification is that uncoated tablets and film coated tablet should disintegrate within 15 min and coated tablets should disintegrate within 30 min while USP/BP specifies that un coated and film coated tablets should disintegrate within 15 min. Table 7 shows that brand A, brand B, brand C, brand D, brand E, brand F disintegrate within 15 min that fulfills the requirement of USP specification.

We have found that the length, thickness, friability, weight variation, hardness test and disintegration time of Ciprofloxacin tablet were compliant to BP or USP guidelines. Tablet formulations should have adequate hardness and minimum friability to uphold its mechanical strength and stability which are important resulting factors of critical quality attributes (CQAs). Again, hardness of a tablet can affect the disintegration and dissolution, overall the release of the active pharmaceutical ingredient from the dosage form which is another resulting factor of critical quality attribute. All parameters assay result show that all brands are within the pharmacopoeial requirements. Ciprofloxacin tablets from different pharmaceutical companies showed significant differences in weight variation, hardness, and disintegration probably because of the process factor and variation in formulation parameters from manufacturer to manufacturer. But it shows less deviation in length, thickness and friability. The critical quality attributes indicate that these tablets would have desired dissolution pattern in the body after administration.

CONCLUSION

Ciprofloxacin is a second-generation fluoroquinolone derivative that exerts its effects by inhibiting bacterial DNA gyrase (Topoisomerase II). It is used for the treatment of bacterial gastroenteritis, respiratory tract infections, controlling bronchitis and pneumonia caused by Gram negative bacteria. We have studied the Critical Quality Attributes including length, thickness, friability, weight variation, hardness test and disintegration time of Ciprofloxacin tablet to study whether the ciprofloxacin immediate release tablets of different pharmaceutical companies available in the Bangladeshi market to assess whether they are compliant to BP or USP guidelines in respect of physical parameters. The statistical analysis of the results shows that all the tablets from different brands are within the BP or USP requirements. The tablets are expected to show desired dissolution pattern in the body. So, from the study, we reached the conclusion that the critical quality attributes for ciprofloxacin immediate release tablets of different pharmaceutical companies in Bangladesh ensure the appropriateness of their strength, purity, release of the API from SDFs, and stability.

Conflict of interest

The research has no conflict of interest.

ACKNOWLEDGEMENT

We are grateful to Department of Pharmacy, ASA and BCSIR, Chittagong Laboratories for University Bangladesh for the research facilities provided.

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