RESEARCH ARTICLE

Quality Assurance Analysis of Branded Marketed Preparation Vs. Generic Drug Product of Ofloxacin Tablets: Evaluation of Pharmaceutical Characteristics under Short-Term Accelerated Conditions

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ABSTRACT

Ofloxacin is a 4-quinolone derivative with therapeutic activity against various gram-positive, fastidious gram-negative aerobic, facultative, and obligate anaerobic bacteria. It is available both in the form of branded products and generic products where both have been seen to have different quality, physicochemical, and stability characteristics. The present exploration involved investigating the quality attributes (assay determination and Impurity testing), physicochemical test (physical appearance of tablets, packaging and labeling of tablets, Tablet diameter and thickness, Weight variation test, Hardness test, Disintegration test, and *In vitro* dissolution study), and accelerated stability study (1, 3, and 6 months under temperature 40 ± 2°C and humidity 75 ± 5% RH) of a branded ofloxacin product and five different generic ofloxacin products available in the Indian market as per the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines (Q2 and Q3) and the United States Pharmacopeia (USP) guidelines. A comparison between the branded product and the generic products has been made in terms of the quality attributes. The study will open new doors of analysis of pharmaceutical quality assurance and provide avenues for both branded products and generic products to maintain the quality attributes on a regular basis.

Keywords: Ofloxacin, Branded, Generic, Accelerated Stability Study, Impurity, Degradation.

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INTRODUCTION

Quality assessment is a complete system to create and follow the procedures and policies for providing the most reliable laboratory results and minimize errors in the pre-analytical, analytical, and post-analytical phases (Brook *et al*., 1976). Quality assessment is one of the two major modules of the general quality management of the transplant program. Quality assessment and performance improvement are separate progressions that have activities related to and persuade the other procedures' activities (Kessner, 1978). Quality assessment service in retort to emergent administrative level primarily focused on the data quality and the recognition, especially within the financial services industry, that data accuracy and veracity are decisive to fulfillment with legislative and regulatory authorizations (Farris and Kirking, 1993).

Ofloxacin is a 4-quinolone derivative having therapeutic activity against a variety of gram-positive, fastidious gram-negative aerobic, facultative, and obligate anaerobic bacteria such as enteropathogens, Chlamydias, mycoplasmas, *Pseudomonas aeruginosa*, Legionellas, *Neisseria gonorrhoeae*, Enterobacteriaceae, *Chlamydia trachomatis*, mycobacteria, *Mycobacterium tuberculosis*, and methicillin-resistant *Staphylococcus aureus* with minimum inhibitory concentration (MIC) value of <2 µg/mL (Monk and Campoli-Richards, 1987). It is specifically recommended in treating urinary tract infections, sexually transmitted diseases, lower respiratory tract infections, etc. (Smythe and Rybak, 1989). The drug is rapidly absorbed from the gastrointestinal tract (GIT) and shows bioavailability of ~100%, is excreted in urine and feces with minimal xenobiotic transformations (Wise and Lockley, 1988). However, the drug expresses mild to severe adverse effects pertaining to hypersensitivity reactions, gastrointestinal disorders, and central nervous system-related issues (Sanders, 1992). It is available both in the form of branded products

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and the generic products where both have been seen to have different quality, physicochemical, and stability characteristics.

A branded medicine is an original product that has been developed by a pharmaceutical company. When a company develops a new medicine, its product must undergo and pass quality-control tests and evaluations to ensure that it is effective in curing conditions to treat and safe for human use (Ahire *et al*., 2013). Because pharmaceutical companies invest considerable amounts of money in developing a new medicine, they are given the sole right to manufacture and distribute the medicine for a period of time (Bera and Mukherjee, 2012). When a pharmaceutical company is given only rights of manufacture and distribution, the medicine is to have a patent on it. For a period of time, after the patent is granted, no one besides can produce a drug that is the same as the patented drug; the medicine belongs exclusively to the original company (Dadhich and Upadhyaya, 2011). For this reason, branded medicines are the most well known and most trusted type of that particular medicine.

A generic medicine is a drug product that is analogous to a particular drug brand or reference listed drug (RLD) product in terms of quality, dosage form, performance characteristics, route of administration, strength, and its intended use, which may be recognized as chemical equivalent, pharmaceutical equivalent, and bioequivalent to RLD (Greene, 2014). A generic medicine is actually a copy of the original branded drug product (Smit and Bredenkamp, 2013). Once the legal patent for the original product has run out, the pharmaceutical company that has developed the medicine has no longer possesses the exclusive official right to produce and distribute the medicine (Dylst *et al*., 2013). Other pharmaceutical companies can now create their own version of the same medicine with the same quality attributes and can be sell in the market at a much affordable price (Simoens, 2007).

The present exploration involved investigating the quality attributes (assay determination and impurity testing), physicochemical test (Physical appearance of tablets, packaging, and labeling of tablets, Tablet diameter and thickness, Weight variation test, Hardness test, Disintegration test, and *In vitro* dissolution study), and accelerated stability study (1, 3, and 6 months under temperature 40°C ± 2°C and humidity 75% ± 5% RH) of a branded ofloxacin product and five different generic ofloxacin products available in the Indian market as per the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines (Q2 and Q3) and the UUSP guidelines. A comparison between the branded product and the generic products has been made in terms of the quality attributes.

MATERIALS AND METHODS

Instruments

The UV-Vis spectroscopic analysis was performed using the double-beam Shimadzu® Ultraviolet-Visible Spectrophotometer (Model: UV-1800, Japan) which was connected with a computer desktop system. The system has a spectral bandwidth of 1 nm with wavelength accuracy of ±0.3 nm and comprises a pair of matched quartz cells with a 10 mm path length. All weighing of chemicals were carried out using Wensar® high precision electronic balance (Model: PGB100, USA). The sonication was done using the Transonic Digital S (Sonicator), USA. The hardness testing was achieved by using a Monsanto hardness tester (Model: Campbell, USA). Electrolab® disintegration tester USP (Model: ED2L) was employed for studying the disintegration of the tablets. Electrolab® dissolution tester (Model: TDT-08L) was utilized for studying the dissolution of the tablets. The HPLC study was carried out on a Waters® 2695 system with PDA detector 2996 on a reverse-phase Denali C_{18} column (250 mm × 4.6 mm dimension, 5 µm particle size). The system was equipped with EMPOWERS v.2 software comprising of 20-µl loop manual rheodyne injector.

Chemicals

The High performance liquid chromatography (HPLC) grade methanol, acetonitrile, glacial acetic acid, and distilled water, as well as analytical grade phosphoric acid, monobasic potassium phosphate, and concentrated hydrochloric acid were procured from Himedia Ltd., Mumbai, India. The ofloxacin branded product and the five generic products were purchased from various Pharmacies across the city limit of Nagpur, Maharashtra, India.

Spectral Analysis of Ofloxacin

Preparation of Stock Solution

Accurately weighed 50 mg of ofloxacin was transferred in a 50 mL volumetric flask and further dissolved in methanol. The final volume of this stock solution (A) was made up to 50 mL with methanol to make 1000 µg/mL concentration.

Determination of λmax in 0.1 N HCl (for dissolution)

From the above stock solution (A), 5 mL of the solution was taken and further diluted to 50 mL with 0.1 N HCl to make 100 µg/mL concentration (referred to as stock solution (B)). From the above solution, 5 mL content was taken and again diluted to 25 mL with 0.1 N HCl to make 25 µg/mL concentration (referred to as stock solution (C)). This solution was scanned in the range of 400–200 nm using a blank and the λmax was determined.

Preparation of Standard Curve of Ofloxacin

The dilutions were prepared from the stock solution (C) where the UV absorbance of 5 µg/mL, 10 µg/mL, 15 µg/mL, 20 µg/mL, and 25 µg/mL solutions were measured on UV-visible spectroscopy at 292 nm for the preparation of standard curve of ofloxacin.

Evaluation parameters for Marketed Branded and Generic Products

The test methods given under the USP monograph for ofloxacin tablets were employed for the evaluation of all products.

Tablet Description

The color, shape, and size were examined by visual observation.

Tablet Diameter and Thickness

The diameter and thickness of tablets are important for determining the uniformity of tablet size. Thickness and diameter were measured using Screw Guage Micrometer, which permits accurate measurements and provides information on variation between tablets (Mahajan *et al*., 2017a).

Weight Variation

As per the USP, weight variation test was performed by weighing 20 tablets individually, calculating the average weight, and comparing the individual tablet weight with that of the average. According to the specification outlined in USP, the test for the uniformity of weight for drug products; 130–324 mg is ± 7.5%, and >324 mg is ± 5% of the average pass. Then, the tolerance limit for weight variation was estimated (Mahajan *et al*., 2017).

Tablet Hardness

The tablets require a certain amount of strength and resistance to friability and also to withstand mechanical shocks during handling in manufacture, packaging, and shipping. It is the property of a tablet that is measured to assess its resistance to permanent deformation. The tablet hardness tester device (Monsanto tester) was used to test tablet hardness. The hardness of each branded tablet and generic tablets were measured in unit kg/cm^2. Each sample was analyzed in a triplicate manner (Patil *et al*., 2016).

Disintegration Study

Disintegration is the breakdown of the tablets into smaller particles or granules when it comes in contact with a solution. The time taken by a tablet to disintegrate was measured in a USP disintegration apparatus. For determining the disintegration time, one tablet was placed in each tube and the basket rack was positioned in 1 L simulated gastric fluid without enzymes at pH 1.2 under a temperature of 37 ± 1°C. The frequency of cycles per minute was 28 to 32 (Gangane *et al*., 2018).

Dissolution Study

The release rate of ofloxacin film-coated tablets was determined by using USP dissolution testing apparatus-I (Basket type). The dissolution test was performed using 900 mL (0.1 N HCl) volume at a temperature of 37 ± 0.5°C with 100 rpm stirring. An aliquot (10 mL) of the solution was collected from the dissolution vessel, filtered through 0.45 µm Whatman filter paper, and diluted 2 mL of the filtered content with dissolution medium at time intervals 10 min, 20 min, and 30 min. Each aliquot was replaced with a fresh dissolution medium to maintain the sink conditions. The absorbance of diluted solutions was measured at 292 nm (Dangre *et al*., 2016).

Accelerated Stability Studies

The branded ofloxacin product and generic ofloxacin products were placed inside a polyvinyl chloride (PVC) container, and aluminum foil was wrapped over it. The stability studies were performed under the accelerated conditions of temperature (40 ± 2°C) and moisture (75 ± 5% RH) for the duration of 1, 3, and 6 months (Godbole *et al*., 2017).

Assay Preparation

Preparation of Buffer Solution

2.72 g of monobasic potassium phosphate was dissolved in 1000 mL of water, and the pH 3.3 ± 0.1 was adjusted with dilute phosphoric acid.

Preparation of Mobile Phase

A filtered and degassed mixture of buffer solution and acetonitrile in the ratio of 88:12 was prepared.

Preparation of Diluent-1

A mixture of methanol and glacial acetic acid in the ratio of 75:25 was prepared.

Preparation of Diluent-2

A mixture of water and acetonitrile in the ratio of 90:10 was prepared.

Standard Preparation

Dissolve an accurately weighed quantity of ofloxacin in diluent-1 to obtain a solution with a known concentration of about 1 mg/mL and diluted stepwise with diluent-2 to obtain a solution concentration of about 20 µg/mL.

Assay Procedure

Finely powdered 20 tablets were accurately weighed and a portion of the powder equivalent to 100 mg of ofloxacin was transferred to a 100 mL volumetric flask. 70 mL of the diluent was added and sonicated for 20 minutes duration. Then, the content was diluted with diluent-1 to the marked volume and mixed well. This solution was further passed through 0.45 µm filter paper and the filtrate was collected. Then 2 mL of the filtrate was diluted to 100 mL of diluent-2 and mixed well. In this assay, the standard was repeated three times and the results presented as the mean of the three determinations. An isocratic mode was used.

Chromatographic System Suitability

The liquid chromatography system was equipped with a 294 nm detector having 150 mm × 4.6 mm dimension packing column. The flow rate was 1 mL/min. The standard and the test preparations were chromatographed and the peak responses were recorded. The percentage of each impurity in the portion of tablets was calculated by the formula:

$$\% \text{ purity} = 100\ (1/F)\ (rU/rS)\ (CS/CU)$$

F is the relative response factor for each impurity; rU is the peak response of the impurity obtained from the test solution; rS is the peak response of ofloxacin obtained from the standard solution; CS is the concentration in mg/mL of ofloxacin in the standard solution and CU is the concentration in mg/mL of ofloxacin in the test solution is based on label claim.

The tailing factor and the relative standard deviation for replicate injection should not more than 2.0.

Impurity Profiling

Preparation of Phosphate Buffer

Phosphate buffer was prepared by dissolving 2.72 g of monobasic potassium phosphate in 1000 mL of HPLC grade

water, and the pH was adjusted with dilute phosphoric acid to a pH of 3.3 ± 0.1.

Preparation of Solution-A

Solution A was prepared by taking a mixture of phosphate buffer and acetonitrile in a ratio of 88:12. The content was further filtered and degassed.

Preparation of Solution-B

Solution A was prepared by taking a mixture of acetonitrile and phosphate buffer in a ratio of 60:40. The content was further filtered and degassed.

Preparation of Mobile Phase

The mobile phase of the chromatographic system involved the utilization of variable mixtures of solution-A and solution-B.

Preparation of Standard Solution

An accurately weighed quantity of ofloxacin RS was dissolved in methanol and further stepwise diluted quantitatively to obtain a solution of strength 4 µg/mL.

Preparation of Test Solution

Finely powdered 20 tablets were accurately weighed and a portion of the powder equivalent to 100 mg of ofloxacin was transferred to a 100 mL volumetric flask. 70 mL of the diluent was added and sonicated for 20 minutes duration. The content was further diluted with methanol to the desired volume. This solution was further passed through 0.45 µm filter paper and the filtrate was collected. The first 5 mL of the solution was discarded before use.

Chromatographic System

The liquid chromatography system was equipped with a 294 nm detector having 250 mm × 4.6 mm dimension packing column. The flow rate was 1-mL/min. The standard and the test preparations were chromatographed and the peak responses were recorded according to the following gradient procedure: 0-8 minutes [isocratic, solution A (100%), solution B (0%)]; 8-25 min [linear gradient, solution A (100%→40%), solution B (0%→60%)]; 25–26 minutes [linear gradient, solution A (40%→100%), solution B (60%→0)%]; and 26–40 minutes [isocratic, solution A (100%), solution B (0%)]. The tailing factor and the relative standard deviation for replicate injection should not more than 2.0.

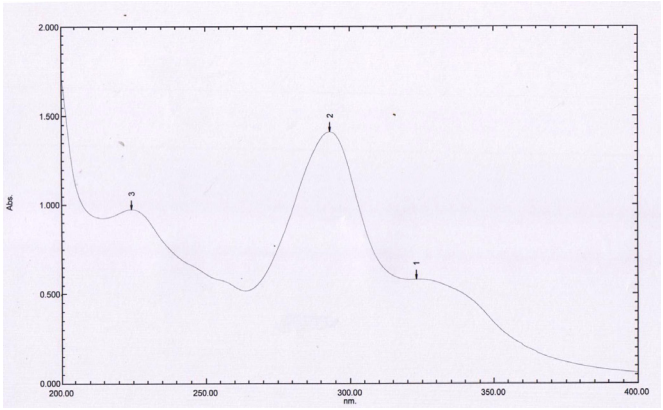

Figure 1: UV Spectra of ofloxacin in 0.1 N HCl.

RESULTS AND DISCUSSION

Spectral Analysis of Ofloxacin

λmax determination

The prominent wavelengths at 323.20 nm, 292.30 nm, and 224.20 nm were predominantly seen (Figure 1). An absorption maximum was found to be at 292 nm. Hence, 292 nm was selected as the λmax for further studies.

Prepared standard curve

Ofloxacin showed maximum absorption at wavelength 292 nm in 0.1 N HCl. The calibration curve was prepared by taking the UV absorption of solutions at 5–25 µg/mL concentration (Table 1). The details of calibration curve include $y = 0.0549x + 0.0301$ with $R^2 = 0.9997$ (Figure 2).

where, y = Absorbance, M = Slope, x = Concentration, C = Constant.

Evaluation Parameters for Marketed Branded and Generic Products

Tablet Description

The color, shape, and size were examined by visual observation where the factory manufactured ofloxacin products (1×10 tablets in blister packaging) had the same attributes as per pharmacopeia recommendation and the manufacturer's claim (Table 2). The visual appearance of the product is an important factor for patient compliance. The branded product was bioconvex on both sides, creamish colored, and film-coated caplet shape tablet whereas the generic products were bioconvex on both sides, lemon yellow-colored, film-coated oval shape tablet (G1 product), bioconvex on both sides with embossing (200), white color, film-coated circular shape tablet (G2 product), bioconvex on both sides, orange-colored, film-coated circular shape tablet (G3 product), and bioconvex on both sides, white color, film-coated circular shape tablet (G4

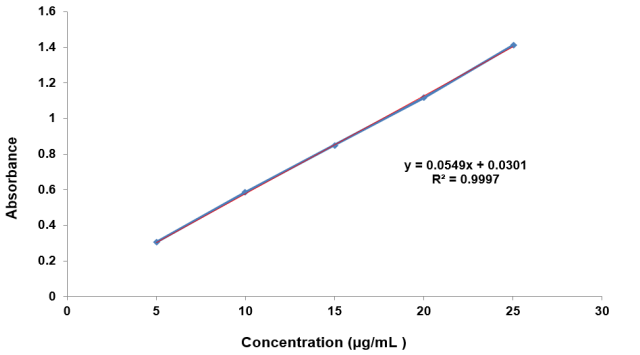

Figure 2: Standard calibration curve of ofloxacin in 0.1 N HCl.

Table 1: Observed absorbances in standard calibration curve.

Concentration (µg/mL)	*Absorbances*
5	0.328
10	0.600
15	0.832
20	1.25
25	1.573

and G5 products). After performing the accelerated stability studies, no changes were observed. The physical appearances and the physical stability of the products were found to be very uniform.

Tablet Diameter and Thickness

All the generics and the branded ofloxacin tablets were found to be within the acceptable range of thickness (2–3 mm), length (11 mm), width (7 mm), and diameter (8–10 mm). The thickness and the diameter uniformity of the tablets are a necessary factor for the consumer requirements and also important for better packaging. No changes occurred in branded and generic products after stability study (Table 3).

Weight Variation

The average weight of 20 tablets was calculated, and the individual tablet weight was compared to the average weight. The weight variation test is required to ensure that each unit dose's drug content is distributed in a narrow range around the label strength. If the drug substance forms the greater part of the oral solid dosage form, the weight variation obviously reflects variation in the content of active ingredient. The results indicate that five generics (G1-G5) products and one branded (B1) product possess acceptable uniformity of weight as per the USP limit. After the stability shelf period, there were no prominent changes observed (Table 4).

Tablet Hardness

The hardness test showed tablets' ability to withstand the pressure or stress during handling, packaging, and transportation. The results indicated that the branded tablet product B1 had the highest strength; *i.e.,* 5.7 kg/cm^2 as compared to all the five generic products (G1-G5). The branded product B1 and generic products G1 and G5 retained the hardness across the 6 months accelerated stability period while generics G2, G3, and G4 showed a decrease in the hardness value. The reason for the decline in the hardness value may be due to the porous nature and the specific excipients used. The moisture absorption and temperature might affect the breaking strength. Generic product G4 showed a very less hardness at the initial level and this is not a true sign of good compressibility (Table 5).

Disintegration Study

The disintegration test is the most important step in the release of drugs from the immediate release dosage forms. The rate of

Table 2. Physical appearance of branded and generic products at initial condition and under accelerated stability conditions.

Product code	*Initial*	*After 1 months*	*After 3 months*	*After 6 months*
B1	Bioconvex on both sides, cream coloured, film coated caplet shape tablet (1×10 tablets in blister packaging)	No change	No change	No change
G1	Bioconvex on both sides, lemon yellow coloured, film coated oval shape tablet (1×10 tablets in blister packaging)	No change	No change	No change
G2	Bioconvex on both sides with embossing (200), white colour, film coated circular shape tablet (1×10 tablets in blister packaging)	No change	No change	No change
G3	Bioconvex on both sides, orange coloured, film coated circular shape tablet (1×10 tablets in blister packaging)	No change	No change	No change
G4	Bioconvex on both sides, white colour, film coated circular shape tablet (1×10 tablets in blister packaging)	No change	No change	No change
G5	Bioconvex on both sides, white coloured, film coated circular shape tablet (1×10 tablets in blister packaging)	No change	No change	No change

Table 3: Initial values of thickness and diameter of branded and generic products.

Product code	*Thickness (mm) ± SD*	*Length (mm) ± SD*	*Width (mm) ± SD*	*Diameter (mm) ± SD*
B1	3 ± 0.001	11 ± 0.000	7 ± 0.000	_
G1	2 ± 0.021	11 ± 0.000	7 ± 0.000	_
G2	3 ± 0.001	_	_	10 ± 0.000
G3	3 ± 0.026	_	_	8 ± 0.000
G4	2 ± 0.003	_	_	10 ± 0.000
G5	3 ± 0.005	_	_	10 ± 0.000

Table 4: Values of weight variation test of branded and generic tablets at initial condition and under accelerated stability conditions.

Product code	*Initial study*	*After 1 months*	*After 3 months*	*After 6 months*
B1	305.65 ± 6.523	300.45 ± 5.072	302.35 ±5.860	306.75 ± 7.390
G1	255.45 ± 4.370	251.15 ± 4.770	252.65 ± 6.698	253.24 ± 3.893
G2	347.90 ± 6.488	352.33 ± 3.798	352.35 ± 7.292	350.65 ± 6.301
G3	229.95 ± 2.258	228.25 ± 2.844	229.44 ± 4.247	229.57 ± 2.665
G4	289.47 ± 4.581	289.45 ± 4.738	287.73 ± 7.554	288.65 ± 5.091
G5	358.55 ± 3.486	362.82 ± 2.353	358.19 ± 4.241	358.66 ± 4.717

disintegration is directly proportional to the rate of dissolution. The rate of disintegration is straightly influenced by the rate of influx of water into the tablets and also depends on the porosity of the tablets. The above results indicated that the branded product B1 and four generic products G1, G2, G3, and G5 passed the disintegration test throughout the stability period according to the USP (Table 6). While the product G4 generic passed the other tests as per specification, it presented a very less disintegration time at initial and stability study. It can be concluded from the disintegration study that the generic G4 failed to comply at the manufacturing stage of the film-coated tablet itself but as per the official monograph testing method, quality control has a right to release such batch into market.

Dissolution Study

The dissolution test of the drug from a solid dosage form is important for drug bioavailability. Six tablets of each product sample (one branded and five generic products) were employed for the dissolution test and % drug release for branded product and generic products were measured in accordance with the method described for the ofloxacin tablet in the USP monograph. The dissolution monograph stated that the amount of ofloxacin released within 45 minutes should not be less than 80% of the stated amount.

The *in vitro* dissolution rate is used to simulate the bioequivalency of different formulation of generics (ofloxacin film-coated tablet) in relation to the branded product. The results of the drug release of Branded B1 product and Generic G1, G2, G4, and G5 products were obtained in the range of 85-107% in 10 minutes. The release for generic G3 was 49% in 10 minutes and 78% in 30 min. According to Biopharmaceutics Classification System (BCS), the ofloxacin comes under Class-I (high solubility and permeability) where it is expected that the dosage form should release >70% drug and as per specification (30 min). In the case of batch G3, the dissolution limit was not less than 80%, and therefore the batch failed in dissolution within 10 minutes duration.

After the initial study, the sample was placed in the stability chamber under accelerated stability condition (40 ± 2°C and 75 ± 5% RH). After 1-month of accelerated stability study, the results showed a slight variation in the drug release rate of some generic products as compared to the branded product for 30 min. The % dissolution of Branded B1 and all Generic G1, G2, G4, and G5 dissolution were >80% for 30 minutes. While in comparison to the initial result of 1-month stability, the results showed no significant deviation in the dissolution limit but generic G3 showed largest differences at all dissolution time intervals, which can be concluded from the non-uniformity between the tablet to tablet and poor production batch.

After 3 months of accelerated stability study, the drug release rate of all generic products as compared to the branded product was found to be decreased considerably. The result of branded B1 was 92.65% in 10 minutes and generic products G1, G2, G4, and G5 also demonstrated >80% of drug release

Table 5: Values of hardness test of branded and generic tablets at initial condition and under accelerated stability conditions.

	Hardness (Kg/cm^2) ± SD			
Product code	*Initial study*	*After 1 months*	*After 3 months*	*After 6 months*
B1	5.7 ± 0.378	5.3 ± 0.351	4.5 ± 0.450	5.93 ± 1.357
G1	3.7± 0.360	3.7± 0.321	3.3 ± 0.251	3.03 ± 0.152
G2	2.0 ± 0.100	1.9 ± 0.152	1.6 ± 0.400	1.5 ± 0.200
G3	2.03 ± 0.208	2.2 ± 0.200	1.5 ± 0.305	3.1 ± 0.100
G4	1.8 ± 0.251	1.8 ± 0.152	1.3 ± 0.124	1.1 ± 0.200
G5	2.1 ± 0.152	2.06 ± 0.251	1.9 ± 0.208	2.1 ± 0.916

Table 6: Disintegration test of branded and generic tablets at initial condition and under accelerated stability conditions.

Product code		*Disintegration time in (Minute : Second) Minimum and Maximum*			
Initial study		*After 1 months*	*After 3 months*	*After 6 months*	
B1	Minimum	2 min. 12 sec.	1 min. 21 sec.	2 min. 14 sec.	3 min. 23 sec.
	Maximum	2 min. 50 sec.	1 min.36 sec.	2 min. 45 sec.	4 min. 03 sec.
G1	Minimum	2 min. 10 sec.	2 min. 7 sec.	3 min.13 sec.	2 min. 59 sec.
	Maximum	2 min. 30 sec.	3 min 16 sec.	3 min. 58 sec.	3 min. 31 sec.
G2	Minimum	2 min. 25 sec.	1 min. 21 sec.	1 min. 28 sec.	1 min. 01 sec.
	Maximum	2 min. 47 sec.	1 min. 37 sec.	1 min.58 sec.	1 min.26 sec.
G3	Minimum	3 min. 5 sec.	4 min. 38 sec.	6 min. 38 sec.	8 min. 06 sec.
	Maximum	4 min. 40 sec.	4 min. 52 sec.	7 min. 13 sec.	8 min. 47 sec.
G4	Minimum	40 sec.	32 sec.	23 sec.	25 sec.
	Maximum	56 sec.	46 sec.	33 sec.	45 sec.
G5	Minimum	1 min. 54 sec.	2 min. 37 sec.	1 min. 20 sec.	1 min. 30 sec.
	Maximum	2 min. 40 sec.	2 min. 42 sec.	1 min. 37 sec.	2 min. 09 sec.

in 30 minutes. The generic product G3 had a highly decreased drug release rate after 10 and 30 minutes, respectively. Product G4 has a decreased release rate as compared to the initial and after 1 month of accelerated stability study (Table 7).

After 6 months of accelerated stability study, the drug release rate of all generic products as compared to the branded product was drastically decreased. The result of the drug release rate of branded B1 was 93.19% in 10 minutes, while the remaining generic products (G1, G2, G4, and G5) were slightly reduced. The generic G3 had an extreme reduction in the drug release rate at 10 and 30 minutes as compared to the initial and after the accelerated stability study. The G4 has a decrease release rate as compared to the initial and after 1 month of accelerated stability study but the release got increased after 6 months of the accelerated stability study.

According to the USP monograph, the tolerance limit for ofloxacin tablets should be >80% generic in 30 minutes. The generic products G3 and G4 showed considerable variation in the % drug dissolution release. All generics except G3 and branded tablets of ofloxacin released more than 80% within 30 min duration in the initial study and after 1 month of the accelerated stability period. The branded batch B1 and generic products (G1, G2, and G4) passed the test after 3 and 6 months of the accelerated stability study. The generic product G2 displayed a decrease in % drug dissolution and closer to the tolerance limit. The generic batch G3 showed the largest inter-tablet variation in the drug release which may be due to the poor quality manufacturing from batch to batch. The generic product G4 presented a great effect of temperature and humidity for the duration of 3 and 6 months, where the difference in the % drug dissolution was seriously noticed. The generic batch G5 was found to be near to tolerance limit after 6 months of accelerated stability period while the other showed satisfactory results during stability time testing. The difference may be due to the altered physical characteristics and content non-uniformity.

Table 7: Dissolution test of branded and generic tablets at initial condition and under accelerated stability conditions.

	Drug release in % ± SD											
	10 min				*20 min*				*30 min*			
Product code	*Initial*	*1 months*	*3 months*	*6 months*	*Initial*	*1 months*	*3 months*	*6 months*	*Initial*	*1 months*	*3 months*	*6 months*
B1	90.50 ± 1.523	85.23 ± 5.979	88.21 ± 1.299	91.80 ± 1.944	89.71 ± 3.141	92.85 ± 5.388	90.9 ± 3.512	90.9 ± 3.512	89.32 ± 2.527	93.19 ± 0.678	92.65 ± 1.106	94.08 ± 1.682
G1	92.91 ± 3.357	105.95 ± 4.435	109.76 ± 3.018	107.22 ± 2.849	90.46 ± 4.046	96.49 ± 6.051	95.02 ± 11.528	95.02 ± 11.528	91.01 ± 4.428	88.00 ± 5.255	89.28 ± 2.802	89.38 ± 1.299
G2	91.54 ± 2.544	85.94 ± 2.025	87.08 ± 2.061	87.36 ± 0.899	92.77 ± 2.842	88.12 ± 6.931	86.32 ± 1.795	86.32 ± 1.795	92.41 ± 3.870	75.44 ± 5.207	85.28 ± 6.562	83.69 ± 3.525
G3	49.67 ± 17.76	50.87 ± 4.672	76.53 ± 1.902	90.42 ± 1.855	69.31 ± 6.303	26.90 ± 4.127	37.44 ± 5.823	37.44 ± 5.823	78.31 ± 7.101	18.50 ± 5.367	28.77 ± 6.354	47.87 ± 9.289
G4	101.18 ± 2.163	107.5 ± 4.270	109.23 ± 2.074	105.50 ± 3.215	101.43 ± 3.763	78.60 ± 3.223	81.61 ± 2.474	81.61 ± 2.474	101.38 ± 3.453	86.32 ± 2.230	86.96 ± 1.416	86.27 ± 3.175
G5	97.93 ± 4.225	85.84 ± 1.441	85.23 ± 1.742	84.86 ± 2.032	96.36 ± 7.468	82.55 ± 4.812	82.50 ± 4.351	82.50 ± 4.351	98.59 ± 4.470	87.68 ± 2.080	87.63 ± 0.663	88.40 ± 1.504

Assay of Products

All the five generics products and one branded product were assayed for the drug content according to the isocratic mode based HPLC method (buffer solution and acetonitrile in the ratio of 88:12) outlined in the individual drug monographs of the USP (acceptance limit: 90–110%). The content of ofloxacin in the drug products was calculated from the peak areas of the chromatograms of the test solution and reference standard solutions.

Initially, the retention time of ofloxacin in the branded product was observed in 4.068 min and generic products lie in the range of 4.063 to 4.101 minutes (Figure 3). After 1 month (Figure 4) and 3 months (Figure 5) of accelerated stability study, it has been noticed that the retention time and the area of ofloxacin peak enhance to a minor extent. In contrast to it, after 6 months (Figure 6) of accelerated stability study, the retention time and the area of ofloxacin peak decreases to some extent. The retention time of ofloxacin peak and the area of ofloxacin peak under initial and accelerated stability conditions are mentioned in Table 8.

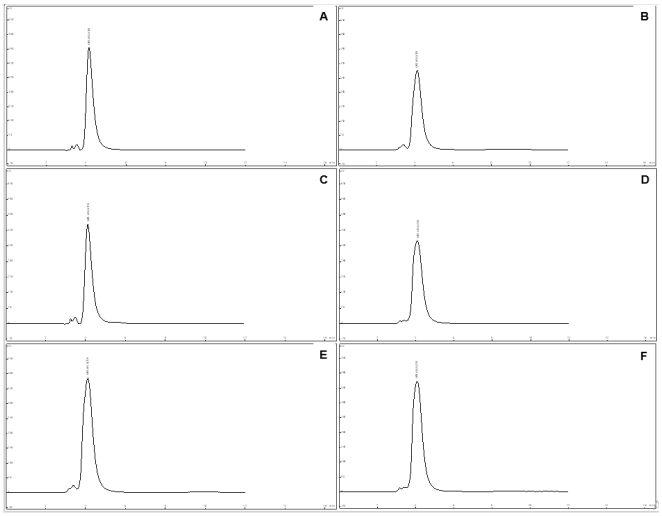

Figure 3: Chromatogram of products at initial conditions: (A) Product B1; (B) Product G1; (C) Product G2; (D) Product G3; (E) Product G4; and (F) Product G5.

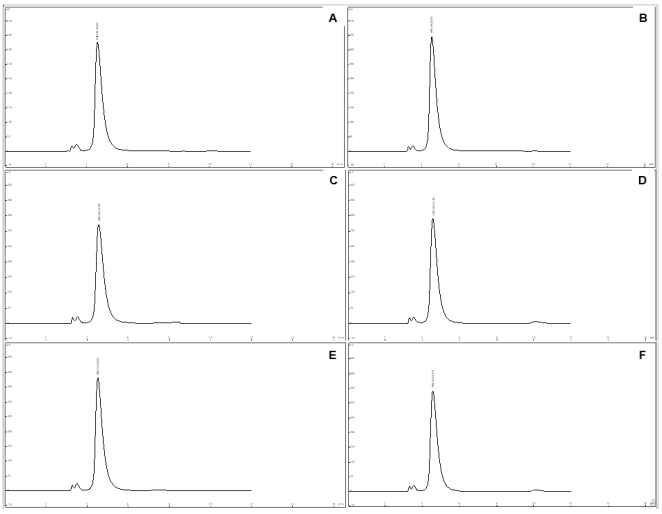

Figure 5: Chromatogram of products under 3 months stability conditions: (A) Product B1; (B) Product G1; (C) Product G2; (D) Product G3; (E) Product G4; and (F) Product G5.

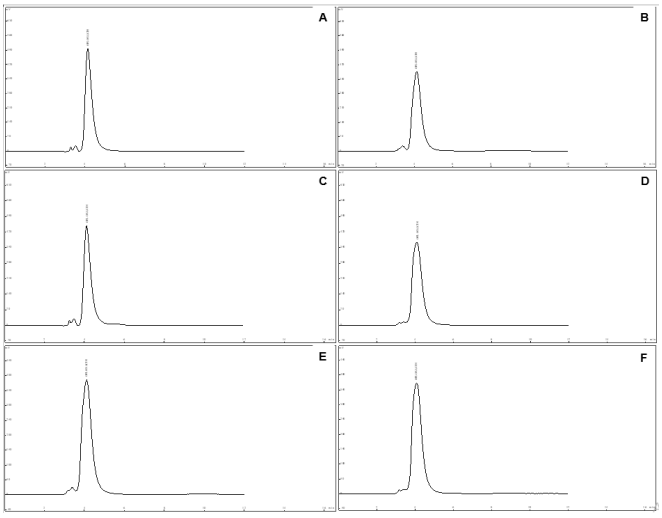

Figure 4: Chromatogram of products under 1 month stability conditions: (A) Product B1; (B) Product G1; (C) Product G2; (D) Product G3; (E) Product G4; and (F) Product G5.

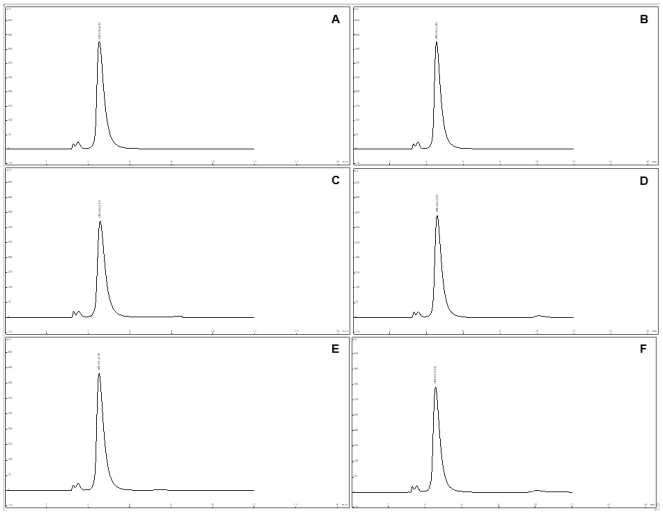

Figure 6: Chromatogram of products under 6 months stability conditions: (A) Product B1; (B) Product G1; (C) Product G2; (D) Product G3; (E) Product G4; and (F) Product G5.

The percent assay of Branded product B1 and Generics G3, G4, and G5 in the initial study were within the range of acceptance criteria, but the remaining Generic products G1 and G2 showed initial % drug contents of 137.25% and 92.73%, respectively. It can be concluded that the G1 batch gets failed while G2 was at a lower limit. Generic G1 product failed in assay after 1 month, 3 months, as well after 6 months of accelerated stability period (Table 9).

After 3 months of accelerated stability study, the % assay of all generics as compared to the branded product was reduced. The result of branded B1 was 99.89% and other remaining generics like Generic G2, G3, G4, and G5 had in the range of 90.53-102%. The generic G1 had 118.28% of the drug content, which was above acceptance criteria, but it decreased than the initial and after 1 month of the accelerated stability study. After 6 months of stability study, the % assay of generics as compared to the branded product was decreased considerably and the result of branded B1 was 90.85%, and generics G1, G2, G3, G4, and G5 showed 110.44%, 90.32%, 91.22%, 97.01%, and 98.57%, respectively.

The percent decrease in the potency after 1 month was found to be 1.95, 1.72, 1.67, 3.67, 0.75, and 0.39% for products B1, G1, G2, G3, G4, and G5, respectively. The percent decrease in potency after 3 months was found to be 6.65, 3.67, 2.38, 5.31, 6.35, and 4.19% for products B1, G1, G2, G3, G4, and G5, respectively. The percent decrease in potency after 6 months was found to be 15.1, 19.17, 2.6, 8.47, 6.95, and 7.47% for products B1, G1, G2, G3, G4, and G5, respectively. The percent decrease in potency for Generic G1 product was found to be highest and the product failed after 6 months of stability period as per regulatory ICH guidelines. The percent decrease in the potency for the products B1, G3, and G4 was also seen to be moderately increased.

Table 8: Retention time and peak area of ofloxacin at initial condition and under accelerated stability conditions.

Product code	*Retention time of ofloxacin peak*				*Area of ofloxacin peak*			
	Initial	*1 months*	*3 months*	*6 months*	*Initial*	*1 months*	*3 months*	*6 months*
B1	4.068	4.079	4.523	4.495	14445853	14625913	14407365	13946651
G1	4.093	4.098	4.526	4.537	17850810	17803274	17226947	16315857
G2	4.099	4.103	4.543	4.569	12343299	12177386	13181129	13121023
G3	4.098	4.125	4.539	4.426	13241775	13652764	13734861	13546711
G4	4.101	4.084	4.518	4.493	13693829	13869403	14219771	14268994
G5	4.063	4.086	4.506	4.498	14047739	14067336	14810840	14521932

Table 9: Percentage assay of branded and generic products in initial condition and under accelerated stability conditions.

	Assay (%)			
Product code	*Initial study*	*After 1 months*	*After 3 months*	*After 6 months*
B1	107.00	110.92	99.89	90.85
G1	137.25	134.89	118.28	110.94
G2	92.73	92.91	90.53	90.32
G3	99.66	103.32	94.37	91.22
G4	104.25	105.04	97.64	97.01
G5	106.46	106.88	102.00	98.51

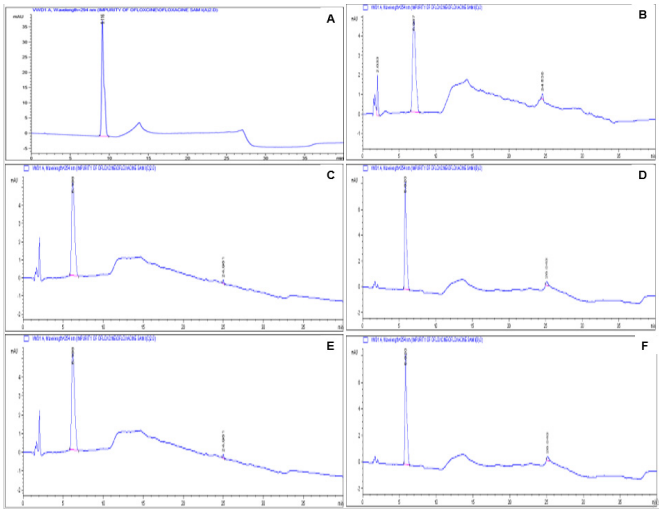

Figure 7: Product impurities at initial conditions: (A) Product B1; (B) Product G1; (C) Product G2; (D) Product G3; (E) Product G4; and (F) Product G5.

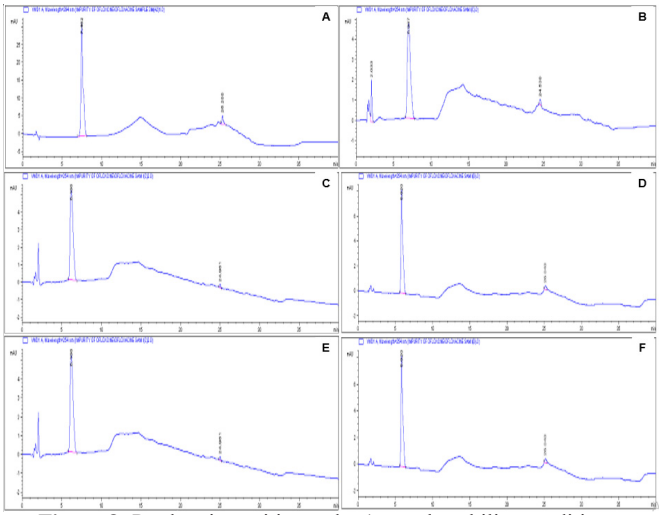

Figure 8: Product impurities under 1 month stability conditions: (A) Product B1; (B) Product G1; (C) Product G2; (D) Product G3; (E) Product G4; and (F) Product G5.

Impurity Profiling

The impurities present in the branded product B1 and generic products (G1-G5) are determined using the isocratic and linear-gradient mode. The impurity peaks of branded product B1 were found to be 9.116 minutes (initial), 7.452 minutes (1 month stability), 7.462 min (3-month stability), and 6.104 minutes (6-month stability) (Figure 7). Initially, the generic products' impurity peaks appear at 5.83–6.98 min range, which in turn showed retention in the range of 5.82–6.90 min after 1-month of accelerated stability study (Figure 8). After 3 months of accelerated stability study (Figure 9), the impurity peaks for the generic products were predominantly seen at 5.28–8.24 min range, which further changed to 5.8–6.55 min after 6 months of accelerated stability study (Figure 10), depicting those degradations are within limits. Prominent degradation was observed in the case of branded ofloxacin products. Brand B1 passes at initial and 1-month stability study but failed after 3-month stability study and 6-month stability study while all generics failed at all levels. In impurity testing no other impurity was reported like impurity A (2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid) and other unspecified impurities, only impurity B (9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid) was reported by all products; *i.e.* branded & generics. The generation of impurity B is specified in the USP monograph, which increases due to the processing while manufacturing and storage conditions also. Similarly, the composition, process, and storage optimization are also a basic requirement for all the generic products. The results were found not within the specified limit; *i.e.* not more than 0.3% and due to more than 1% individual impurity, all the products failed in context to

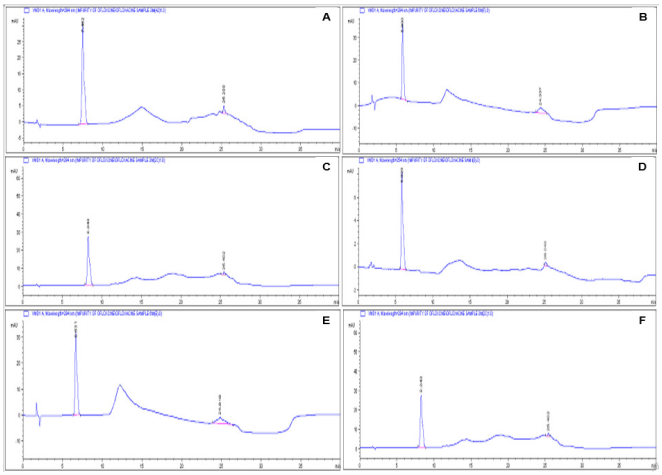

Figure 9: Product impurities under 3 months stability conditions: (A) Product B1; (B) Product G1; (C) Product G2; (D) Product G3; (E) Product G4; and (F) Product G5.

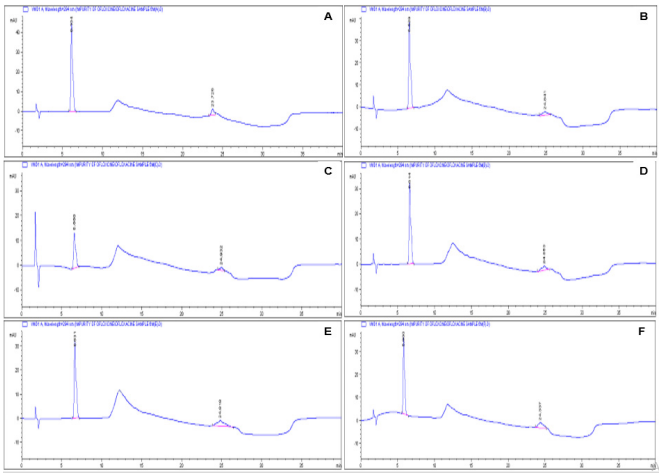

Figure 10: Product impurities under 6 months stability conditions: (A) Product B1; (B) Product G1; (C) Product G2; (D) Product G3; (E) Product G4; and (F) Product G5.

Table 10: Percentage impurity of branded and generic products in initial condition and under accelerated stability conditions.

			% Impurity				
Product code	*RRT*	*RRF*	*Limit*	*Initial*	*After 1 months stability*	*After 3 months stability*	*After 6 months stability*
Standard							
Impurity A	0.5	1	NMT-0.3%	-	-	-	-
Impurity B	3.6	0.22	NMT-0.3%	-	-	-	-
Other impurity	-	1	NMT-0.2%	-	-	-	-
Total impurity	-	-	NMT-1.0%	-	-	-	-
B1							
Impurity A	0.5	1	NMT-0.3%	-	-	-	-
Impurity B	3.6	0.22	NMT-0.3%	-	-	1.26%	1.53%
Other impurity	-	1	NMT-0.2%	-	-	-	-
Total impurity	-	-	NMT-1.0%	-	-	1.26%	1.53%
G1							
Impurity A	0.5	1	NMT-0.3%	-	-	-	-
Impurity B	3.6	0.22	NMT-0.3%	1.08%	1.26%	1.72%	1.99%
Other impurity	-	1	NMT-0.2%	-	-	-	-
Total impurity	-	-	NMT-1.0%	1.08%	1.26%	1.72%	1.99%
G2							
Impurity A	0.5	1	NMT-0.3%	-	-	-	-
Impurity B	3.6	0.22	NMT-0.3%	0.99%	1.17%	1.90%	1.9%
Other impurity	-	1	NMT-0.2%	-	-	-	-
Total impurity	-	-	NMT-1.0%	0.99%	1.17%	1.90%	1.9%
G3							
Impurity A	0.5	1	NMT-0.3%	-	-	-	-
Impurity B	3.6	0.22	NMT-0.3%	1.44%	1.53%	1.72%	1.6%
Other impurity	-	1	NMT-0.2%	-	-	-	-
Total impurity	-	-	NMT-1.0%	1.44%	1.53%	1.72%	1.6%
G4							
Impurity A	0.5	1	NMT-0.3%	-	-	-	-
Impurity B	3.6	0.22	NMT-0.3%	1.08%	1.44%	1.99%	1.4%
Other impurity	-	1	NMT-0.2%	-	-	-	-
Total impurity	-	-	NMT-1.0%	1.08%	1.44%	1.99%	1.4%
G5							
Impurity A	0.5	1	NMT-0.3%	-	-	-	-
Impurity B	3.6	0.22	NMT-0.3%	1.35%	1.53%	1.62%	1.9%
Other impurity	-	1	NMT-0.2%	-	-	-	-
Total impurity	-	-	NMT-1.0%	1.35%	1.53%	1.62%	1.9%

the total impurities. In general observation, ofloxacin was pure and any impurity peaks in chromatographs are not reported as such. The complete impurity profile of both branded product and generic products are depicted in Table 10.

CONCLUSION

The study revealed that all the generics and the branded ofloxacin tablets were found to be within the acceptable range in terms of tablet diameter and thickness. Weight variation study revealed that all the five generics products and the branded product possess acceptable uniformity of weight as per the USP limit. The hardness test concluded that branded product B1 and generic products G1 and G5 retained the hardness across while generics G2, G3, and G4 showed a decrease in the hardness value due to the porous nature and the specific excipients used. The disintegration study concluded that the generic G4 failed to comply at the manufacturing stage of film-coated tablet. The product assay revealed that the percent decrease in potency for Generic G1 product was found to be highest and the product failed after 6 months of stability period as per regulatory ICH guidelines. The percent decrease in the potency for the products B1, G3, and G4 was also seen to be moderately increased. Prominent degradation was observed in the case of branded ofloxacin products. Brand B1 passes at initial and 1-month stability study but failed after 3 months of stability study and 6 months of stability study while all generics failed at all levels. The study will open new doors of analysis of pharmaceutical quality assurance and provide avenues for both branded products and generic products to maintain quality attributes regularly.

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