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Comparative Quality Analysis of Cefpodoxime Proxetil Branded Tablet Product with Available Indian Generic Products: Short-Term Accelerated Study

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ABSTRACT

Introduction: Cefpodoxime is a safe, short course, effective, semi-synthetic, third-generation cephalosporin available for use as a prodrug known as Cefpodoxime proxetil and is recommended for treating sinusitis, otitis media, urinary tract infection, respiratory tract infections (upper and lower), skin infections, and soft tissue infections. 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.

Objective: To explore the quality attributes of a branded cefpodoxime proxetil product and five different generic cefpodoxime proxetil products available in the Indian market.

Methods: The present exploration involved investigating the quality attributes (Assay determination and Impurity testing), physicochemical test (Physical appearance of tablets, Packaging and labelling of tablets, Tablet diameter and thickness, Weight variation test, Friability Test, Hardness test, Disintegration test, and In vitro dissolution study), and accelerated stability study (1 month, 3 months, and 6 months under temperature 40°C ± 2°C and humidity 75% ± 5% RH) of a branded cefpodoxime proxetil product and five different generic cefpodoxime proxetil 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.

Results: All the generics and the branded cefpodoxime proxetil tablets were found to be within the acceptable range.

Conclusion: The study will open new doors of analysis of pharmaceutical quality assurance and provide avenues for both branded products and generic products in maintaining the quality attributes regularly.

Key Words: Cefpodoxime proxetil, Branded, Generic, Accelerated Stability Study, Impurity, Degradation

INTRODUCTION

The concept of quality assessment is an absolute system to create and follow the practices and strategies for providing the most consistent laboratory outcomes and to lessen the errors involved in the pre-analytical, analytical, and post-analytical stages.[1] Among the two foremost elements, Quality Assessment is one of the universal quality management systems. Performance Improvement is one of the headways that have activities related to the activity of the other processes.[2] Quality assessment service in context to growing organizational stages principally highlighting the data quality and the detection, particularly contained by the monetary sectors, that data correctness and veracity are critical to execution with lawmaking and regulatory approvals.[3]

Cefpodoxime is a safe, short course, effective, semi-synthetic, third-generation cephalosporin available for use as a prodrug known as Cefpodoxime proxetil.[4] It is absorbed readily from the human gastrointestinal tract. It is an active drug given in various regimens for diverse infections caused by Gram-positive cocci such as *streptococci*, *staphylococci*,

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penicillinase-producing strains as well as Gram-negative bacteria such as *Meningococci*, *Hemophilus*, *Gonococci*, *Klebsiella*, *Moraxella*, *E. coli*, etc.[5] It is highly recommended for treating sinusitis, otitis media, urinary tract infection, respiratory tract infections (upper and lower), skin infections, and soft tissue infections.[6] The drug can be recommended as a parenteral cephalosporin with a maximum dose of 8–10 mg/kg/d.[7] It is majorly excreted by the kidneys in an unchanged form. In renal compromised patients, dose adjustments are required.[8] It attains sufficient stages beyond the minimum inhibitory concentration (MIC) in several body fluids, therefore, the doses need to be adjusted (single or double doses).[9]

A branded medication is an innovative creation that has been created by an innovator organization. When an innovator develops a new medication, the developed novel drug product must endure and pass recommended quality tests and evaluate to make sure its effectiveness in remedial situations to treat and safely administer for human use.[10] As innovator organizations spend a substantial amount of resources to formulate a novel drug product, they are provided with the exclusive right to produce and market the medications for a given duration.[11] When an organization is provided exclusive rights to produce and market, the medicament is credited to patent(s). For a given duration of the patent award to the original company, no other organizations have the right to manufacture the same drug.[12] For this motive, a branded medicine is well known and that particular medication is generally very much trusted.

A generic medicine may be defined as a drug product that corresponds to a meticulous reference listed drug product (RLD) or drug brand in the context of strength, type of dosage form, route of administration, performance characteristics, quality, and its application, which may be distinguished as a pharmaceutical equivalent, bioequivalent, and chemical equivalent to RLD.[13] A generic medicine, is in reality, a replica of the innovative recognized drug product.[14] Once the lawful exclusive rights for the original product have been exhausted over time, the organizations that innovated the product are devoid of the elite certified right to create and share out the medicine.[15] Other organizations will produce the same adaptation of the identical medication with the equivalent excellence characteristics and can be put up for trade in the marketplace at a much reasonable cost.[16]

The present exploration involved investigating the quality attributes (Assay determination and Impurity testing), physicochemical test (Physical appearance of tablets, Packaging and labelling of tablets, Tablet diameter and thickness, Weight variation test, Friability Test, Hardness test, Disintegration test, and *In vitro* dissolution study), and accelerated stability study (1 month, 3 months, and 6 months under temperature 40°C ± 2°C and humidity 75% ± 5% RH) of a branded cefpodoxime proxetil product and five different generic cefpodoxime proxetil 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.

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 also comprises a pair of matched quartz cells having 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. Electrolab® Roche Friabilator (Model: EF2) was used for studying the friability 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 (150 mm × 4.6 mm dimension, 5 µm particle size). The system was equipped with EMPOWERS v.2 software comprising of a 20-µl loop manual rheodyne injector.

Chemicals

HPLC grade methanol, acetonitrile, glacial acetic acid, and water, as well as analytical grade glycine, sodium chloride, and ammonium acetate, were procured from Himedia Ltd., Mumbai, India. The cefpodoxime proxetil branded product and the five generic cefpodoxime proxetil products were purchased from various Pharmacies across the city limit of Nagpur, Maharashtra, India.

Spectral analysis of cefpodoxime proxetil

Preparation of stock solution

Accurately weighed 25 mg of cefpodoxime proxetil was transferred in a 25 mL volumetric flask and further dissolved in methanol. The final volume of this stock solution **(A)** was made up to 25 mL with methanol to make 1000 µg/mL concentration.

Preparation of dissolution medium pH 3.0

In a 1000 mL volumetric flask, 54.5 g of glycine and 42.6 g of sodium chloride were dissolved in 500 mL of water and 14.2 mL of hydrochloric acid was added with swirling. The content was allowed to cool, further diluted with water, and mixed well. 50 mL of the stock solution was transferred to a volumetric flask and diluted with 900 mL of water to obtain a solution. A pH of 3.0 ± 0.1 of the stock solution was adjusted with 10 N NaOH.

Determination of λmax for dissolution

From the above stock solution **(A)**, 10 ml of the solution was taken and further diluted to 100 mL with dissolution medium pH 3.0 to make 100 µg/mL concentration (referred to as stock solution **(B)**). From the above solution, 25 mL content was taken and again diluted to 100 mL with dissolution medium pH 3.0 to make 25 µg/mL concentration (referred to as stock solution **(C)**). This solution was scanned in the range of 400 nm to 200 nm using a blank and the λmax was determined.

Preparation of standard curve of cefpodoxime proxetil

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 261 nm for the preparation of standard curve of cefpodoxime proxetil.

Evaluation parameters for marketed branded and generic products

The test methods given under the USP monograph for cefpodoxime proxetil 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.[17]

Weight variation

As per the USP, the 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.[18]

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.[19]

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°C ± 1°C. The frequency of cycles per minute was 28 to 32.[20]

Dissolution study

The release rate of cefpodoxime proxetil film-coated tablets was determined by using USP dissolution testing apparatus-II (Paddle type). The dissolution test was performed using 900 mL (0.1 N HCl) volume at a temperature of 37°C ±0.5°C with 100 rpm stirring. An aliquot (10 mL) of the solution was collected from the dissolution vessel, filtered through a 0.45 µm Whatman filter paper, and diluted 2 mL of the filtered content with a 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 261 nm.[21]

Accelerated stability studies

The branded cefpodoxime proxetil product and generic cefpodoxime proxetil products were placed inside a polyvinyl chloride (PVC) container and aluminium foil was wrapped over it. The stability studies were performed under the accelerated conditions of temperature (40°C ± 2°C) and moisture (75% ± 5% RH) for the duration of 1 month, 3 months, and 6 months.[22]

Assay preparation

Preparation of mobile solution

A filtered and degassed mixture of 0.02 M ammonium acetate and acetonitrile was prepared in the ratio of 6:4.

Preparation of diluent

A filtered and degassed mixture of water and acetonitrile was prepared in the ratio of 6:4.

Standard preparation

25 mg of cefpodoxime proxetil was weighed accurately and transferred in a 50 ml of volumetric flask. The content was dissolved in 5 mL of methanol, further diluted with the diluent to the desired volume and mixed. 5 mL of the above solution was transferred to 100 mL of the volumetric flask, further diluted with the diluent to the desired volume, mixed, and passed through a filter having 0.45-µm porosity.

Assay procedure

Finely powdered 20 tablets were accurately weighed and a portion of the powder equivalent to 50 mg of cefpodoxime proxetil was transferred to a 100 mL volumetric flask. The content was dissolved in 10 mL of methanol, further diluted with the diluent to the desired volume and mixed. 5 mL of the above solution was transferred to 100 mL of the volumetric flask, further diluted with the diluent to the desired volume, mixed, and passed through a filter having 0.45-µm porosity.

Chromatographic system suitability

The liquid chromatography system was equipped with a 235 nm detector having a 250 mm × 4.6 mm dimension packing column. The flow rate was 2 mL/min at ambient temperature (30°C). The standard and the test preparations were chromatographed and the peak responses were recorded. About 0.9 for S-epimer cefpodoxime proxetil and 1.0 for R-epimer cefpodoxime proxetil are the relative retention periods. The resolution, R, is not less than 2.5 between the S-epimer cefpodoxime proxetil and the R-epimer cefpodoxime proxetil. No more than 1.5 is the cefpodoxime proxetil R-epimer tailing factor and no more than 1.0 percent is the relative standard deviation measured for replication injections from the cefpodoxime proxetil S-epimer and cefpodoxime proxetil R-epimer regions. Not more than 1.0% for any peak at relative retention times is desirable. Not more than 0.5% of any other individual impurity and not more than 6.0% of total impurities is desired. Not more than 3.0% of any peak at a relative retention time and individual peaks having relative retention times not higher than 2.0 is desired.

The percentage of each impurity in the portion of tablets was calculated by the formula:

% purity = 2000 (CP/W) (rU/rS)

C is the concentration (in mg per mL) of cefpodoxime proxetil in the standard preparation; P is the designated potency (in µg per mg) of cefpodoxim in USP cefpodoxime proxetil; W is the weight (in mg) of cefpodoxime proxetil taken to prepare the assay preparation; rU and rS are the peak response numbers obtained from the preparation of the assay and the standard preparation of cefpodoxime proxetil S-epimer and cefpodoxime proxetil R-epimer, respectively.

Impurity profiling

Preparation of Solution-A

Solution A was prepared by taking filtered and degassed 0.02 M ammonium acetate.

Preparation of Solution-B

Solution A was prepared by taking filtered and degassed acetonitrile.

Preparation of the mobile phase

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

Preparation of diluent

A filtered and degassed mixture of water and acetonitrile was prepared in the ratio of 2:1.

System suitability solution

A quantity of cefpodoxime proxetil was dissolved in the diluent to obtain a solution containing 10 µg/mL. A volume of methanol not exceeding 10% of the total volume in the final solution may be used to facilitate dissolution.

Standard solution

50 mg of cefpodoxime proxetil was accurately weighed and transferred to a 50 ml of volumetric flask. The content was dissolved in 5 mL of methanol, using sonication if necessary, diluted with diluent to the desired volume, and mixed well. The solution was injected promptly and analyzed within 24 hours when stored at 8ºC temperature.

Test solution

50 mg of cefpodoxime proxetil was accurately weighed and transferred to a 50 ml of volumetric flask. The content was dissolved in 10 mL of methanol, using sonication if necessary, diluted with diluent to the desired volume, and mixed well. The solution was injected promptly and analyzed within 24 hours when stored at 8ºC temperature.

Chromatographic system

The liquid chromatography system was equipped with a 261 nm detector having 250 mm × 4.6 mm dimension packing column (5 µm particle size). The flow rate was 2 mL/min. The standard and the test preparations were chromatographed and the peak responses were recorded according to the following gradient procedure: 0 min [equilibration (10 min), solution A (90%), solution B (10%)]; 0-10 min [linear gradient, solution A (90%→68%), solution B (10%→32%)]; 10-40 min [isocratic, solution A (68%), solution B (32%)]; 40-80 min [linear gradient, solution A (68%→50%), so-

lution B (32%→50%)]; 80-85 min [isocratic, solution A (50%), solution B (50%)]; 85-90 [linear gradient, solution A (50%→25%), solution B (50%→75%)]; 90-95 [isocratic, solution A (25%), solution B (75%)]; 95-100 [linear gradient, solution A (25%→90%), solution B (75%→10%)]. The tailing factor and the relative standard deviation for replicate injection should not more than 2.0.

Assay Procedure

20 µL of test solution was injected into the chromatography system and the chromatogram was recorded. All the measurements were done by the peak areas. The percentage of each impurity in the portion of cefpodoxime proxetil was obtained from the formula:

% Impurity = 100 (*ri* / *rs*)

Where *ri* is the peak area for each impurity and *rs* is the sum of the areas of all the peaks.

RESULTS AND DISCUSSION

Spectral analysis of cefpodoxime proxetil

λmax determination

The prominent wavelengths at 261.40 nm, 213.20 nm, and 208.80 nm were predominantly seen (**Figure 1**). An absorption maximum was found to be at 261 nm. Hence, 261 nm was selected as the λmax for further studies.

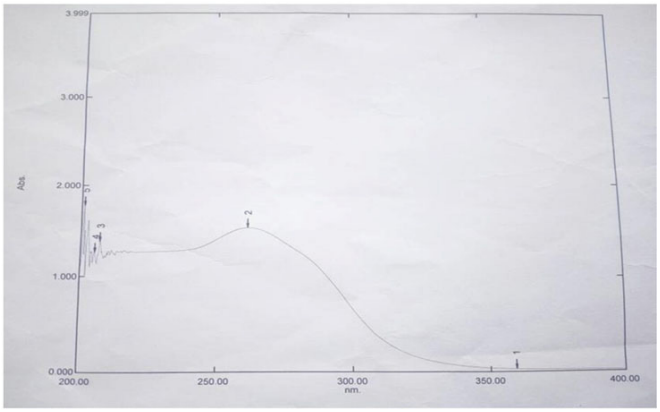

Figure 1: UV Spectra of cefpodoxime proxetil

Prepared standard curve

Cefpodoxime proxetil showed maximum absorption at wavelength 261 nm in glycine medium. 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 = 0.0294x + 0.0027* with $R^2 = 0.9994$ (**Figure 2**).

Table 1: Observed absorbances in the standard calibration curve.

Concentration (µg/mL)	Absorbances
5	0.149
10	0.304
15	0.437
20	1.587
25	1.743

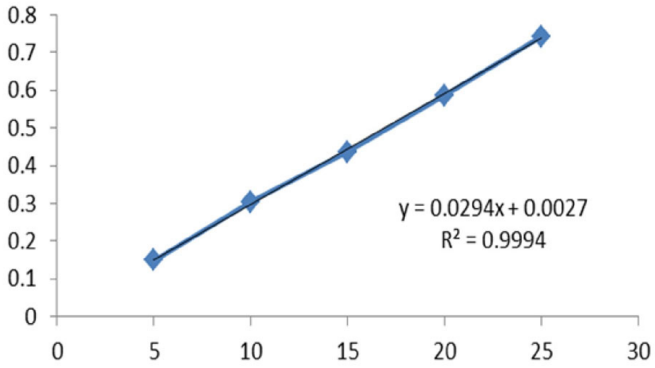

Figure 2: Standard calibration curve of cefpodoxime proxetil

Evaluation parameters for marketed branded and generic products

Tablet description

The colour, shape, and size were examined by visual observation where the factory manufactured cefpodoxime proxetil products (1×10 tablets in blister packaging) had the same attributes as per pharmacopoeia 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 a white colour, uncoated, round shape tablet whereas the generic products were white color uncoated, caplet shape tablet (G1 product), pale yellow color, uncoated, round shape tablet (G2 product), White color, uncoated, round shape tablet (G4 product), and pale orange color, uncoated, round shape tablet (G3 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.

Table 2: The physical appearance of branded and generic products at the initial condition and under accelerated stability conditions.

Product code	Appearance	Packaging	Initial	After 1 months	After 3 months	After 6 months
B1		1×10 tablets in blister packaging	White colour, uncoated, round shape tablet	No change	No change	No change
G1		1×10 tablets in strip packaging	White colour uncoated, caplet shape tablet	No change	No change	No change
G2		1×10 tablets in blister packaging	Pale yellow colour, uncoated, round shape tablet	No change	No change	No change
G3		1×10 tablets in blister packaging	Pale orange colour, uncoated, round shape tablet	No change	No change	No change
G4		1×10 tablets in blister packaging	White colour, uncoated, round shape tablet	No change	No change	No change
G5		1×10 tablets in blister packaging	Pale orange colour, uncoated, round shape tablet	No change	No change	No change

Tablet Diameter and Thickness

All the generics and the branded cefpodoxime proxetil tablets were found to be within the acceptable range of thickness (0.2-0.36 mm), length (11-14 mm), width (0.7 mm), and diameter (11 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 the stability study (**Table 3**).

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	0.36 ± 0.001	14 ± 0.000	-	_
G1	0.3 ± 0.021	11 ± 0.000	0.7 ± 0.000	_
G2	0.23 ± 0.001	_	_	11 ± 0.000
G3	0.2 ± 0.026	_	_	11 ± 0.000
G4	0.2 ± 0.003	_	_	11 ± 0.000
G5	0.3 ± 0.005	_	_	11 ± 0.000

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 assure that the drug content in each unit dose 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 reflects variation in the content of the 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**).

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

Product code	Initial study	After 1 month	After 3 months	After 6 months
B1	714 ± 21.5	697.9 ± 10.1	704.8 ± 14.9	706.8 ± 14.9
G1	504 ± 13.2	251.15 ± 4.77	506 ± 25.4	496.8 ± 17.3
G2	277.6 ± 789	276.45 ± 8.7	284.3 ± 4.2	277.1 ± 16.1

Table 4: *(Continued)*

Product code	Initial study	After 1 month	After 3 months	After 6 months
G3	265.85 ± 4.05	262.15 ± 2.58	259.9 ± 5.1	261.2 ± 3.6
G4	280.2 ± 3.38	270.1 ± 6.81	277.6 ± 1.8	276.1 ± 3.5
G5	266.6 ± 4.79	274. ± 2.35	261.4 ± 3.4	263.9 ± 3.9

Tablet hardness

The hardness test showed the ability of tablets to withstand pressure or stress during handling, packaging, and transportation. The results indicated that the branded tablet product B1 had the highest strength; *i.e.* 1.96 kg/cm^2 as compared to all the five generic products (G1-G5). The generic products G2 and G5 retained the hardness across the 6 months accelerated stability period while branded tablet product B1 as well as generics G1, G3, and G4 showed an increase in the hardness value after 6 months of the accelerated stability period. The reason for the augmentation of hardness value (breaking strength) may be due to the specific excipients used, moisture absorption, and temperature. Generic products G1, G2, G4, and G5 showed a hardness value of less than 2 kg/cm^2, after accelerated stability studies which are not a good sign of compressibility and therefore the batches failed. Only branded tablet product B1 and generic product G3 showed a good sign for tablets dosage form (**Table 5**).

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

Product code	Hardness (Kg/cm^2) ± SD			
	Initial study	After 1 month	After 3 months	After 6 months
B1	1.96 ± 0.057	2.2 ± 0.1	2.26 ± 0.20	2.7 ± 0.2
G1	1.4 ± 0.529	0.9 ± 0.1	1.03 ± 0.05	1.9 ± 0.05
G2	1.8 ± 0.26	1.5 ± 0.1	1.5 ± 0.1	1.8 ± 0.1
G3	1.7 ± 0.43	2.0 ± 0.05	2.14 ± 0.11	2.1 ± 0.1
G4	1.26 ± 0.20	1.66 ± 0.40	1.3 ± 0.1	1.8 ± 0.1
G5	1.63 ± 0.37	1.86 ± 0.05	1.9 ± 0.1	1.8 ± 0.1

Friability study

6 tablets of each product were used for the friability test. The branded product B1 and generic tablet products (G1-G5) demonstrated friability of not more than 1% in both initial study and for 6 months accelerated stability study. The friability values were observed to be decreased over time which may be due to retaining product hardness owing to moisture absorption and temperature. All these products passed the friability test (**Table 6**).

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

Product code	Friability (%)			
	Initial study	After 1 month	After 3 months	After 6 months
B1	0.56	0.8	0.27	0.311
G1	0.628	0.2	0.15	0.31
G2	0.98	8.4	0.39	3.93
G3	0.7	0.9	0.19	0.22
G4	0.57	0.1	0.25	0.5
G5	0.679	0.11	0.11	0.22

Disintegration study

The disintegration test is the most important step in the release of drugs from the immediate release dosage forms. The rate of 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 three generic products G2, G3, and G5 passed the disintegration test at initial levels but branded product B1 and two generic products G2 and G3 failed after the accelerated stability period according to the USP guidelines (**Table 7**). It was observed that the G1 generic product displayed out of limit at both initial and accelerated stability levels. Generic products G4 and G5 presented variable results after the 3rd month and 6th month of accelerated stability period which may be due to tablet to tablet variation.

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

Product code		Disintegration time in (Minute: Second) Minimum and Maximum			
		Initial study	After 1 month	After 3 months	After 6 months
B1	Minimum	23 sec.	33 sec.	38 sec.	36 sec.
	Maximum	25 sec.	51 sec.	42 sec.	44 sec.
G1	Minimum	1 min. 8 sec.	1 min. 20 sec.	1 min. 12sec.	1 min. 20 sec.
	Maximum	1 min. 10 sec.	1 min. 38 sec.	1 min. 40sec	1 min. 30 sec
G2	Minimum	30 sec.	43 sec.	42 sec.	42 sec.
	Maximum	32 sec.	58 sec.	49 sec.	56 sec.
G3	Minimum	20 sec.	30 sec.	33 sec.	36 sec.
	Maximum	21 sec.	34 sec.	36 sec.	51 sec.
G4	Minimum	38 sec.	56 sec.	27 sec.	1 min. 13 sec.
	Maximum	40 sec.	60 sec.	29 sec.	1 min. 32 sec.
G5	Minimum	25 sec.	24 sec.	1 min. 11 sec.	23 sec.
	Maximum	27 sec.	31 sec.	1 min. 14 sec.	30 sec.

Dissolution study

The dissolution test of the drug from a solid dosage form is important for drug bioavailability. In the dissolution study, 6 tablets of one branded product B1 and generic products (G1-G5) were tested for the % drug release, according to the method described for the cefpodoxime proxetil tablet in the USP monograph. It is stated in the monograph that the amount of cefpodoxime proxetil released within 30 minutes should not less than 70% of the stated amount.

The *in vitro* dissolution rate is used to simulate the bioequivalency of different formulation of generics (cefpodoxime proxetil tablet) concerning the branded product. Initial dissolution study was performed and the results suggested that the branded product B1, generic products G1 and G3 passed the test while generic products G4 and G5 were at borderline; *i.e.* ~71% while the generic batch G2 failed in the dissolution testing. The reason may be due to the altered physical characteristics and content non-uniformity.

The 1st month accelerated stability samples were analyzed for the dissolution test. Branded product B1 passes with best results; *i.e.* 86.89% after 30 min. The generic products G1 and G3 were observed to release the drugs at 73.26% and 72.68%, respectively (**Table 8**). At the same time, generic product G5 passes the critical lower limit of drug release; *i.e.* 71.8%. However, generic products G2 (59.74%) and G4 (58.71%) failed to show desired dissolution results. A great effect of temperature and humidity may be the plausible reason. Generic product GS4 passed the initial study with a close limit but after 1-month stability, a decrease in the drug dissolution was perceived due to poor production batch.

Table 8: Dissolution test of branded and generic tablets at the initial condition and under accelerated stability conditions.

Product code	Drug release in % ± SD											
	10 min				20 min				30 min			
	Initial	1 months	3 months	6 months	Initial	1 months	3 months	6 months	Initial	1 months	3 months	6 months
B1	79.0 ± 2.2	79.23 ± 8.1	74.27 ± 2.0	60.35 ± 2.2	84.6 ± 3.1	83.27 ± 1.8	76.21 ± 1.0	61.6 ± 2.7	88.71 ± 2.4	86.89 ± 2.0	81.14 ± 0.5	69.4 ± 5.0
G1	72.2 ± 5.1	64.17 ± 2.8	60.11 ± 1.7	64.8 ± 2.7	72.2 ± 4.2	68.91 ± 4.3	63.9 ± 4.3	65.5 ± 2.7	74.3 ± 4.7	73.26 ± 4.6	70.2 ± 0.5	66.2 ± 2.1
G2	41.3 ± 4.7	55.87 ± 3.4	54.63 ± 0.87	45.16 ± 0.7	53.3 ± 4.1	58.30 ± 2.8	55.3 ± 2.8	45.7 ± 1.2	56.7 ± 3.4	59.74 ± 4.5	55.7 ± 4.5	46.7 ± 1.8
G3	71.4 ± 1.1	67.45 ± 2.1	64.4 ± 2.0	55.17 ± 4.2	74.4 ± 0.8	70.81 ± 2.4	69.81 ± 2.5	57.24 ± 4.6	74.7 ± 0.8	72.86 ± 1.8	71.8 ± 0.8	60.1 ± 4.6
G4	56.1 ± 3.1	54.68 ± 4.7	53.6 ± 5.1	48.73 ± 0.7	67.8 ± 8.1	57.4 ± 2.9	55.4 ± 2.0	46.4 ± 2.2	71.2 ± 2.1	58.71 ± 1.3	56.8 ± 0.5	48.8 ± 4.3
G5	67.7 ± 3	68.23 ± 2.9	67.2 ± 0.9	52.6 ± 2.4	± 3.7	69.09 ± 2.8	69.05 ± 8.1	53.6 ± 1.1	71.3 ± 3.3	81.33 ± 2.6	70.2 ± 6.1	54.1 ± 0.4

The 3rd month accelerated stability results presented that the branded product B1 passed the dissolution test while the generic products G1, G3, and G5 demonstrated the % drug release close to the limit; *i.e.* 70%. In contrast to it, two generic products G2 and G4 failed to meet the desired limit. According to Biopharmaceutics Classification System (BCS), cefpodoxime proxetil comes under Class-II (high permeability, low solubility) where it is expected that the dosage form should release >70% drug and as per specification (30 min). There was a decrease in the drug release for the branded product B1 and the generic products G1, G3, and G5, they closely met the required limit. The generic products G2 and G4 failed.

The 6th month accelerated stability results concluded that the branded product B1, as well as generic products (GS1-GS5), failed the dissolution study. Only the branded product B1 complied with the dissolution test until 3rd-month stability while generic products G1, G3, and G5 passed at a boundary level till the 3rd month stability period. Generics G2 and G4 were regarded as failed products during the initial study to 6 months accelerated stability study (40°C ± 2°C and 75°C ± 5% RH).

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 (0.02 M ammonium acetate and acetonitrile in the ratio of 6:4) outlined in the individual drug monographs of the USP (acceptance limit: 90-110%). The content of cefpodoxime proxetil equivalent to cefpodoxime was calculated from the peak areas of the chromatograms of test and reference standard solutions (**Table 9**).

Table 9: Peak area of cefpodoxime proxetil at the initial condition and under accelerated stability conditions.

Product code	Area of Cefpodoxime Proxetil peak			
	Initial	1 months	3 months	6 months
B1	18796054	18838936	17035330	17933970
G1	18768272	18716480	16933202	17629856
G2	19404029	18783563	19052262	16071107
G3	15797805	16161214	17890370	15593136
G4	19464989	16773315	17457906	17446414
G5	17842382	17943043	17943043	16259467

The % assay of branded product B1 and generic products (G1, G2, G4, and G5) were found to be within the range of acceptance criteria, but the generic product G3 failed; *i.e.* 82.26%. When samples were analyzed for assay after 1 month of accelerated stability study, the branded product B1 and the generic products G1, G2, and G3 passed the pharmacopoeia limit (**Table 10**). In contrast it, generic products G3 and G4 failed in the product assay due to the predicted increased rate of degradation and a decrease in potency. After the 3rd month of accelerated stability study, the branded product B1 and two generic products G2 and G5 passed the product assay as per USP guidelines. The generic products G1 and G3 passed with a marginal limit. After the 6th month of accelerated stability study, the branded product B1 passed the % assay. The generic products G1 and G4 passed the critical limit of pharmacopoeia guideline; *i.e.* 90%. In contrast, generic products G2, G3, and G5 failed to meet the desired limit.

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

Product code	Assay (%)			
	Initial study	After 1 month	After 3 months	After 6 months
B1	97.89	98.11	94.12	93.26
G1	97.74	97.47	88.82	91.67
G2	101.00	97.82	99.22	83.09
G3	82.26	87.34	92.78	80.19
G4	101.3	87.35	90.83	91.11
G5	92.92	93.44	93.44	84.68

Impurity profiling

The impurities present in the branded product B1 and generic products (G1-G5) were determined using the isocratic and linear-gradient mode. The retention time peaks of the branded product ranged from 28.386 min to 30.491 min (for *S*-epimer) and 31.57 min to 33.99 min (for *R*-epimer) from the initial (**Figure 3**), 1 month (**Figure 4**), 3 months (**Figure 5**), 6 months (**Figure 6**) of accelerated stability study that represent not much difference. However, a decrease in the peak area was perceived from 443.84 to 72.17 from the initial to 6 months of accelerated stability study (**Table 11**). However, a reverse phenomenon was observed for generic products (G1-G5). The area of the drug peak in generic products enhances concurrently with the duration of the accelerated stability study.

Table 11: Impurity profiling of branded cefpodoxime proxetil product and generic cefpodoxime proxetil products in the initial condition and under accelerated stability conditions.

Product code	Epimer	Retention time of Cefpodoxime Proxetil peak				Area of Cefpodoxime Proxetil peak			
		Initial	1 months	3 months	6 months	Initial	1 months	3 months	6 months
B1	S-epimer	29.496	28.386	30.491	29.554	443.84979	181.57028	192.74	72.17
	R-epimer	32.841	31.57	33.991	32.98	548.54199	186.54	223.54	109.04
G1	S-epimer	28.722	28.722	30.937	30.073	106.19	106.09	190.58	415.50
	R-epimer	31.957	31.856	34.658	33.571	107.057	107.154	236.88	546.37
G2	S-epimer	28.734	28.734	30.861	30.091	97.41	97.40	156.40	211.18
	R-epimer	31.935	31.935	34.581	33.575	98.82	98.72	206.61	247.22
G3	S-epimer	29.808	29.808	29.080	30.295	106.83	106.85	99.46	195.32
	R-epimer	33.284	33.283	32.346	33.833	149.47	149.49	97.63	234.54
G4	S-epimer	29.025	29.025	28.716	30.035	123.77	123.71	86.98	169.78
	R-epimer	32.306	32.306	32.019	33.489	230.33	230.34	76.00	206.19
G5	S-epimer	29.325	29.325	30.977	30.075	112.75	112.74	407.61	507.53
	R-epimer	32.689	32.589	34.710	33.548	151.73	151.76	397.94	505.44

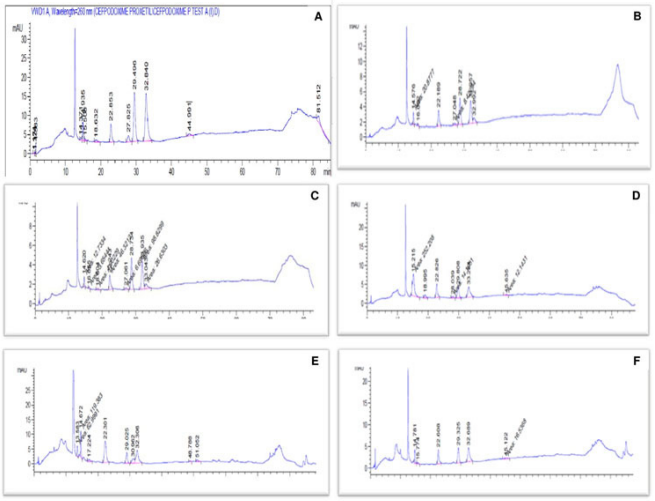

Figure 3: Product impurities at initial conditions: (A) Product B1; (B) Product G1; (C) Product G2; (D) Product G3; (E) Product G4; and (F) Product G5

The individual impurity of the relative retention time (RRT) 0.86 for reference standard cefpodoxime proxetil was 2.15% and total content of 2.15% because there were no other impurity peaks. Hence, the sample passed through the impurity test by the cefpodoxime Proxetil Tablet USP monograph. Following ICH information (condition for zone-IV) for the development guidelines and shelf-life assessment through short-term (6 months) stability study (40°C ± 2°C and 75°C ± 5% RH), it is mandatory to check the degradation of API and impurity generation which leads to a loss in potency. It is one of the study parameters to check the safety and efficacy of formulation during the complete shelf life.

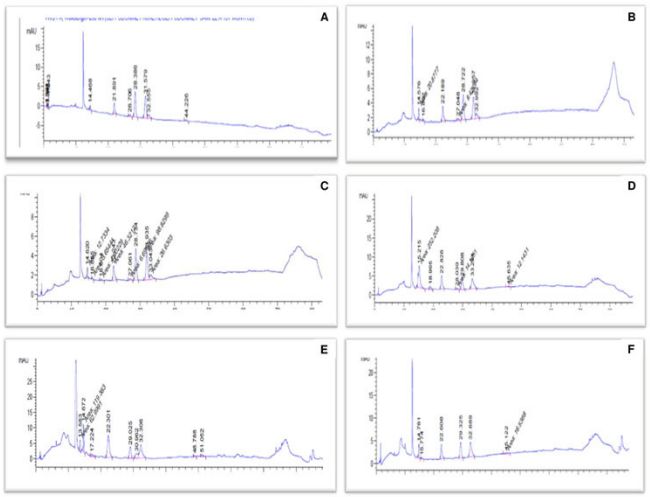

Figure 4: Product impurities under 1-month stability conditions: (A) Product B1; (B) Product G1; (C) Product G2; (D) Product G3; (E) Product G4; and (F) Product G5.

Market brand product B1 passed in total impurity; *i.e.* 3.75% but failed in single individual impurity while other impurity peaks were not detected in chromatograph at initial study (**Table 12**). Similar conditions were observed even after the 1st, 3rd, and 6th month of the accelerated stability period. However, only the difference was the rise in the same individual impurity at RRT 0.86 and the maximum found after the 6th-month stability was 5.46%.

Table 12: Percentage impurity profiling of branded and generic products in the initial condition and under accelerated stability conditions

Product code	% Impurity					
	RRT	Limit	Initial	After 1 Month of stability	After 3 Months of stability	After 6 Months of stability
Standard						
Standard	0.86	NMT-3.00%	2.15% Pass			
	1.27	NMT-1.00%	-			
	1.29	NMT-1.00%	-			
	More than - 2	NMT-0.5%	-			
	Total	NMT-6.00%	2.15%			

Table 12: ***(Continued)***

Product code			% Impurity			
	RRT	Limit	Initial	After 1 Month of stability	After 3 Months of stability	After 6 Months of stability
Branded B1						
B1	0.86	NMT-3.00%	3.75%	3.87%	4.21%	5.46%
	1.27	NMT-1.00%	-	-	-	-
	1.29	NMT-1.00%	-	-	-	-
	More than - 2	NMT-0.5%	-	-	-	-
	Total	NMT-6.00%	3.75%	3.87%	4.21%	5.46%
Generic G1						
G1	0.86	NMT-3.00%	5.76%	5.81%	6.02%	6.98%
	1.27	NMT-1.00%	-	-	1.05%	2.35%
	1.29	NMT-1.00%	-	-	-	-
	More than - 2	NMT-0.5%	-	-	-	-
	Total	NMT-6.00%	5.76%	5.81%	7.07%	9.33%
Generic G2						
G2	0.86	NMT-3.00%	2.66%	2.89%	1.76%	6.18%
	1.27	NMT-1.00%	-	-	-	-
	1.29	NMT-1.00%	-	-	-	-
	More than - 2	NMT-0.5%	-	-	2.79%	2.60%
	Total	NMT-6.00%	2.66%	2.89%	4.55%	8.78%
Generic G3						
G3	0.86	NMT-3.00%	2.13%	3.01%	4.73%	5.75%
	1.27	NMT-1.00%	-	-	-	-
	1.29	NMT-1.00%	-	-	-	-
	More than - 2	NMT-0.5%	-	-	-	-
	Total	NMT-6.00%	2.13%	3.01%	4.73%	5.75%
Generic G4						
G4	0.86	NMT-3.00%	1.98%	2.75%	4.81%	6.28%
	1.27	NMT-1.00%	-	-	-	-
	1.29	NMT-1.00%	-	-	-	-

Table 12: ***(Continued)***

Product code	% Impurity					
	RRT	Limit	Initial	After 1 Month of stability	After 3 Months of stability	After 6 Months of stability
	More than - 2	NMT-0.5%	-	-	-	-
	Total	NMT-6.00%	1.98%	2.75%	4.81%	6.28%
Generic G5						
G5	0.86	NMT-3.00%	1.86%	1.86%	1.87%	7.0%
	1.27	NMT-1.00%	-	-	-	-
	1.29	NMT-1.00%	-	-	-	-
	More than - 2	NMT-0.5%	-	-	2.92%	2.08%
	Total	NMT-6.00%	1.86%	1.86%	4.79%	9.08%

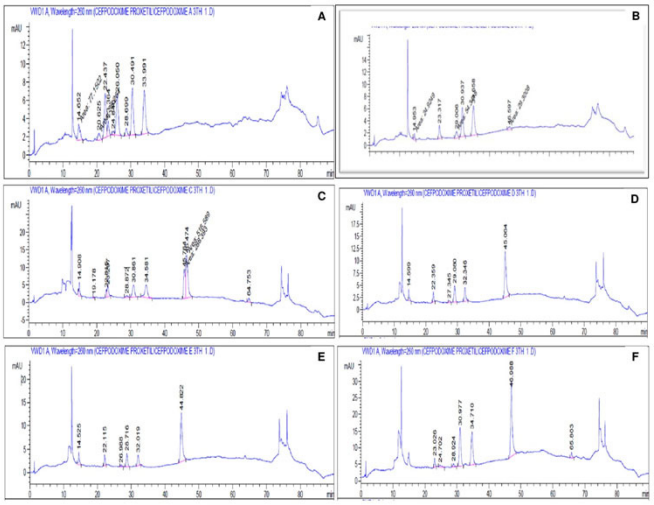

Figure 5: Product impurities under 3 months stability conditions: (A) Product B1; (B) Product G1; (C) Product G2; (D) Product G3; (E) Product G4; and (F) Product G5.

The generic product G1 failed in impurity at RRT 0.86 at all-time points and was close to the total impurity value; *i.e.* 5.75% at the initial and 1st month of the accelerated stability period. Generic product G1 failed in the 3rd month and 6th month of accelerated stability period for total impurity and newly generated impurity at RRT 1.27. Generic product G2 passed in the initial and 1st month of accelerated stability period but failed in the 3rd month and 6th month of accelerated stability by impurity at RRT >2. Generic product G3 passed at the initial level but failed in the 1st month, 3rd month, and 6th month of accelerated stability with a rise in the individual impurity at RRT 0.86, passed by total impurity. Generic product G4 passed in the initial and 1st month of accelerated stability period with impurity less than the limit specified at RRT 0.86; therefore passes in total impurity also. There were no other impurity peaks generated throughout the stability period but the same impurity rise beyond 6.0% and thus failed in the 6th month of the accelerated stability study. Generic product G5 passed the individual impurity level. At RRT 0.86, till the 3rd month of accelerated stability study but it was found to rise to the very high level; *i.e.* 7.0 % after 6 months of the accelerated stability. After 3rd month, one more impurity was generated at RRT level >2 was also failed in the individual limit; *i.e.* not more than 0.5%. In the total impurity context, generic product G5 passed till the 3rd month but failed after 6th month of the accelerated stability study.

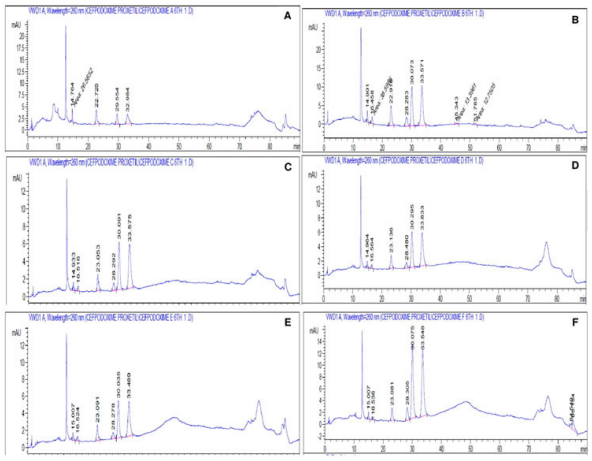

Figure 6: Product impurities under 6 months stability conditions: (A) Product B1; (B) Product G1; (C) Product G2; (D) Product G3; (E) Product G4; and (F) Product G5.

CONCLUSION

The study revealed that all the generics and the branded cefpodoxime proxetil 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 generic products G2 and G5 retained the hardness across the 6 months accelerated stability period while branded tablet product B1 as well as generics G1, G3, and G4 showed an increase in the hardness value. The branded product B1 and generic tablet products (G1-G5) demonstrated friability of not more than 1% in both initial study and for 6 months accelerated stability study. branded product B1 and three generic products G2, G3, and G5 passed the disintegration test at initial levels but branded product B1 and two generic products G2 and G3 failed after the accelerated stability period. The % assay of branded product B1 and generic products (G1, G2, G4, and G5) were found to be within the range of acceptance criteria, but the generic product G3 failed; *i.e.* 82.26%. When samples were analyzed for assay after 1 month of accelerated stability study, the branded product B1 and the generic products G1, G2, and G3 passed the pharmacopoeia limit. The study will open new doors of analysis of pharmaceutical quality assurance and provide avenues for both branded products and generic products in maintaining the quality attributes regularly.

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